2.学生发表学术论文情况

2015年至今，本科生发表SCI论文114篇（其中以第一作者发表36篇）；以第一作者发表中文论文12篇。

本科生以第（并）一作者或并列第一作者发表36篇SCI论文清单

序号	题目	作者	期刊	卷期号	JCR 分区	影响因子
1	Synthesis of High-Quality N-Acetyl-L-Cysteine-Capped CdTe Quantum Dots by Hydrothermal Route and the Characterization through MALDI-TOF Mass Spectrometry	Jiaotian Li（本科生）, Tianming Yang, W. H. Chan, Martin M. F. Choi, and Dan Zhao*,	*Journal of Physical Chemistry C*	2013, 117, 19175-19181	Q1	4.177
2	Hypoglycemic Activity and the Potential Mechanism of the Flavonoid Rich Extract from Sophora tonkinensis Gagnep. In KK-Ay Mice	Mi Huang（本科生）, Shihao Deng（本科生）, Qianqian Han, Ping Zhao, Qi Zhou, Sijian Zheng（本科生）, Xinhua Ma, Chan Xu, Jing Yang, Xinzhou Yang*	*Frontiers in Pharmacology*	2016, 7: 288	Q1	5.988
3	Cloning, expression and identification of KTX-Sp4, a selective Kv1.3 peptidic blocker from Scorpiops pococki	Yan Zou#, Feng Zhang#（本科生）, Yaxian Li（本科生）, Yuanfang Wang（本科生）, Yi Li（本科生）, Zhengtao Long（本科生）,Shujuan Shi, Li Shuai, Jiukai Liu, Zhiyong Di, Yin Shijin*	*Cell and Bioscience*	2017, 7: 60	Q1	8.113
4	“Turn-off” fluorescent sensor for highly sensitive and specific simultaneous recognition of 29 famous green teas based on quantum dots combined with chemometrics	Li Liu（本科生）, Yao Fan, Haiyan Fu*, Feng Chen, Chuang Ni（本科生）, Jinxing Wang(本科生), Qiaobo Yin, Qingling Mu（本科生）, Tianming Yang, Yuanbin She*	*Analytica Chimica Acta*	2017, 963: 119-128	Q1	6.911

5	β-ecdysterone from Cyanotis arachnoidea exerts hypoglycemic effects through activating IRS-1/Akt/GLUT4 and IRS-1/Akt/GLUT2 signal pathways in KK-Ay mice	Li Chen（本科生）, Sijian Zheng（本科生）, Mi Huang（本科生）, Xinhua Ma, Jie Yang, Shihao Deng(本科生), Yun Huang, Yanzhang Wen, Xinzhou Yang*	*Journal of Functional Foods*	2017, 39: 123-132	Q1	5.223
6	Hepatoprotective activity of iridoids, seco-iridoids and analog glycosides from Gentianaceae on HepG2 cells via CYP3A4 induction and mitochondrial Pathway	Kang Dai#, Xuejia Yi#（本科生）, Xianju Huang*, Azhar Muhammad, Mei Li, Jun Li, Guangzhong Yang, Yue Gao	*Food & Function*	2018, 9(5), 2673-2683	Q1	6.317
7	Trichothecrotocins A–C, antiphytopathogenic agents from potato endophytic fungus Trichothecium crotocinigenum	Huixiang Yang#（本科生）, Honglian Ai#, Tao Feng*, Wenxuan Wang, Bin Wu, Yongsheng Zheng, Huan Sun, Juan He, Zhenghui Li, Jikai Liu*,	*Organic Letters*	2018, 20(24): 8069-8072	Q1	6.072
8	Antroalbocin A, an antibacterial sesquiterpenoid from higher fungus antrodiella albocinnamomea	Wei Li#（本科生）, Juan He#, Tao Feng*, Huixiang Yang（本科生）, Honglian Ai, Zhenghui Li*, Jikai Liu*, Antroalbocin A	*Organic Letters*	2018, 20(24), 8019-8021	Q1	6.072
9	Dauricine upregulates the chemosensitivity of hepatocellular carcinoma cells: Role of repressing glycolysis via miR-199a: HK2/PKM2 modulation	Wei Li(本科生), YunHan Qiu, Ji Hao(本科生), Chi Zhao, Xukun Deng, Guangwen Shu*	*Food and Chemical Toxicology*	2018, 121, 156-165	Q1	5.572

10	Xanthones from the Bark of Garcinia xanthochymus and the Mechanism of Induced Apoptosis in Human Hepatocellular Carcinoma HepG2 Cells via the Mitochondrial Pathway	Shan Jin（本科生）, Kuan Shi, Liu Liu, Yu Chen, Guangzhong Yang*	*International Journal of Molecular Sciences*	2019, 20(19), 4803	Q1	6.208
11	Immunosuppressive Effects of a Novel Potassium Channel Toxin Ktx-Sp2 from Scorpiops Pocoki	Yubiao Zhang#, Feng Zhang#（本科生）, Shujuan Shi, Xinqiao Liu, Weisong Cai, Guangtao Han, Caihua Ke（本科生）, Siru Long（本科生）, Zhiyong Di, Shijin Yin*, Haohuan Li*	*Cell Biosci*	2019, 9: 99	Q1	9.584
12	Enantiomeric NMR discrimination of carboxylic acids using actinomycin D as a chiral solvating agent	Liwen Bai# (本科生), Pian Chen#, Jiangxia Xiang(本科生), Jiarui Sun(本科生), Xinxiang Lei*	*Organic & Biomolecular Chemistry*	2019, 17: 1466–1470	Q1	3.89
13	Cardiolipin Synthase 1 Ameliorates NASH Through Activating Transcription Factor 3 Transcriptional Inactivation	Chuyue Tu（本科生）, Hui Xiong, Yufeng Hu, Wen Wang, Gui Mei, Hua Wang, Ya Li, Zelin Zhou, Fengping Meng, Peng Zhang*, Zhinan Mei*	*Hepatology*	2020, 72(6): 1949-1967	Q1	17.298
14	Carboxymethyl chitosan microspheres loaded hyaluronic acid/gelatin hydrogels for controlled drug delivery and the treatment of inflammatory bowel disease	Shangwen Zhang（本科生）, Li Kang, Sheng Hu, Jie Hu, Yanping Fu, Yan Hu*, Xinzhou Yang*	*International Journal of Biological Macromolecules*	2021, 167, 1598-1612	Q1	8.025

15	A characterized saponin extract of Panax japonicus suppresses hepatocyte EMT and HSC activation in vitro and CCl 4-provoked liver fibrosis in mice: Roles of its modulatory effects on the Akt/GSK3β/Nrf2 cascade	Chenxi Dai（本科生）, Arslan Yusuf, Hui Sun, Guangwen Shu , Xukun Deng*	*Phytomedicine*	2021, 93, 153746	Q1	6.656
16	Discovery of Novel Polycyclic Polyprenylated Acylphloroglucinols from the Fruits of Garcinia xanthochymus as Antitumor Agents by Suppressing the STAT3 Signaling	Shan Jin（本科生）, Wen Wang, Fei Gan, Wenli Xie（本科生）, Jing Xu, Yu Chen,Zhinan Mei*, Guangzhong Yang*	*International journal of molecular sciences*	2021, 22(19): 10365	Q1	6.208
17	Methylgerambullin derived from Glycosmis pentaphylla mediates anti hepatocellular carcinoma cancer effect by activating mitochondrial and endoplasmic reticulum stress signaling and inhibiting AKT and STAT3 pathways	Chaoqun Wu（本科生）, Guangwen Shu, Huiqi Huan（本科生）g, Kejian Pang, Xinzhou Yang*, Guangzhong Yang*	*Food and Chemical Toxicology*	2021, 149, 112032	Q1	5.572
18	[3 + 2] Cycloaddition of Nitrile Imines with Enamides: An Approach to Functionalized Pyrazolines and Pyrazoles	Liang Tu(本科生), Limei Gao, Xiaomeng Wang, Ruijie Shi, Rupei Ma(本科生), Junfei Li(本科生), Xiaoshuang Lan(本科生), Yongsheng Zheng*, Jikai Liu*	*The Journal of Organic Chemistry*	2021, 86: 559–573	Q1	4.198
19	Peroxidative depolymerization of fucosylated glycosaminoglycan: Bond-cleavage pattern and activities of oligosaccharides	Xuelin Tao(本科生), Weili Wang , Xiang Shi , Di Lan , Hui Mao , Zimo Ning , Li Gao , Zhichuang Zuo , Chen Xu, Zaiqing Yang(本科生), Yu Wang(本科生), Zhili Zuo *, Na Gao *, Jinhua Zhao *	*Carbohydrate Polymers*	2022, 295: 119855	Q1	10.723

20	A novel·visual sensing method based on Al@AuNCs for rapid identification of Chrysanthemum morifolium from different origins	Shuo Wang[#], Xueqing Zeng[#](本科生)，Hengye Chen, Gaoqiong Deng, Xiuyun Bai, Jian Yang*, Haiyan Fu*	*Sensors and Actuators B: Chemical*	2022, 356: 131307	Q1	9.221
21	Integrative Analysis of Metabolome and Transcriptome Identifies Potential Genes Involved in the Flavonoid Biosynthesis in Entada phaseoloides Stem	Min Lin(本科生）, Zhuqing Zhou, Zhinan Mei*	*Frontiers in Plant Science*	2022，13: 792674	Q1	6.627
22	A Fucan Sulfate with Pentasaccharide Repeating Units from the Sea Cucumber Holothuria floridana and Its Anticoagulant Activity	Zimo Ning（本科生）, Pin Wang, Zhichuang Zuo, Xuelin Tao（本科生）, Li Gao, Chen Xu, Zhiyue Wang, Bin Wu *, Na Gao *and Jinhua Zhao	*Marine Drugs*	2022, 20: 377	Q1	6.085
23	Cloning and functional characterization of the polyketide synthases based on genome mining of Preussia isomera XL-1326	Qingpei Liu, Dan Zhang（本科生）, Yao Xu, Shuaibiao Gao（本科生）, Yifu Gong, Xianhua Cai（本科生）, Ming Yao, Xiaolong Yang	*Frontiers in Microbiology*	2022，13: 819086	Q1	6.064
24	Sesquiterpenes with diverse skeletons from histone deacetylase inhibitor modified cultures of the basidiomycete Cyathus stercoreus (Schwein.) De Toni HFG134	ShuiLin Liu（本科生）, Lin Zhou , Heping Chen *, Ji-Kai Liu **	*Phytochemistry*	2022, 195, 113048	Q1	4.004
25	The preparation of high-quality water-soluble silicon quantum dots and their application in the detection of formaldehyde	Xiaoling Xu[#](本科生), Shiyao Ma, Xincai Xiao, Yan Hu, Dan Zhao*	*RSC Advances*	2016, 6(101): 98899-98907	Q2	3.748

26	Anti-diabetic activity of stigmasterol from soybean oil by targeting the GLUT4 glucose transporter	Jialin Wang（本科生）, Mi Huang（本科生）, Jie Yang, Xinhua Ma, Sijian Zheng, Shihao Deng（本科生）, Yun Huang（本科生）, Xinzhou Yang*, Ping Zhao*	*Food & Nutrition Research*	2017, 61: 1364117	Q2	3.89
27	Fine classification and untargeted detection of multiple adulterants for Gastrodia elata BI. (GE) by near-infrared spectroscopy coupled with chemometrics	Gangfeng Li$^{\#}$, Qiaobo Yin$^{\#}$（本科生）, Lin Zhang, Ming Kang, Haiyan Fu*, Chenbo Cai, Lu Xu*	*Analytical Methods*	2017, 9(12): 1897-1904	Q2	3.532
28	Chemical constituents from Sophora tonkinensis and their glucose transporter 4 translocation activities	Xinzhou Yang$^{\#}$, Shihao Deng$^{\#}$（本科生）, Mi Huang（本科生）, Jialin Wang（本科生）, Li Chen（本科生）, Mingrui Xiong, Jie Yang, Sijiang Zheng, Xinhua Ma, Ping Zhao*, Yunjiang Feng*.	Bioorganic & Medicinal Chemistry Letters	2017, 27: 1463-1466	Q2	2.94
29	Non-targeted detection of multiple frauds in orange juice using double water-soluble fluorescence quantum dots and chemometrics	Lu Xu$^{\#}$, Liuna Wei$^{\#}$（本科生）, Qiong Shi, Chenbo Cai, Haiyan Fu*, Yuanbin She.	*Food Analytical Methods*	2019, 12: 2614-2622	Q2	3.498
30	Recent Advances about the Applications of Click Reaction in Chemical Proteomics	Tingting Yao（本科生）, Xiaowei Xu*. Rong Huang	*Molecules*	2021, 26: 5368	Q2	4.927
31	Formal [2 + 2 + 2] Cycloaddition Reaction of 1,3,5-Triazinanes with diethyl acetylene dicarboxylate: Approachto Tetrahydropyrimidines	Ruijie Shi(本科生), Limei Gao, Weiji Chen(本科生), Yangqing Shi(本科生), Zhixing Cao, Yong-sheng Zheng*, Jikai Liu*	*European Journal of Organic Chemistry*	2021, 44: 5941-5945	Q2	3.261

32	Isopimarane diterpenes from the rice fermentation of the fungicolous fungus Xylaria longipes HFG1018	Qingyuan Wang（本科生）, Heping Chen *, Jikai Liu *	*Phytochemistry Letters*	2021, 45: 100-104	Q2	1.873
33	One-step synthesis of high-quality water-soluble CdSe quantum dots capped by N-Acetyl-L-cysteine via hydrothermal method and their characterization	Chunjin Wei（本科生）, Jinyu Li（本科生）, Fang Gao, ShuxiaGuo（本科生）, Yongcui Zhou（本科生）, Dan Zhao*	*Journal of Spectroscopy*	2014, 369145	Q3	1.750
34	Cytotoxic polyketides from endophytic fungus Phoma bellidis harbored in Ttricyrtis maculate	Wenxuan Wang[#], Meijia Zheng[#](本科生), Jing Li, Tao Feng, Zheng-Hui Li, Rong Huang, Yong-Sheng Zheng, Huan Sun, Honglian Ai*, Jikai Liu*	*Phytochemistry Letters*	2019, 29: 41-46	Q3	1.873
35	Diastereoselective [3 + 3] cycloaddition reaction of 2-arylideneindan1,3-diones with b-naphthols: Efficient assemble of immunosuppressive pentacyclic chromanes	Na Li(本科生), Liang Tu(本科生), Guiguang Cheng, Houling Sa(本科生), Zhenghui Li, Tao Feng, Yongsheng Zheng*, Jikai Liu*	*Tetrahedron Lett*	2020, 61: 151579	Q3	2.032
36	New cytochalasan alkaloids and cyclobutane dimer from an endophytic fungus Cytospora chrysosperma in Hippophae rhamnoides and their antimicrobial activities	QingLin Mou(本科生), ShengXiang Yang, Ting Xiang, WenWen Liu, Jian Yang, LanPing Guo*, WenJing Wang*, XiaoLong Yang*	*Tetrahedron Letters*	2021, 87: 153207	Q3	2.032

本科生以共同作者参与发表 78 篇 SCI 论文清单

序号	题目	作者	期刊	卷期号	JCR 分区	影响因子
1	Synthesis of N-acetyl-L-cysteine -capped ZnCdSe quantum dots via hydrothermal method and their characterization	Fang Gao, Yuying Liu（本科生）, Yao Fan, Dan Zhao*	*Science and Technology of Advanced Materials*	2014, 15, 055001 (9pp)	Q1	7.381
2	Gynura procumbens Reverses Acute and Chronic Ethanol-Induced Liver Steatosis through MAPK/SREBP-1c-Dependent and -Independent Pathways	XiaoJun Li, YunMei Mu, TingTing Li, YanLing Yang, MeiTuo Zhang（本科生）, YuSang Li, Wei Kevin Zhang, HeBin Tang*, HongCai Shang*	*Journal of Agricultural and Food Chemistry*	2015, 63: 8460-8471	Q1	5.895
3	Isoliensinine, a Bioactive Alkaloid Derived from Embryos of Nelumbo nucifera, Induces Hepatocellular Carcinoma Cell Apoptosis through Suppression of NF-κB Signaling	Guangwen Shu, Ling Yue, Wenhao Zhao（本科生）, Chan Xu, Jing Yang, Shaobing Wang, Xinzhou Yang*	*Journal of Agricultural and Food Chemistry*	2015, 63: 8793-8803	Q1	5.895
4	Synthesis and characterization of high-quality water-soluble CdMnTe quantum dots capped by N-Acetyl-L-Cysteine via hydrothermal method	Fang Gao, Jiaotian Li, Fengxue Wang（本科生）, Tanming Yang, Dan Zhao*	*Journal of Luminescence*	2015, 159, 32-37	Q1	4.171
5	Simultaneous determination of repaglinide and irbesartan in biological plasmas using micellar enhanced excitation-emission matrix fluorescence coupled with ATLD method.	Haiyan Fu, Hedong Li, Mei Shao（本科生）, Tianming Yang*, Xu Zhang（本科生）, Rujing Xu, Yujuan Wei（本科生）, Shuhua Chen, Chuang Ni（本科生）, Hailong Wu*	*Science China Chemistry*	2016, 59: 816-823	Q1	10.152
6	“Turn-off” fluorescent data array sensor based on double quantum dots coupled with chemometrics for highly sensitive and selective detection of multicomponent pesticides	Yao Fan, Li Liu, Donglei Sun（本科生）, Hanyue Lan（本科生）, Haiyan Fu*, Tianming Yang*, Yuanbin She*, Chuang Ni（本科生）	*Analytica Chimica Acta*	2016, 916: 84-91	Q1	6.911

7	Protective effect of luteolin on streptozotocin-induced diabetic renal damage in mice via the regulation of RIP140/NF-kB pathway and insulin signalling pathway.	Lvyi Chen*, Guowen Tian（本科生）, Weidong Tang, Wei Luo, Peng Liu（本科生）, Zhanqiang Ma	*Journal of Functional Foods*	2016, 22: 93-100	Q1	5.223
8	A Self-Assembled Oligopeptide as a Versatile NMR Alignment Medium for the Measurement of Residual Dipolar Couplings in Methanol	Xinxiang Lei*, Feng Qiu, Han Sun, Liwen Bai（本科生）, Wenxuan Wang, Wensheng Xiang, Hongping Xiao	*Angewandte Chemie International Edition*	2017, 56:12857-12861	Q1	16.823
9	The antimicrobial peptide human beta-defensin 2 promotes itch through Toll-like receptor 4 signaling in mice	Jing Feng, Jialie Luo, Madison R. Mack, Pu Yang, Feng Zhang（本科生）, Guan Wang（本科生）, Xuan Gong（本科生）, Tao Cai, Zhinan Mei, Brian S. Kim, Shijin Yin*, Hongzhen Hu*	*Journal of Allergy and Clinical Immunology*	2017, 140: 885-888	Q1	11.022
10	Detection of unexpected frauds: Screening and quantification of maleic acid in cassava starch by fourier transform near-infrared spectroscopy	Haiyan Fu*, Hedong Li, Lu Xu*, Qiaobo Yin（本科生）, Tianming Yang, Chuang Ni（本科生）, Chenbo Cai, Ji Yang（本科生）, Yuanbin She*	*Food Chemistry*	2017, 227: 322-328	Q1	9.231
11	Antidiabetic Activity of Ergosterol from Pleurotus Ostreatus in KK-Ay Mice with Spontaneous Type 2 Diabetes Mellitus	Mingrui Xiong, Yun Huang（本科生）, Yajing Liu, Mi Huang(本科生), Guanjun Song, Qian Ming, Xinhua Ma, Jie Yang, Shihao Deng（本科生）, Yanzhang Wen, Jinhua Shen, QingHua Liu, Ping Zhao*, Xinzhou Yang*	*Molecular Nutrition & Food Research*	2017, 62: 1700444	Q1	5.91
12	Activity of Isoliensinine in Improving the Symptoms of Type 2 Diabetic Mice via Activation of AMP-Activated Kinase and Regulation of PPARγ	Xinzhou Yang, Mi Huang, Jie Yang, Jialin Wang（本科生）, Sijian Zheng, Xinhua Ma, Jinyan Cai, Shihao Deng, Guangwen Shu*, Guangzhong Yang*	*Journal of Agricultural and Food Chemistry*	2017, 65: 7168-7178	Q1	5.895

13	Digestibility of fucosylated glycosaminoglycan from sea cucumber and its effects on digestive enzymes under simulated salivary and gastrointestinal conditions	Longyan Zhao, Yujing Qin(本科生）, Ruowei Guan, Wenqi Zheng, Jikai Liu, Jinhua Zhao*	*Carbohydrate Polymers*	2018, 186: 217-225	Q1	10.723
14	“Turn-off” fluorescent sensor based on double quantum dots coupled With chemometrics for highly sensitive and specific recognition of 53 famous green teas	Ou Hu[#], Lu Xu[#], Haiyan Fu*, Tianming Yang, Yao Fan, Wei Lan, Hebing Tang, Yu Wu（本科生）, Lixia Ma（本科生）, Di Wu（本科生）, Yuan Wang, Zuobing Xiao, Yuanbin She*	*Analytica Chimica Acta*	2018, 1008: 103-110	Q1	6.911
15	Chlorogenic acid methyl ester exerts strong anti-inflammatory effects via inhibiting the COX-2/NLRP3/NF-κB pathway	Lang Zhang[#], Ya Fan[#], HanWen Su[#], Li Wu（本科生）, YuYing Huang, Lei Zhao, Bing Han, GuangWen Shu, MeiXian Xiang*, JinMing Yang*	*Food & Function*	2018, 9: 6155-6164	Q1	6.317
16	Anti-diabetic activity of a polyphenol-rich extract from Phellinus igniarius in KK-Ay mice with spontaneous type 2 diabetes mellitus	Sijian Zheng[#], Shihao Deng[#], Yun Huang（本科生）, Mi Huang（本科生）, Ping Zhao, Xinhua Ma, Yanzhang Wen, Qiang Wang*, Xinzhou Yang*	*Food & Function*	2018, 9: 614-623	Q1	6.317
17	Anti-Proliferative and Anti-Inflammatory Lanostane Triterpenoids from the Polish Edible Mushroom Macrolepiota procera	Heping Chen, Zhenzhu Zhao, Zhenghui Li, Ying Huang, Shuaibing Zhang, Yang Tang, Jianneng Yao, Lin Chen（本科生）, Masahiko Isaka, Tao Feng*, Jikai Liu*	*Journal of Agricultural and Food Chemistry*	2018, 66: 3146-3154	Q1	5.895
18	Liensinine suppresses STAT3-dependent HK2 expression through elevating SHP-1 to induce apoptosis in hepatocellular carcinoma cells in vitro and in vivo	Guangwen Shu, Ji Hao（本科生）, Wei Li, Lang Zhang, YunHan Qiu, XinZhou Yang*	*Journal of Functional Foods*	2018, 45: 288-297	Q1	5.223

19	Tibetan medicine Kuan-Jin-Teng exerts anti-arthritic effects on collageninduced arthritis rats via inhibition the production of pro-inflammatory cytokines and down-regulation of MAPK signaling pathway	Hui Xiong, Xin Ding, Hua Wang, Haiqin Jiang（本科生）, Xinyan Wu, Chuyue Tu, Chaoqun Wu, Yang Pi, Guangzhong Yang, Zhongqiu Zhao, Zhinan Mei*	*Phytomedicine*	2019, 57: 271-281	Q1	6.656
20	γ-Oryzanol alleviates acetaminophen-induced liver injury: roles of modulating AMPK/GSK3β/Nrf2 and NF-κB signaling pathways	Guangwen Shu, Yunhan Qiu, Ji Hao（本科生）, Qian Fua, Xukun Deng*	*Food & Function*	2019, 10: 6858-6872	Q1	6.317
21	Precise structure and anticoagulant activity of fucosylated glycosaminoglycan from Apostichopus japonicus: Analysis of its depolymerized fragments	Ruowei Guan, Yuan Peng（本科生）, Lutan Zhou, Wenqi Zheng, Xixi Liu, Pin Wang, Qingxia Yuan, Na Gao*, Longyan Zhao*, Jinhua Zhao*	*Marine Drugs*	2019,17: 195	Q1	6.085
22	Inverse-Electron-Demand[4+2]-Cycloaddition of 1,3,5-triazinanes:Facile Approaches to Tetrahydroquinazolines	Yongsheng Zheng, Liang Tu（本科生）, Na Li(本科生), Rong Huang, Tao Feng, Huan Sun, Zhenghui Li, Jikai Liu*	*Advanced Synthesis & Catalysis*	2019, 361: 44-48	Q1	5.981
23	Fluorescence paper-based sensor for visual detection of carbamate pesticides in food based on CdTe quantum dot and nano ZnTPyP	Hengye Chen$^{\#}$, Ou Hu$^{\#}$, Yao Fan, Lu Xu, Lei Zhang, Wei Lan, Ying Hu, Xingrui Xie（本科生）, Lixia Ma（本科生）, Yuanbin She, Haiyan Fu*	*Food Chemistry*	2020, 327: 127075	Q1	9.231
24	Environmentally Friendly Protocol for 2,3-Difunctionlization of Indole Derivatives	Wenwu Sun*, Na Chen（本科生）, Tingting Wei（本科生）, Guojing You（本科生）, Hao Yang, Jikai Liu*, Bin Wu*	*Journal of Medicinal Chemistry*	2020, 85:10143−10151	Q1	8.039

25	Chrysanthemum ethanol extract induced loss of Kupffer cells via the mitochondria-dependent apoptotic pathway	Wanli Liang, Yanzhang Wen, Fang Huang（本科生）, Qin Hu, XiaoJun Li, Wei Kevin Zhang*, Xinzhou Yang*	*Food & Function*	2020, 10: 8866-8877	Q1	6.317
26	Paper-based sensor for visual detection of Ag^+ based on a “turn-ff-on” fluorescent design.	Hengye Chen$^{\#}$, Ou Hu$^{\#}$, Haiyan Fu*, Yao Fan, Lu Xu, Qingjun Meng, Lei Zhang, Wei Lan, Chunying Wu(本科生), Siyi Tang（本科生）, Yuanbin She*	*Microchemical Journal*	2020, 157: 104887	Q1	5.304
27	Dual-QDs ratios fluorescent probe for sensitive and selective detection of silver ions contamination in real sample	Hengye Chen$^{\#}$, Shuo Wang$^{\#}$, Haiyan Fu*, Hongliang Xie（本科生）, Wei Lan, Lu Xu, Lei Zhang, Yuanbin She*	*Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*	2020, 234: 118248	Q1	4.831
28	Sesquiterpenoids from Cultures of the Basidiomycetes Irpex lacteus	Mengwang, Jiaoxian Du（本科生）, Huixiang Yang, Quandai, Yapei Liu（本科生）, Juan He, Yi Wang, Zhenghui Li, Tao Feng*, Jikai Liu*	*Journal of Natural Products*	2020, 83: 1524-1531	Q1	4.803
29	Environmentally Friendly Protocol for 2,3-Difunctionlization of Indole Derivatives	Wenwu Sun*, Na Chen, Tingting Wei, Guojing You, Hao Yang（本科生）, Jikai Liu*, Bin Wu*	*Journal Of Organic Chemistry*	2020, 85(15): 10143-10151	Q1	4.198
30	Rapid detection of five pesticide residues using complexes of gold nanoparticle and porphyrin combined with ultraviolet visible spectrum	Hengye Chen$^{\#}$, Qiong Shi$^{\#}$, Haiyan Fu*, Ou Hu, Yao Fan, Lu Xu, Lei Zhang, Wei Lan, Donglei Sun（本科生）, Tianming Yang, Yuanbin She*	*Journal of the Science of Food and Agriculture*	2020, 100: 4464-4473	Q1	4.125

31	A novel fluorescence sensing strategy based on nanoparticles combined with spectral splicing and chemometrics for the recognition of Citrus reticulata ‘Chachi’ and its storage year	Wei Lan[#], Shuo Wang[#], Yue Wu（本科生）, Hengye Chen, Jian Yang, Liuna Wei, Hongliang Xie（本科生）, Sijia Li（本科生）, Lanping Guo*, Haiyan Fu*	*Journal of the Science of Food and Agriculture*	2020, 100(11): 4199-4207	Q1	4.125
32	Chemical constituents and their cytotoxicities from mushroom Tricholoma imbricatum	Falei Zhang, Huixiang Yang, Xing Wu, Jiayi Li（本科生）, Shiqin Wang（本科生）, Juan He, Zhenghui Li, Tao Feng*, Jikai Liu*	*Phytochemistry*	2020, 177: 112431	Q1	4.004
33	Acid-promoted synthesis and photophysical properties of substituted acridine derivatives	Zilong Bian, Xinxin Lv（本科生）, Yalan Li, Wenwu Sun*, Jikai Liu*, Bin Wu*	*Organic & Biomolecular Chemistry*	2020, 18: 8141−8146	Q1	3.89
34	Diterpenes with bicyclo[2.2.2]octane moieties from the fungicolous fungus Xylaria longipes HFG1018	Heping Chen, Jing Li, Zhenzhu Zhao, Xinyang Li, Shuilin Liu（本科生）, Qingyuan Wang, Jikai Liu*	*Organic & Biomolecular Chemistry*	2020, 18(13): 2410-2415	Q1	3.89
35	A novel thioctic acid-carbon dots fluorescence sensor for the detection of Hg2+ and thiophanate methyl via S-Hg affinity	Shuo Wang[#], Hengye Chen[#], Hongliang Xie（本科生）, Liuna Wei, Lu Xu, Lei Zhang, Wei Lan, Chunsong Zhou, Yuanbin She, Haiyan Fu*	*Food Chemistry*	2021, 346: 128923	Q1	9.231
36	Rapid and highly sensitive colorimetric biosensor for the detection of glucose and hydrogen peroxide based on nanoporphyrin combined with bromine as a peroxidase-like catalyst	Hengye Chen[#], Qiong Shi[#], Gaoqiong Deng, Xiahe Chen, Yunfang Yang, Wei Lan, Ying Hu, Lei Zhang, Lu Xu, Chunyuan Li（本科生）, Chunsong Zhou, Yuanbin She, Haiyan Fu*	*Sensors and Actuators B: Chemical*	2021, 343: 130104	Q1	9.221

37	Rapid and low-temperature synthesis of N, P co-doped yellow emitting carbon dots and their applications as antibacterial agent and detection probe to Sudan Red I	Dan Zhao*, Zhixia Zhang （本科生）, Xuemei Liu, Rui Zhang, Xincai Xiao	*Materials science & engineering. C, Materials for biological applications*	2021, 119, 111468	Q1	8.457
38	Five distinct fucan sulfates from sea cucumber Pattalus mollis: Purification, structural characterization and anticoagulant activities.	Yan Ma, Na Gao, Zhichuang Zuo, Shanni Li, Wenqi Zheng, Xiang Shi, Qipei Liu (本科生), Ting Ma (本科生), Ronghua Yin*, Xian Li*, Jinhua Zhao*	*International Journal of Biological Macromolecules*	2021, 186: 535–543	Q1	8.025
39	An Integrated Approach to Determine the Boundaries of the Azaphilone Pigment Biosynthetic Gene Cluster of Monascus ruber M7 Grown on Potato Dextrose Agar	Qingpei Liu, Siyu Zhong（本科生）, Xinrui Wang（本科生）, Shuaibiao Gao（本科生）, Xiaolong Yang*, Fusheng Chen*, István Molnár*	*Frontiers in microbiology*	2021, 12: 680629	Q1	6.064
40	Structural characterization and heparanase inhibitory activity of fucosylated glycosaminoglycan from Holothuria floridana	Xiang Shi, Ruowei Guan, Lutian Zhou, Zhichuang Zuo, Xuelin Tao, Pin Wang, Yanrong Zhou（本科生）, Ronghua Yin, Longyan Zhao*, Na Gao*, Jinhua Zhao	*Marine Drugs*	2021,19: 162	Q1	6.085
41	A double-layer hydrogel based on alginate-carboxymethyl cellulose and synthetic polymer as sustained drug delivery system	Yan Hu*, Sheng Hu, Shangwen Zhang, Siyi Dong（本科生）, Jie Hu, Li Kang*, Xinzhou Yang	*Scientific Reports*	2021, 11: 9142	Q1	4.996
42	$Ti_3C_2T_X$ MXene Liquid Crystal: Access to Create Background-Free and Easy-Made Alignment Medium	You Zhao, Qinghua Yu, Weiwei Cheng, Jiaqian Li（本科生）, Aiqing Zhang, Xinxiang Lei*, Yingkui Yang, Siyong Qin*	*ACS nano*	2022, 16(4): 5454-5462	Q1	18.027

43	Re-understanding of structure and anticoagulation: Fucosylated chondroitin sulfate from sea cucumber Ludwigothurea grisea	Ronghua Yin, Ying Pan, Ying Cai, Fan Yang（本科生）, Na Gao, Dilihumaer Ruzemaimaiti, Jinhua Zhao*	*Carbohydrate Polymers*	2022, 294: 119826	Q1	10.723
44	Construction of high internal phase Pickering emulsions stabilized by bamboo fungus protein gels with the effect of pH.	Minghao Zhang , Li Zhou*, Fu Yang, Jiaxu Yao（本科生）, Yue Ma, Jikai Liu*	*Food chemistry*	2022 369, 130954	Q1	9.231
45	Digital image colorimetry in combination with chemometrics for the detection of carbaryl based on the peroxidase-like activity of nanoporphyrins and the etching process of gold nanoparticles.	Gaoqiong Deng$^{\#}$, Shuo Wang$^{\#}$, Hengye Chen, Lixue Ren, Ke Liang（本科生）, Liuna Wei, Wanjun Long, Jian Yang, Lanping Guo*, Xiaole Han, Yuanbin She, Haiyan Fu*	*Food Chemistry*	2022;394: 133495.	Q1	9.231
46	Visual classification for sesame oil adulteration detection and quantification of compounds used as adulterants using flavor compounds targeted array sensor in combination with DD-SIMCA and PLS.	Rui Liu, Hengye Chen, Xiuyun Bai, Yun Huang（本科生）, Huiling Li, Wanjun Long, Wei Lan, Yuanbin She, Haiyan Fu*	*Sensors and Actuators: B. Chemical*	2022, 357: 131335	Q1	9.221
47	Synthesis of Nucleoside and Nucleotide Analogues by Cyclization of the Guanine Base with 1,1,3,3-Tetramethoxypropane	Tingting Deng, Yibing Xie, Wenwu Sun, Jie Huang, Tingting He(本科生), Jikai Liu*, Bin Wu*	*Organic Letters*	2022,24(42):7834-7838	Q1	6.072
48	Preparation of green luminescent silicon quantum dots by synergistic method for VB12 detection and antimicrobial property research application	Dan Zhao *, Huan Liu , Zhixia Zhang(本科生) ,Xincai Xiao, Jun Li	*Colloids and Surfaces B: Biointerfaces*	2022, 220: 112868	Q1	5.999
49	Enhanced healing of oral chemical burn by inhibiting inflammatory factors with an oral administration of ShengFu oil	Xin Yin, Jing Hong(本科生),Binhe Tang*, Min Liu, Yusang Li*	*Frontiers in pharmacology*	2022,13:913098	Q1	5.988

50	Immunosuppressive Isopimarane Diterpenes From Cultures of the Endophytic Fungus Ilyonectria robusta	Ke Ye, Xiao Lv（本科生）, Xian Zhang（本科生）, Pan-Pan Wei, Zheng-Hui Li, Hong-Lian Ai*, Dake Zhao*, Jikai Liu*	*Frontiers In Pharmacology*	2022, 12: 766441	Q1	5.988
51	Colorimetric assay based on peroxidase-like activity of dodecyl trimethylammonium bromide-tetramethyl zinc (4-pyridinyl) porphyrin for detection of organophosphorus pesticides	Gaoqiong Deng[#], Hengye Chen[#], Qiong Shi, Lixue Ren, Ke Liang（本科生）, Wanjun Long, Wei Lan, Xiaole Han*, Yuanbin She, Haiyan Fu*.	*Microchimica Acta*	2022, 189(10): 375.	Q1	5.888
52	Immunosuppressive Sesquiterpenoids from the Edible Mushroom Craterellus odoratus	Quan Dai, Falei Zhang（本科生）, Zhenghui Li, Juan He*, Tao Feng*	*Journal Of Fungi*	2022, 7(12): 1052	Q1	5.724
53	Rapid identification of the geographical origin of Eucommia ulmoides by using excitation-emission matrix fluorescence combined with chemometric methods	Tingkai Liu[#], Wanjun Long[#], Zikang Hu, Yuting Guan, Guanghua Lei, Jieling He（本科生）, Xiaolong Yang, Jian Yang*, Haiyan Fu*.	*Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*	2022, 277: 121243	Q1	4.831
54	Cu(I)-catalyzed cross-coupling rearrangements of terminal alkynes with tropylium tetrafluoroborate: Facile access to barbaralyl substituted allenyl acid esters and 7-alkynyl cycloheptatrienes	Zhe Fan, ShaoFei Ni,JinYu Pang（本科生）, LiTing Guo（本科生）,HaoYang（本科生）, Ke Li（本科生）, Cheng Ma, Jikai Liu*, BinWu*, Jinming Yang*	*Journal of Organic Chemistry*	2022, 87: 3066	Q1	4.198
55	Nutmeg oil alleviates chronic inflammatory pain through inhibition of COX-2 expression and substance P release in vivo.	Weikevin Zhang[#], Shanshan Tao[#], Tingting Li(本科生), Yusang Li, Xiaojun Li, Hebin Tang*, Renhuai Cong, Fangli Ma*, Chujun Wan	*Food&Nutrition Research*	2016, 60: 30849	Q2	4.739

56	Salidroside suppressing LPS-induced myocardial injury by inhibiting ROS-mediated PI3K/Akt/mTOR pathway in vitro and in vivo	Lvyi Chen*, Peng Liu（本科生）, Xin Feng, Chunhua Ma*	*Journal of Cellular and Molecular Medicine*	2017, 21: 3178-3189	Q2	5.295
57	Polysaccharides/mesoporous silica nanoparticles hybrid composite hydrogel beads for sustained drug delivery	Yan Hu*, Xiaoying Dong, Lei Ke（本科生）, Shangwen Zhang, Dan Zhao, Han Cheng, Xincai Xiao	*Journal of Materials Science*	2017, 52: 3095-3109	Q2	4.128
58	Enzyme-assisted extraction optimization, characterization and antioxidant activity of polysaccharides from sea cucumber Phyllophorus proteus	Yujing Qin, Qingxia Yuan, Yuexing Zhang, Jialu Li, Xinjiao Zhu（本科生）, Lingling Zhao（本科生）, Jing Wen, Jikai Liu, Longyan Zhao, Jinhua Zhao*.	*Molecules*	2018, 23: 590-609	Q2	4.927
59	Isolation, Structural Elucidation of Three New Triterpenoids from the Stems and Leaves of Schisandra chinensis (Turcz) Baill	Qiu Feng, Liu Han, Huan Duan, Pian Chen, Shaojuan Lu（本科生）, Guang-Zhong Yang*, Xin-Xiang Lei*	*Molecules*	2018, 23: 1624	Q2	4.927
60	Efficient Enantiodifferentiation of Carboxylic Acids Using BINOL- based Amino Alcohol as a Chiral NMR Solvating Agent	Gaowei Li, Minshan Ma, Guifang Wang（本科生）, Xiaojuan Wang, Xinxiang Lei*	*Frontiers in Chemistry*	2020, 8: 336	Q2	5.545
61	Illudane sesquiterpenoids from edible mushroom Agrocybe salicacola and their bioactivities	Quan Dai, Falei Zhang（本科生）, Jiaoxian Du（本科生）, Zhenghui Li, Tao Feng*, Jikai Liu*	*ACS Omega*	2020, 5：21961-21967	Q2	4.132

62	Formal [2+2+2] Cycloaddition Reaction of 1,3,5-Triazinanes with diethyl acetylene dicarboxylate: Approach to Tetrahydropyrimidines	Ruijie Shi, Limei Gao, Weiji Chen（本科生）, Yangqing Shi（本科生）, Zhixing Cao, Yongsheng Zheng*, Jikai Liu*	*European Journal of Organic Chemistry*	2021,44: 5941-5945	Q2	3.261
63	Pd(II)-catalyzed Carbonylative Cyclization of N-aryl-2-aminopyrimidines with Mo(CO)6 as Carbon Monoxide Source	Tingting Deng, Jie Huang, Guo Lian（本科生）, Wenwu Sun*, Bin Wu*	*Asian Chemical Editorial Society*	2021, 10: 2880-2882	Q2	3.116
64	Chemo- and Site-Selective Fischer Esterification Catalyzed by B(C6F5)$_3$	Yalan Li, Jinyu Pang（本科生）, Jicong Lou, Wenwu Sun*, Jikai Liu*, Bin Wu*	*Asian Journal Of Organic Chemistry*	2021,10(6): 1424-1427	Q2	3.116
65	Mechanisms Underlying the Inhibition of KV1.3 Channel by Scorpion Toxin ImKTX58	Xu Zhang[#], Qianru Zhao[#], Fan Yang , Zhen Lan , Yi Li , Min Xiao（本科生）, Hui Yu（本科生）, Ziyi Li , Yongsheng Zhou（本科生）, Yingliang Wu , Zhijian Cao , Shijin Yin*	*Molecolar Pharmacology*	2022, 102(3):150-160	Q2	4.767
66	Thiazolo[5,4-b]pyridine Alkaloid and Seven ar-BisabolSesquiterpenes Produced by the Endophytic Fungus Penicillium janthinellum	Wenjing Wang, Liangxiu Liao, Zediao Huang（本科生）, Futing Wei（本科生）, Xiaolong Yang*	*ACS Omega*	2022, 10.1021/acsomega.2c04434	Q2	4.132
67	Peptide probes with high affinity to target proteinselection by phage display and characterizationusing biophysical approaches	Xiaoqin Yang, Liwen Bai（本科生）, Yu Chen, Yuexiao Lin, Hua Xiang（本科生）, Tingting Xiang, Shuangxing Zhu, Li Zhou, Kai Li*, Xinxiang Lei *	*New Chemistry Journal*	2022, 46(21) ; 10299-10307	Q2	3.925
68	Water-soluble N-Acetyl-L-cysteine-Capped CdTe quantum dots application for Hg(II) detection	Tianming Yang, Qingyi He（本科生）, Yuying Liu（本科生）, Chaozhen Zhu（本科生）, Dan Zhao*	*Journal of Analytical Methods in Chemistry*	2013, 6, 1-6	Q3	2.594

69	Electroacupuncture Treatment Alleviates Central Poststroke Pain by Inhibiting Brain Neuronal Apoptosis and Aberrant Astrocyte Activation	Guihua Tian, Shanshan Tao（本科生）, Mantang Chen, Yusang Li, Youping Li, Hongcai Shang, Xiaoyi Tang, Jianxin Chen, Hebin Tang*	*Neural Plasticity*	2016, 2016: 1437148	Q3	3.144
70	Accessing substituted pyrrolidines via formal [3+2] cycloaddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes	Zhiyao Chu, Na Li(本科生), Dan Liang(本科生), Zhenghui Li, Yongsheng Zheng*, Jikai Liu*	*Tetrahedron Lett*	2018, 59: 715-718	Q3	2.032
71	Cadinane-type sesquiterpenoids and an indolizine alkaloid from the rice fermentation of the fungus Rigidoporus microporus	Qian Li, Heping Chen, Rong Huang, Huixiang Yang（本科生）, Rui Ma, Yueling Peng, Zhenghui Li, Tao Feng*, Jikai Liu*	*Phytochemistry Letters*	2019, 32: 119-122	Q3	1.873
72	Cytotoxic ergosteroids from the fungus Stereum hirsutum	Zhenzhu Zhao, Kaiyue Han（本科生）, Zhenghui Li, Tao Feng, Heping Chen*, Jikai Liu*	*Phytochemistry Letters*	2019，30：143-149	Q3	1.873
73	Iron-Catalyzed Tandem Radical Addition/Cyclization: Highly Efficient Access to Methylated Quinoline-2,4-diones	Huan Sun, Yue Jiang, Mingkun Lu（本科生）, Yunyun Li, Jikai Liu	*Synlett*	2020, 31(20): 2049-2053	Q3	2.206
74	Bisabolane sesquiterpenes and alpha-pyrone derivative from endophytic fungus Zopfiella sp	Litang Sun, Yao Chen, Huixiang Yang(本科生）, Zhenghui Li, Jikai Liu, Guokai Wang*, Tao Feng*	*Phytochemistry Letters*	2020, 37: 29-32	Q3	1.873

75	Secondary metabolites from cultures of the kiwi-associated fungus Diaporthe phragmitis and their antibacterial activity assessment	Junjie Yu , Huixiang Yang(本科生) , Falei Zhang (本科生), Juan He, Zhenghui Li , Jikai Liu, Tao Feng*	*Phytochemistry Letters*	2021，46：143-148	Q3	1.873
76	New chromone analog and pyrrole alkaloid produced by Penicillium sclerotiorum and their antibacterial activity	Liangxiu Liao, Zediao Huang (本科生), Futing Wei (本科生), Wenjing Wang, Xiaolong Yang	*Journal Of Asian Natural Products Research*	2022, 10.1080/10286020.2022.2084585	Q3	1.61
77	The complete chloroplast genome sequence of a traditional Chinese medicine: Achyranthes bidentata (Amaranthaceae)	Zhenghui Li, Xiaohua Li(本科生), Lizhen Ling, Honglian Ai*, Shudong Zhang*	*Mitochondrial DNA Part B Resources*	2020, 5: 158 159	Q4	0.628
78	Characterization of the complete chloroplast genome of a well-known Chinese medicinal herb, Scrophularia ningpoensis	Honglian Ai, Chunlun Qin(本科生), Ke Ye, Zhenghui Li*	*Mitochondrial DNA Part B Resources*	2020, 5: 484-485	Q4	0.628

本科生以第一作者发表 12 篇中文论文清单

序号	题目	作者	期刊	卷期号
1	近红外光谱指纹图谱的灵芝品种快速鉴别方法	杨吉（本科生）,冼玲（本科生）,钟天圣（本科生）,韦柳娜（本科生）,李仪容（本科生）,付海燕*,杨天鸣	时珍国医国药	2017, 28(6): 1359-1361
2	石见穿多糖对脂多糖和 D-氨基半乳糖胺联合诱导小鼠急性肝衰竭的保护作用	黄旭（本科生），张浪，郝吉，程卓，冯天辉，舒广文*	中国药理学与毒理学杂志	2017, 31(4): 311-317
3	近红外光谱模式识别三聚氰胺掺假牛奶	魏玉娟（本科生），李琳（本科生）,杨笑亚（本科生），黎丹薇（本科生），付海燕*，杨天鸣	中国乳品工业	2016, 44(10): 48-51.
4	恩施建始县土家族、苗族常见药用植物资源调查	谢红亮(本科生),艾洪莲*,李正辉	亚太传统医药	2021, 17(1): 8-12
5	黎族医药的特色与发展现状调查-以昌江黎族自治县为例	吴坤林（本科生）,陈红利,吴宗旻,王晓婷,高叶星,李元,王婷婷,黄先菊,程寒*	亚太传统医药	2018, 14(10): 24-25
6	土家药千足虫草抗胃溃疡作用的实验研究	蒙湘(本科生)，彭小欢，许馨怡，谭艳颖，王丽华，黄先菊，董悦	中国民族民间医药	2022,31（3）： 11-16
7	2-苯基吡啶钴配合物的合成、表征与晶体结构	孙文武*，魏婷婷（本科生），谢艳丽，刘斌，吴滨	中南民族大学学报（自然科学版）	2018, 37(3): 19-22
8	石榴籽油在 D-半乳糖诱导的衰老小鼠体内的抗氧化作用	李薇（本科生）,郝吉,张浪,黄旭（本科生）,邓旭坤,舒广文*	中国油脂	2018, 43(2): 55-64
9	中华本草——地黄	梁馨琳（本科生），陈艳梅*	生命科学	2021, 7: 60-63
10	脊椎动物 GSDM 基因家族的生物信息学分析	焦文浩（本科生），杨晶，雷霄（本科生），舒广文*	基因组学与应用生物学	2021,40（Z2）:2565-2573
11	二氧化硫残留量检测新方法研究进展	陈晓磊（本科生）,邓高琼，王硕，韦柳娜，陈亨业，付海燕，兰薇*	化学试剂	2021, 43(12): 1688-1676
12	药物化学专业《药物评价学》课程教学内容的更新研究	孙文武*，毕雅君（本科生）	广东化工	2021，48（24）：230-231

附：学生一作SCI论文首页

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Synthesis of High-Quality *N*-Acetyl-L-Cysteine-Capped CdTe Quantum Dots by Hydrothermal Route and the Characterization through MALDI-TOF Mass Spectrometry

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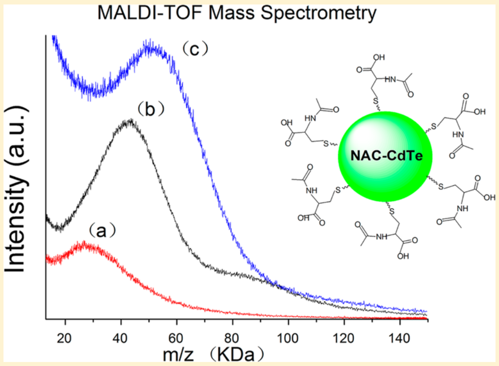
Supporting Information

ABSTRACT: High-quality water-soluble *N*-acetyl-L-cysteine-capped CdTe quantum dots (QDs) have been synthesized through a hydrothermal route, which allows a rapid preparation time (<1 h) and tunable emitting peaks (from 535 to 650 nm) with excellent quantum yields as high as 45%. The influences of different synthetic parameters upon the growth kinetics and the quantum yields of prepared QDs have been systematically studied. The electron diffraction spectroscopy technique was employed to examine the impacts of the molar ratio of reactants and reaction time on the element compositions of prepared QDs. In particular, matrix-assisted laser desorption ionization time-of-flight mass spectrometry has been used for the first time to systematically study the sizes of CdTe QDs.



1. INTRODUCTION

Quantum dots (QDs) have received considerable attention over the last few decades, and their unique optical properties guarantee their potential applications as fluorescent imaging agents and probes.[1−4] Therefore, the synthesis of high-quality QDs with a high quantum yield (QY), tunable emission peak, long luminescence lifetime, and excellent stability has been the focus of research.[5−7] The traditional organometallic route-synthesized QDs require modification before their applications in aqueous systems due to their hydrophobic property, while the modification process would greatly decrease their QY and stability. The aqueous synthesis is an alternative to nonaqueous synthesis, and the as-prepared products have excellent water-solubility, stability, and biological compatibility.[8−12] One of the representative studies of this method is the synthesis of CdTe QDs.[12−15] The functionalized CdTe QDs coupled with proteins,[16] DNA,[2] or selective ligands[17] and unfunctionalized ones have been used as biolabels in cell imaging[3](especially the imaging of specific positions[18]), and as fluorescence probes in immunofluorescence assay,[19] as well as in detections of metal ions,[1] anions,[20] DNA,[2,4] and chiral drugs.[21] Additionally, the aqueous methods have been extended to the synthesis of core/shell QDs (CdTe/CdS,[22] CdTe/CdS/ZnO[15]), alloyed CdETe QDs (E: Zn,[23] Se,[24] Hg[25]), CdTe nanowires,[26] and nanorods.[27] However, hydrophilic thiols (such as thioglycolic acid (TGA) and 3-mercaptopropionic acid (MPA)), the most commonly used stabilizers in aqueous synthesis, are highly toxic and not environmentally friendly to their users.[28,29] Some research groups chose *N*-acetyl-L-cysteine (NAC), a good cell protector against oxidative stress and QD-induced cytotoxicity,[30,31] as the alternative of the traditional stabilizers, and synthesized NAC-capped CdTe QDs through a refluxing route.[32] However, the low QY (ca. 3−10%) and wide emission peak width of prepared QDs caused by the long reaction time of the refluxing route greatly limited their practical applications.[9−13]

The newly developed hydrothermal route is an excellent method for directly synthesizing QDs in aqueous solution.[22,23,33,34] Thanks to the high reaction temperature of this route (>100 °C), the rapid growth rate reduces the surface defects and thus ensures the high-quality of as-prepared QDs. Herein, we present a simple and facile hydrothermal route for a series of high-quality NAC-capped QDs with excellent water solubility, stability, and high QYs (∼45%) and investigate the impacts of various experimental parameters (viz. reaction temperature, pH, and molar ratio of reactants) to find out the optimum reaction conditions. Furthermore, though the optical properties of QDs are greatly influenced by their compositions, the quantitative studies on the compositions of as-prepared QDs synthesized with varied reaction conditions are deficient in the literature. Thus, we used electron diffraction spectroscopy (EDS),[35,36] a good qualitative and semiquantitative analysis method for the composition of nanocrystals, to provide theoretical support for optimizing reaction conditions of QDs.[15,37]

Because of the size-dependent nature of QDs, the size, shape, and size distribution of as-prepared QDs, which are often

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Hypoglycemic Activity and the Potential Mechanism of the Flavonoid Rich Extract from *Sophora tonkinensis* Gagnep. in KK-Ay Mice

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This study investigated the active principles, hypoglycemic activity and potential mechanisms of the flavonoid rich extract from *Sophora tonkinensis* Gagnep. (ST-EtOAc) in KK-Ay diabetic mice. An off-line semipreparative liquid chromatography-nuclear magnetic resonance (LC-NMR) and liquid chromatography-ultraviolet-electrospray ionization mass spectrometry (LC-UV–ESIMS) protocol was performed to determine 13 flavonoids from ST-EtOAc. ST-EtOAc administrated orally to the KK-Ay mice significantly increased their sensibility to insulin, reduced fasting blood-glucose levels and blood lipid indexes such as triglyceride and cholesterol. Moreover, ST-EtOAc exhibited a strong effect of stimulation on glucose transporter 4 (GLUT4) translocation by 2.7-fold in L6 cells. However, the selective AMP-activated protein kinase (AMPK) inhibitor compound C can completely inhibit the activation of the AMPK pathway and prevent the GLUT4 translocation caused by ST-EtOAc. *In vivo*, phosphorylation of the AMPK expression in the liver and skeletal muscle was measured. The results showed phosphorylation of the AMPK had been improved and GLUT4 expression had been also enhanced. In this paper, we conclude that, ST-EtOAc seems to have potential beneficial effects on the treatment of type 2 diabetes mellitus with the probable mechanism of stimulating GLUT4 translocation modulated by the AMPK pathway.

Keywords: hypoglycemic agents, *Sophora tonkinensis* Gagnep., KK-Ay mice, GLUT4, p-AMPK

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INTRODUCTION

Type 2 diabetes mellitus (T2DM), a metabolic disorder of the endocrine system characterized by abnormal glucose and lipid metabolism, is caused by insulin resistance and relative insulin deficiency (Shulman, 2000). Because insulin resistance is the main metabolic abnormality of T2DM, there has been considerable interest in insulin-sensitizing agents for the treatment of this disease (Moller, 2001; Ju et al., 2014). One of the most appealing targets for drug development is the insulin-responsive glucose transporter 4 (GLUT4), which is vital to glucose homeostasis (Bryant et al., 2002). Increasing evidence suggests that enhanced translocation of GLUT4 can improve insulin resistance of T2DM. Therefore, this protein may lead to the discovery of the next generation of anti-diabetic drugs (Zhang et al., 2007; Tsuchiya et al., 2015).

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RESEARCH

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Cloning, expression and identification of KTX-Sp4, a selective Kv1.3 peptidic blocker from *Scorpiops pococki*

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Abstract

Background: Specific and selective peptidic blockers of Kv1.3 channels can serve as a valuable drug lead for treating T cell-mediated autoimmune diseases, and scorpion venom is an important source of kv1.3 channel inhibitors. Through conducting transcriptomic sequencing for the venom gland of *Scorpiops pococki* from Xizang province of China, this research aims to discover a novel functional gene encoding peptidic blocker of Kv1.3, and identify its function.

Results: We screened out a new peptide toxin KTX-Sp4 which had 43 amino acids including six cysteine residues. Electrophysiological experiments indicated that recombinant expression products of KTX-Sp4 blocked both endogenous and exogenous Kv1.3 channel concentration-dependently, and exhibited good selectivity on Kv1.3 over Kv1.1, Kv1.2, respectively. Mutation experiments showed that the Kv1 turret region was responsible for the selectivity of KTX-Sp4 peptide on Kv1.3 over Kv1.1.

Conclusions: This work not only provided a novel lead compound for the development of anti autoimmune disease drugs, but also enriched the molecular basis for the interaction between scorpion toxins and potassium channels, serving as an important theoretical basis for designing high selective Kv1.3 peptide inhibitors.

Keywords: Peptide KTX-Sp4, *Scorpiops pococki*, Kv1.3, Channel turret, Selectivity

Background

About 7% of the population are seriously threatened by nearly 80 kinds of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and type 1 diabetes [1]. As traditional immunosuppressants, steroids [2] and cyclophosphamides [3] have been widely used to treat autoimmune diseases. However, they often cause side effects, such as reducing the patient's normal protective immune response and increasing the risk of infection. Therefore, inhibiting the abnormal autoimmune reaction and maintaining the normal protective immune response is a big challenge in the treatment of autoimmune diseases [4]. More and more researches have demonstrated that the pathogenesis of autoimmune diseases involves activation and proliferation of effector memory T cells (T_{EM} cells) [5]. During the activation of T_{EM} cells, the expression of the Kv1.3 channel was up-regulated significantly, from about 300 molecules to about 1500–2000 molecules per cell [6]. Selective blockage of Kv1.3 channels was experimentally demonstrated to suppress T_{EM} cell proliferation [7]. There is also a growing body of evidence suggesting that Kv1.3 channel blockers have beneficial therapeutic effect on rheumatoid arthritis [8], autoimmune encephalitis [9] and other autoimmune diseases [10]. With the establishment of Kv1.3 channel as an excellent drug target for autoimmune diseases, extensive efforts have been made to develop selective and efficient

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“Turn-off” fluorescent sensor for highly sensitive and specific simultaneous recognition of 29 famous green teas based on quantum dots combined with chemometrics

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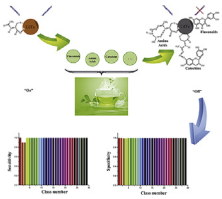
HIGHLIGHTS

- LCNC would bring new challenges to traditional classification methods.
- An excellent fluorescent probe QDs are designed for sensing various green teas.
- The fluorescent data array sensor is firstly developed to tackle LCNC.
- The new detection mode is superior to the conventional fluorescent method for LCNC.

GRAPHICAL ABSTRACT



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ABSTRACT

Fluorescent “turn-off” sensors based on water-soluble quantum dots (QDs) have drawn increasing attention owing to their unique properties such as high fluorescence quantum yields, chemical stability and low toxicity. In this work, a novel method based on the fluorescence “turn-off” model with water-soluble CdTe QDs as the fluorescent probes for differentiation of 29 different famous green teas is established. The fluorescence of the QDs can be quenched in different degrees in light of positions and intensities of the fluorescent peaks for the green teas. Subsequently, with aid of classic partial least square discriminant analysis (PLSDA), all the green teas can be discriminated with high sensitivity, specificity and a satisfactory recognition rate of 100% for training set and 98.3% for prediction set, respectively. Especially, the “turn-off” fluorescence PLSDA model based on second-order derivatives (2nd der) with reduced least complexity ($LVs = 3$) was the most effective one for modeling. Most importantly, we further demonstrated the established “turn-off” fluorescent sensor mode has several significant advantages and appealing properties over the conventional fluorescent method for large-class-number classification (LCNC) of green teas. This work is, to the best of our knowledge, the first report on the rapid and effective identification of so many kinds of famous green teas based on the “turn-off” model of QDs combined with chemometrics, which also implies other potential applications on complex LCNC

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β-ecdysterone from *Cyanotis arachnoidea* exerts hypoglycemic effects through activating IRS-1/Akt/GLUT4 and IRS-1/Akt/GLUT2 signal pathways in KK-Ay mice

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ABSTRACT

Our present study investigated the anti-diabetic activity and potential mechanism of β-ecdysterone (β-EC) derived from *Cyanotis arachnoidea*. *In vitro*, β-EC exhibited a promising effect on increasing GLUT4 translocation by 1.6 folds and glucose uptake by 1.75 folds in L6 cells. *In vivo*, KK-Ay mice's body weight, blood glucose levels and other related blood–lipid indexes can be significantly reduced with β-EC treatment. For the mechanism study, we have found that β-EC exhibited a significant protective effect on insulin resistance (IR) in L6 and HepG2 cells through increasing expressions of IRβ, p-Akt, p-IRS-1 and increasing the expressions of GLUT4 and GLUT2. The phosphorylation of Akt, IRS-1 and the expression of IRβ, GLUT4 and GLUT2 in the liver and skeletal muscle in KK-Ay mice were also significantly ameliorated after 4-weeks treatment with β-EC. According to our present findings, we could conclude that β-EC possessed the potential anti-diabetic effects through activating IRS-1/AKT/GLUT4 and IRS-1/AKT/GLUT2 pathways.

1. Introduction

Hyperglycemia and insulin resistance (IR) are the principal characteristics of type 2 diabetes mellitus (T2DM) (Lowe & Bain, 2013). The incidence of T2DM is increasing at an alarming rate, having become the third largest non-communicable disease in terms of threatening people's lives and health, after cardiovascular disease and tumors (Wild, Roglic, Green, Sicree, & King, 2004). T2DM is mainly due to the absolute or relative shortage of insulin and the decreased sensitivity of target cells to insulin, which is associated with high rates of mortality because of diabetes' severe complications, such as nephropathy, retinopathy, cardiovascular disease, and peripheral vascular disease (Kazeem & Davies, 2016). The major tissues responsive to insulin are those of the liver, skeletal muscle, and adipose tissue (Lin & Sun, 2015). Insulin resistance in these peripheral tissues is indispensable to the evolution of T2DM. These insulin resistances contribute to fasting hyperglycemia and T2DM, and prolonged hyperglycemia can cause IR (Zierath, Krook, & Wallberg-Henriksson, 2000). For all these reasons, it is important to prevent insulin resistance.

A variety of synthetic drugs have been utilized to improve insulin resistance and increase insulin sensitivity. These include thiazolidinediones and metformin. However, these agents produced more or less side effects in clinical settings. These included weight gain, gastrointestinal disturbances, edema, and hypoglycemia (Li, Sui, Li, Xie, & Sun, 2016). There is an urgent need to develop natural remedies that improve insulin resistance without side effects. To date, a number of extracts and natural products derived from edible plants, such as *Momordica charantia*, *Punica granatum*, *Litchi chinensis*, and *Lycium chinensis*, have been proposed as ways to

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Abbreviations: β-EC, β-ecdysterone; ALT, alanine aminotransferase; AMPK, (AMP)-activated protein kinase; DM, diabetes mellitus; FBG, fasting blood glucose; FFA, free fatty acid; GLUT4, insulin-responsive glucose transporter 4; HDL-C, high density lipoprotein cholesterol; HE, hemetoxylin-eosin; IR, insulin resistance; LDL-C, low density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SPF, specific pathogen-free; TC, total cholesterol; TCMs, the Traditional Chinese medicines; TG, triacylglycerols; T2DM, type 2 diabetes mellitus.

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Trichothecrotocins A−C, Antiphytopathogenic Agents from Potato Endophytic Fungus *Trichothecium crotocinigenum*

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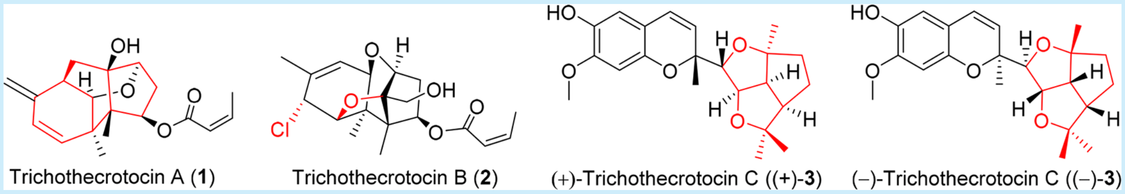
Supporting Information



ABSTRACT: Two trichothecene sesquiterpenoids, trichothecrotocins A (**1**) and B (**2**), and a merosesquiterpenoid racemate, (±)-trichothecrotocin C (**3**), were obtained from potato endophytic fungus *Trichothecium crotocinigenum* by bioguided isolation. Their structures were elucidated by extensive spectroscopic methods, electronic circular dichroism calculations, and single-crystal X-ray diffraction. Compounds **1** and **2** are trichothecenes possessing new ring systems. Compound **3** possesses a novel 6/6−5/5/5 fused ring system. Compounds **1**−**3** showed antiphytopathogenic activities with MIC values of 8−128 μg/mL.

Potato (*Solanum tuberosum*) has become a staple food in many parts of the world and an integral part of the global food supply.[1] As of 2014, potatoes were the fourth largest food crop after corn, wheat, and rice. In 2016, the total world potato production was estimated to be 376 million tons. According to the FAOSTAT database, in 2016, China was the largest producer of potatoes, and almost a quarter of the potatoes grown were harvested in China (99 million tons).[2] In spite of this, several potato diseases caused by plant pathogens, such as *Phytophthora infestans* (late blight), *Alternaria solani* (early blight), *Rhizoctonia solani* (black scurf), and *Fusarium oxysporum* (blast), have caused substantial problems in the production of potatoes.[3,4] Nowadays, common "fighters" against the microorganisms are numerous synthetic fungicides that, besides benefits, have also side effects on host and environment and can cause the development of fungicide resistance in the pathogens.[5−8] Therefore, it is urgent to look for new and effective natural fungicides. Recently we have reported chemically various natural products with different activities from fungi;[9−15] in this Letter, we focused on the secondary metabolites of the potato endophytic fungi and their antifungal activity against the potato pathogens.

In our study, a total of 23 endophytic fungi species were isolated from potato. The preliminary screening experiment showed that the potato endophytic fungi *Trichothecium crotocinigenum* and *Bipolaris eleusines* can inhibit the growth of potato pathogens in potato dextrose agar (PDA) (see the Supporting Information). In addition, the crude extracts of their fermentation broths also exhibited certain inhibitory abilities. Therefore, bioguided isolations of the metabolites of the endophytic fungi were carried out. As a result, the bioactive compounds, namely, trichothecrotocins A−C (**1**−**3**) (Figure 1), were isolated from cultures of the potato endophytic fungus *T. crotocinigenum*. The racemate (±)-**3** was further separated by chiral preparation to (+)-**3** and (−)-**3**, and their absolute configurations were determined by single crystal X-ray diffraction of (−)-**3**. The inhibitory activities of compounds **1**, **2**, (+)-**3**, and (−)-**3** on plant pathogens (*P. infestans, A. solani, R. solani*, and *F. oxysporum*) were evaluated.

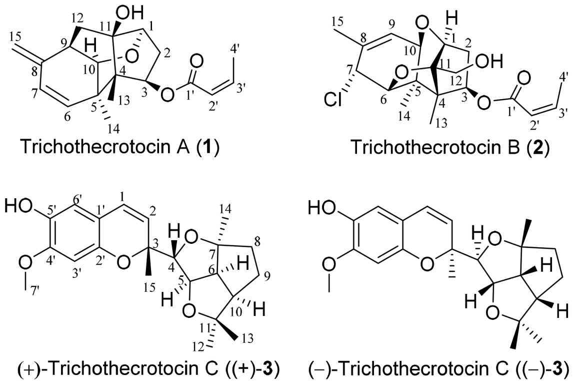

Trichothecrotocin A (**1**)
Trichothecrotocin B (**2**)
(+)-Trichothecrotocin C ((+)-**3**)
(−)-Trichothecrotocin C ((−)-**3**)

Figure 1. Structures of trichothecrotocins A−C (**1**−**3**).

Trichothecrotocin A (**1**) was isolated as a colorless oil. Its molecular formula, $C_{19}H_{24}O_4$, was determined on the basis of its high-resolution ESI mass spectrum (m/z 317.17505 $[M + H]^+$

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Antroalbocin A, an Antibacterial Sesquiterpenoid from Higher Fungus *Antrodiella albocinnamomea*

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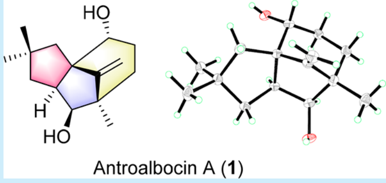
Supporting Information

ABSTRACT: Antroalbocin A (**1**), a sesquiterpenoid possessing a bridged tricyclic system, was isolated from cultures of the higher fungus *Antrodiella albocinnamomea* (Basidiomycota). The structure with the absolute configuration was determined by extensive spectroscopic methods and single-crystal X-ray diffraction. A plausible biosynthetic pathway for **1** was proposed. Compound **1** was found to inhibit *Staphylococcus aureus* with an MIC value of 169 μM.



Antroalbocin A (**1**)

Among the secondary metabolites derived from higher fungi (mushroom), sesquiterpenoids are undoubtedly the most diverse type of compound both in terms of their overall number and the range of structural scaffolds.[1] The biosynthesis of most sesquiterpenoids, derived from higher fungi, subdivision Basidiomycotina, are supposed to start from humulene with three main pathways, which produces diverse backbones including protoilludane, illudane, tremulane, aromadendrane, drimane, hirsutane, sterpurane, lactarane, marasmane, etc.[2] The rich structural variation of sesquiterpenes of higher fungi led to diverse bioactivities as well. For instance, irofulven[3] is a semisynthetic derivative of illudin S, a toxic sesquiterpene isolated from the mushroom *Omphalotus illudens*.[4] It has been extensively investigated in numerous clinical trials and displayed significant activity against ovarian, prostate, and gastrointestinal cancers including hepatocellular tumors.[5−8] Inspired by the diversity of structure and biological activity, our group focused on sesquiterpene metabolites from higher fungi and also reported a number of sesquiterpenoids. Some of them represented divergent types of new carbon skeletons, such as trefolane A, a sesquiterpenoid possessing a novel 5/6/4 system from cultures of the mushroom *Tremella foliacea*,[9] and conosilane A, a sesquiterpene with an unprecedented carbon skeleton from cultures of the mushroom *Conocybe siliginea*.[10]

Antrodiella albocinnamomea, a white-rot fungus belonging to the Basidiomycota, is widely distributed in northeast China.[11] In our previous chemical investigations on the cultures of *A. albocinnamomea* a few sesquiterpenes and steroids were reported.[12−15] Some of them were found to exhibit cytotoxicities and protein tyrosine phosphatase inhibitions.[12−15] Antroalbol H, a sesquiterpenoid from *A. albocinnamomea*, showed promise for the treatment or prevention of diabetes.[16] In the current study, a minor modified fermentation of *A. albocinnamomea* afforded a novel sesquiterpenoid, namely antroalbocin A (**1**) (Figure 1). The structure was elucidated by extensive spectroscopic methods and confirmed by single-crystal X-ray diffraction. Compound **1** had a totally new carbon skeleton which fused in a bridged tricyclic system. Its plausible biosynthetic pathway was proposed. In addition, the bioassay indicated that compound **1** showed certain inhibitory activity against *Staphylococcus aureus*. Herein, we describe the isolation, structural elucidation, biogenetic pathway, and biological evaluation of **1**.

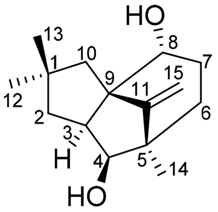


Figure 1. Structure of antroalbocin A (**1**).

Antroalbocin A (**1**) was isolated as colorless crystals. Its molecular formula $C_{15}H_{24}O_2$ was determined on the basis of the positive high-resolution ESI mass spectrum at m/z 237.18498 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$ 237.18491), corresponding to four degrees of unsaturation. The IR spectrum showed absorption bands for hydroxy (3390 cm^{-1}) and olefinic (1653 cm^{-1}) groups. With the aid of DEPT and HSQC spectra, 15 carbons as displayed by the ^{13}C NMR spectrum could be classified into three sp^3 quaternary carbons, three CH (two oxygenated at δ_C 77.2 and 75.7), four CH_2, three CH_3, and two olefinic carbons (Table 1). In consideration of one double bond and four degrees of unsaturation, these data suggested that compound **1** might be a sesquiterpene with a tricyclic ring system. Three sp^3 quaternary carbons at δ_C 40.7, 50.5, and 65.2 suggested that compound **1** might possess a different carbon skeleton with respect to sesquiterpenes found from the same resource.[12−14]

According to the $^1H-^1H$ COSY spectrum, two spin systems were established as $-CH_2(2)-CH(3)-CHOH(4)$ and $-CH_2(6)-CH_2(7)-CHOH(8)-$ as shown in Figure 2. In the HMBC spectrum, the key correlations from H-3 and H-10

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Dauricine upregulates the chemosensitivity of hepatocellular carcinoma cells: Role of repressing glycolysis via miR-199a:HK2/PKM2 modulation

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ABSTRACT

Dauricine (Dau) is a natural alkaloid exhibiting anti-proliferative activity against several different types of malignant cell. However, effects of Dau on hepatocellular carcinoma (HCC) cells and the underlying molecular mechanisms have remained to be fully elucidated. In this study, we found that Dau elevated the sensitivities of HCC cells to chemotherapeutic reagents, including cisplatin, sorafenib, and isoliensinine. Moreover, Dau promoted apoptosis of HCC cells triggered by these chemotherapeutic reagents. Consistently, in a xenograft mouse model, Dau sensitized HCC cells to sorafenib. In HCC cells, Dau dose-dependently inhibited glucose glycolysis and increased oxidative phosphorylation. Mechanistically, Dau downregulated the expression of hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2). HK2 and PKM2 can be directly targeted by miR-199a. Dau dose-dependently increased miR-199a expression in HCC cells. Transfection of anti-miR-199a abrogated Dau-mediated suppression of HK2 and PKM2. Dau-induced metabolic shift was thereby severely crippled by anti-miR-199a. In addition, the incremental activity of Dau on sorafenib sensitivity of HCC cells was diminished in response to the transfection of anti-miR-199a. Taken together, our findings provided novel insights into the impact of Dau on HCC cells and supported considering Dau as an adjuvant reagent in the clinical treatment of HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth-most common malignant worldwide, and the second leading cause of cancer-related mortality (Forner et al., 2012). Chemotherapy is the main strategy for the clinical treatment of middle-late stage HCC. An array of chemicals, such as sorafenib, cisplatin, and 5-fluorouracil, has been conventionally used in the chemotherapy of HCC. However, their prognosis can be severely affected by drug resistance. Therefore, it is imperative to search for novel chemical entities capable of elevating the chemosensitivity of HCC.

In mammalian cells, glycolysis and oxidative phosphorylation (OXPHOS) are two major metabolic pathways producing ATP. In untransformed cells, only approximately 10% of ATP originates from glycolysis, but this ratio is dramatically elevated to about 60% in malignant cells (Vander Heiden et al., 2009). In other words, even in the sufficient supply of oxygen, tumor cells prefer to generate ATP from glycolysis, rather than OXPHOS. Hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2), the major isozymes of hexokinase and pyruvate kinase in tumors catalyzing rate-limiting reactions of glycolysis pathway, have been reported as critical contributors to aerobic glycolysis of malignant cells (Luo and Semenza, 2012; Vander Heiden, 2011). Increased glycolysis and upregulated expression of key enzymes of glycolysis pathway is frequently observed in HCC cells (Nie et al., 2015). This reprogrammed metabolism plays critical roles in drug resistance of HCC cells (Chen et al., 2015; Zhang et al., 2017).

Natural products constitute a group of chemicals with the potential of inhibiting HCC (Fan et al., 2017; Gunasekaran et al., 2017; Roh et al., 2016). Dauricine (Dau) is a natural alkaloid exhibiting anti-proliferative activity against an array of malignant cells (Wang et al., 2012; Yang et al., 2010). However, effect of Dau on HCC cells remains to be fully understood. Here, we reported that Dau is capable of elevating the chemosensitivity of HCC cells. Our further investigations were designed to explore the underlying molecular mechanisms.

2. Materials and methods

2.1. Reagents and antibodies

Dau and isoliensinine (isolie) was purchased from Herbpurify Co., LTD (Chengdu, Sichuan, China). Methyl thiazolyl tetrazolium (MTT) and propidium iodide (PI) were from Beyotime Biotechnology

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Hepatoprotective activity of iridoids, seco-iridoids and analog glycosides from Gentianaceae on HepG2 cells *via* CYP3A4 induction and mitochondrial pathway†

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Gentianaceae herb extracts have been widely used as food additives, teas or medicinal remedies for various diseases and disorders of the human body. Herein, the potential effects of iridoids, seco-iridoids and analog glycosides from gentian on acontine-induced hepatotoxicity were investigated in HepG2 cells to obtain metabolic data of drug-biotarget interactions. Molecular docking analysis was performed to assess the binding efficiencies of 53 iridoids, seco-iridoids and analog compounds obtained from 50 gentian species to the active sites of human CYP3A4 enzyme. The docking scores of 29 iridoids, seco-iridoids and 24 analog glycosides were calculated from the free energy of ligand–protein complexes using a computer-assisted docking simulation. After comprehensive evaluation, 6 of these compounds, *i.e.*, gentiopicroside, sweroside, swertiamarin, loganic acid, 6-*O*-β-D-glucosyl-gentiopicroside and amarogentin were selected to evaluate their hepatoprotective effects. Quantitative real-time PCR was used to measure the expression levels of CYP3A4 mRNA in HepG2 cells. Amarogentin displayed the most clear inductive effect on CYP3A4 mRNA levels in the HepG2 cells. Moreover, amarogentin was further studied for acontine-induced toxicity in the HepG2 cells to determine the potential mechanisms. Amarogentin displayed obvious inductive effect on CYP3A4 mRNA levels in the HepG2 cells. These results elucidated that the hepatoprotective effects were caused by the facilitation of drug metabolism, amelioration of mitochondrial dysfunction and reduction of oxidative stress. Our data demonstrated that the naturally found iridoids, seco-iridoids and analog glycosides in gentian may be responsible for the hepatoprotective effects of gentian-extracted compounds and thus, this study may be useful in the food industry or in clinical practice.

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1 Introduction

Iridoids, seco-iridoids and analog glycosides, mainly including gentiopicroside, sweroside, swertiamarin and loganic acid, are the characteristic compounds found in gentianaceae plants.[1–3] Herbal extracts containing iridoids, seco-iridoids and analogs can exert protective effects in multiple human tissues.[4,5] The consumption of bitter gentian teas is very popular among the nomadic people of Siberia.[6] Gentiopicroside and sweroside have also been reported as specific components in gentian herb teas. These teas have been widely used as a remedy to treat various digestive disorders associated with food consumption.[7] Gentiopicroside and sweroside are first and second on the bitterness index (14 500 and 9500, respectively) in gentian teas.[8] The structure of gentiopicroside and its role as the principal bitter molecule in gentian were proposed in 1961.[9] The gentian root extract, a bitter food additive registered and used in Japan, also contains sweroside and gentiopicroside, with the latter being one of the two major components.[10]

Various studies showed that these kind of plants possess medicinally important natural compounds having antidiabetic,[11,29] anti-inflammatory[12] and liver protection properties.[3,13–16] Our previous study revealed that *Veratrilla baillonii* Franch (*V. baillonii*), a gentian plant found in the Yunnan Province of China, contains large quantities of iri-

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Enantiomeric NMR discrimination of carboxylic acids using actinomycin D as a chiral solvating agent†

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Actinomycin D (Act-D) is a biologically important polypeptide antibiotic clinically used to treat several malignant tumors. Herein, we extended its hitherto-unexplored application as an applicable chiral solvating agent (CSA) for the rapid enantiomeric determination of different chiral carboxylic acids in deuterated chloroform by ^{1}H NMR spectroscopy. Notable enantiodiscrimination with well-splitting α-H or α-CH_3 resonance signals of the enantiomers of carboxylic acids were achieved without significant interference from Act-D. To check its applicability for the determination of enantiomeric excess (ee) values, various mandelic acid (MA) samples were determined and compared with the observed ones, resulting in an excellent linear relationship. To our knowledge, this is the first example of using a natural antibiotic compound as a CSA to achieve chiral recognition for carboxylic acids.

Introduction

Chiral molecular recognition and determination of enantiomeric excess (ee) values are highly important due to the wide applications of chiral compounds in various areas such as asymmetric catalysis, chiral separation, the pharmaceutical industry, biology and materials science.[1] Although multifarious methodologies covering circular dichroism, enantioselective chromatography, and mass spectrometry have been developed for the recognition of chirality,[2] NMR spectroscopy continues to be a powerful and opportune method for the differentiation of enantiomers and the determination of enantiopurity with the aid of chiral solvating agents (CSAs). CSAs could noncovalently interact with racemic analytes to form diastereomeric complexes, resulting in different chemical shifts in the NMR spectrum thus enabling the enantiomer differentiation.[3] They showed more advantages over chiral derivatizing agents and chiral lanthanide shift reagents due to their ease of use, including a less stringent requirement for the optical purity of the chiral molecules, avoidance of derivatization and kinetic resolution issues, and economical availability.[4] Taking the above merits into consideration, CSAs can be better alternatives for enantiodiscrimination.

In the last few years, chiral NMR solvating agents have been developed rapidly.[5] Irrespective of the classical cyclodextrins,[6] calixarenes,[7] crown or aza-crown ethers,[7] quinine and its derivatives,[8] and macrocyclic receptors,[7] a variety of newly reported CSAs including well-known agents or new agents could produce greater enantiomeric discrimination. Water-soluble cationic trialkylammonium-substituted α-, β-, and γ-cyclodextrins[9] and dibenzo-furan-based C_2-symmetric chiral bisureas[10] were synthesized and utilized as CSAs for the differentiation of enantiomeric anionic compounds. Song's group has developed a series of C_2-symmetrical chiral bisthioureas that can be used as highly efficient CSAs for a wide range of chiral compounds.[11] More interestingly, β-cyclodextrin was found to be able to differentiate ibuprofen enantiomers and diastereoisomers of one of its main metabolites in human urine in a direct and rapid way.[12] Structurally new quinine derivatives were reported to be fluorescent sensors for the precise quantitative analysis of ee values of ibuprofen, ketoprofen and naproxen enantiomers.[13] The chiral thiophosphoroamide was applied for the differentiation of diverse chiral acids and large $\Delta\Delta\delta$ values of signals were obtained using ^{1}H NMR, ^{31}P NMR and ^{19}F NMR, separately.[14] Ai and co-workers have recently reported a new family of tetraaza macrocyclic chiral solvating agents (TAMCSAs) that were utilized for chiral recognition of substrates with more than one stereogenic center.[15] A variety of recently achieved chiral macrocyclic receptors, including the macrocyclic amines, amides, and aza-crown macrocycles, have also been reported and summarized.[16] In the previous studies, our group has also developed the chiral salen C_2-symmetric aminophenols,[17] binol-based amine receptors[18] and enantiopure diphenylprolinols,[19] which can be employed for the discrimination of carboxylic acid enantiomers.

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Article

Xanthones from the Bark of *Garcinia xanthochymus* and the Mechanism of Induced Apoptosis in Human Hepatocellular Carcinoma HepG2 Cells via the Mitochondrial Pathway

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Abstract: Xanthones are important chemical constituents of *Garcinia xanthochymus* and varied bioactivities including cytotoxicity. However, their anti-tumor mechanism has remained unknown. Here, we isolated and identified a new xanthone named garciniaxanthone I (**1**) and five known compounds from the bark of *G. xanthochymus*. Their structures were elucidated by NMR analysis and HRESIMS. The anti-proliferation activities of all isolated compounds were evaluated on four human tumor cell lines (HepG2, A549, SGC7901, MCF-7). The results demonstrated that the anti-proliferation activity of xanthone was related to the number and location of prenyl groups. We further found that garciniaxanthone I (GXI) could induce HepG2 apoptosis and enhance the expression of cleaved caspase-8, caspase-9, and caspase-3. GXI could also increase Bax level and concurrently reduce the overexpression of Bcl-2, Bcl-XL, Mcl-1, and surviving in HepG2 cells. Moreover, GXI could inhibit cell migration of HepG2 cells by inhibiting the expressions of MMP-7 and MMP-9. In summary, our study suggests that GXI could induce HepG2 apoptosis via the mitochondrial pathway and might become a lead compound for liver cancer treatment.

Keywords: xanthones; *Garcinia xanthochymus*; apoptosis; HepG2; caspase; Bcl-2 family; MMPs

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1. Introduction

There were 9.6 million cancer deaths in 2018, and liver cancer is one of the top five most common cancers [1]. Molecularly targeted therapy plays an important role in this treatment, and one of the most viable approaches is apoptosis [2]. Apoptosis is a type of programmed cell death. Nature uses it to stabilize the internal environment. However, apoptosis is often inhibited in cancer cells, and apoptosis induction in tumor cells could be an anti-tumor target [3]. Usually, apoptosis relies on a cascade reaction of the caspase family. When signal factors combine with transmembrane death receptors such as CD95, caspase-8/10 levels increase and act as a promoter. In some cases, signals transmit to effector caspase-3/7 via Bcl-2 families and cleaved caspase-9 through the mitochondria. This pathway also finally leads to cell death and is termed the mitochondria pathway [4,5]. Members of the Bcl-2 family are closely related to tumorigenesis, tumor progression, tumor metastasis, drug resistance, and prognosis. Therefore, Bcl-2 inhibitors will become a vital target of oncotherapy [6,7].

The genus *Garcinia* Linn. (Guttiferae) comprises about 450 species mainly distributed in Southeast Asia, South Africa, and West Polynesia. There are 21 species of Guttiferae that grow in Southeast China [8]. Xanthones are a characteristic component of Guttiferae and have anti-tumor, antibiosis,

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Cardiolipin Synthase 1 Ameliorates NASH Through Activating Transcription Factor 3 Transcriptional Inactivation

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BACKGROUND AND AIMS: NASH is an increasingly prevalent disease that is the major cause of liver dysfunction. Previous research has indicated that adipose cardiolipin synthase 1 (CRLS1) levels are associated with insulin sensitivity; however, the precise roles of CRLS1 and underlying mechanisms involving CRLS1 in the pathological process of NASH have not been elucidated.

APPROACH AND RESULTS: Here, we discovered that CRLS1 was significantly down-regulated in genetically obese and diet-induced mice models. *In vitro* studies demonstrated that overexpression of CRLS1 markedly attenuated hepatic steatosis and inflammation in hepatocytes, whereas short hairpin RNA-mediated *CRLS1* knockdown aggravated these abnormalities. Moreover, high-fat diet–induced insulin resistance and hepatic steatosis were significantly exacerbated in hepatocyte-specific *Crls1*-knockout (*Crls1*-HKO) mice. It is worth noting that *Crls1* depletion significantly aggravated high-fat and high-cholesterol diet-induced inflammatory response and fibrosis during NASH development. RNA-sequencing analysis systematically demonstrated a prominently aggravated lipid metabolism disorder in which inflammation and fibrosis resulted from *Crls1* deficiency. Mechanically, activating transcription factor 3 (ATF3) was identified as the key differentially expressed gene in *Crls1*-HKO mice through transcriptomic analysis, and our investigation further showed that CRLS1 suppresses ATF3 expression and inhibits its activity in palmitic acid-stimulated hepatocytes, whereas ATF3 partially reverses lipid accumulation and inflammation inhibited by CRLS1 overexpression under metabolic stress.

CONCLUSIONS: In conclusion, CRLS1 ameliorates insulin resistance, hepatic steatosis, inflammation, and fibrosis during the pathological process of NASH by inhibiting the expression and activity of ATF3. (Hepatology 2020;72:1949-1967).

Nonalcoholic fatty liver disease (NAFLD) is the predominant cause of chronic liver disease worldwide and includes simple steatosis, NASH, and liver cirrhosis.(1) NASH usually follows simple hepatic steatosis and is characterized by lipid accumulation, insulin resistance, severe inflammation, and fibrosis in the liver.(2) As an expanding health problem, NASH has been projected to become the primary cause of liver transplantation in the next decade because of its potentially fatal pathology, leading to increased risks of cirrhosis, hepatocellular carcinoma, and liver failure.(3) Although extensive clinical and basic research has been conducted in this field, there are currently no satisfactory effective therapies for NASH.(4,5) Therefore, studying the complicated

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATF3, activating transcription factor 3; BSA, bovine serum albumin; CL, cardiolipin; Crls1-HKO, hepatocyte-specific Crls1-knockout; CRISPR, clustered regularly interspaced short palindromic repeats; CRLS1, cardiolipin synthase 1; DEG, differentially expressed gene; ECM, extracellular matrix; FASN, fatty acid synthase; FBG, fasting blood glucose; GSEA, gene set enrichment analysis; GTT, glucose tolerance test; H&E, hematoxylin and eosin; HEK, human embryonic kidney; HFD, high-fat diet; HFHC, high-fat and high-cholesterol; HKO, hepatocyte-specific knockout; IκBα, inhibitor of NF-κB α; IL-6, interleukin-6; ITT, insulin tolerance test; MCP, monocyte chemoattractant protein; NAFLD, nonalcoholic fatty liver disease; NC, normal chow; NF-κB, nuclear factor kappa B; n.s., not significant; PA, palmitic acid; p-IKKβ, phospho-inhibitor of NF-κB kinase subunit β; PO, palmitic and oleic acid; PPAR, peroxisome proliferator-activated receptor; RNA-seq, RNA-sequencing; ROS, reactive oxygen species; SCD1, stearoyl-coenzyme A desaturase-1; sgRNA, single guide RNA; shRNA, short hairpin RNA; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor alpha; WT, wild type.

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[3 + 2] Cycloaddition of Nitrile Imines with Enamides: An Approach to Functionalized Pyrazolines and Pyrazoles

Liang Tu,[†] Limei Gao,[†] Xiaomeng Wang, Ruijie Shi, Rupei Ma, Junfei Li, Xiaoshuang Lan, Yongsheng Zheng,* and Jikai Liu*

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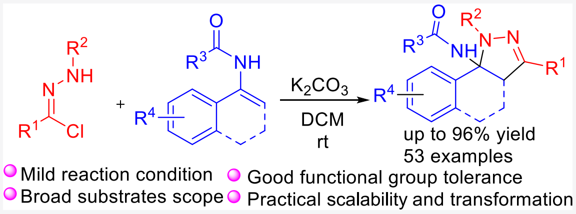
ABSTRACT: An efficient [3 + 2] cycloaddition of in situ generated nitrile imines with enamides has been established. A wide range of functionalized pyrazoline derivatives (53 examples) were obtained in moderate to good yields (up to 96%) under very mild conditions. This protocol features broad substrate scope, good functional group tolerance, and operational simplicity. Practical transformation of the products into useful pyrazoles via a one-pot process and the scalability of this protocol highlight the utility of this synthetic methodology.



INTRODUCTION

Nitrogen-containing heterocyclic compounds represent versatile structural motifs in natural products, pharmaceuticals, and functional materials.[1] In particular, pyrazoline and pyrazole skeletons have received enormous attention as a ubiquitous structural unit in pesticides and pharmaceutical compounds displaying a wide range of biological activities (Figure 1).[2] For instance, compound I showed antitubercular activity.[3] Compound II was reported to be a CB-receptor ligand.[4] Apixaban, which contains a pyrazole core structure, has proved to be a factor Xa inhibitor for the treatment of cardiovascular diseases.[5] Thus, development of efficient and versatile synthetic strategies for the preparation of these moieties has received enormous research interest, and various elegant methods have been reported (Scheme 1). Traditional access to pyrazole and pyrazoline derivatives mainly involves condensation of hydrazines with dicarbonyl compounds or unsaturated carbonyls (Scheme 1a).[6] During the past decade, cycloadditions of two-nitrogen synthons with various partners have been established as the most prominent strategies for the synthesis of pyrazolines. For example, [3 + 2] cycloaddition reactions of Bestmann−Ohira reagent (BOR) and Seyferth−Gilbert reagent (SGR) with olefinic derivatives to access spiro-phosphonylpyrazolines have been developed by Peng and Mohanan (Scheme 1b).[7] In addition, [4 + 1] annulation reactions of in situ formed azoalkenes with C1 synthons were also successfully demonstrated for the construction of pyrazolines by several groups (Scheme 1c).[8] Recently, [3 + 2] cycloadditions of nitrile imines with alkenes represent an attractive strategy to prepare pyrazolines (Scheme 1d).[9] For example, Feng and Stanley developed asymmetric 1,3-dipolar cycloaddition reactions of nitrile imines with 3-alkenyl-oxindoles to afford chiral spiro-pyrazoline-oxindoles, respectively.[10] Guo reported 1,3-dipolar cycloaddition of nitrilimines with allenoates to afford spiro-bidihydropyrazoles.[11] Su described [3 + 2] cycloaddition of nitrile imines with *para*-quinone methides to synthesize spiro-pyrazoline-cyclohexadienones.[12] Despite these elegant strategies, development of a novel method to generate pyrazolines remains highly desirable.

On the other hand, although the cycloadditions of nitrile imines have been well developed in the past decades, the most reported strategies involving cycloaddition of nitrile imines are mainly limited to the electron-deficient olefinic partners[9−13] except for a few examples,[14] which largely limits application of this strategy. Therefore, development of a novel method to construct pyrazolines using nitrile imine with electron-rich C═C derivatives is challenging and highly desirable, which would expand the scope of nitrile imines and access pyrazolines that cannot be obtained by other methods.

Enamides are versatile building blocks in organic synthesis and have been widely employed as substrates in various functionalization reactions[15] and cycloadditions to construct nitrogen-containing compounds.[16] However, to our knowledge, cycloaddition reaction of enamides with nitrile imines has not been reported. We hypothesized that the nucleophilic and electrophilic enamides would be matched with nitrile imines for the preparation of pyrazolines via [3 + 2] cycloaddition. Additionally, biologically important pyrazoles would also be efficiently obtained by subsequent elimination of the acyl group. We herein report the first [3 + 2] cycloaddition reaction

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Discovery of Novel Polycyclic Polyprenylated Acylphloroglucinols from the Fruits of *Garcinia xanthochymus* as Antitumor Agents by Suppressing the STAT3 Signaling

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Abstract: Pharmacologic studies have revealed that polycyclic polyprenylated acylphloroglucinols (PPAPs) collectively exhibit a broad range of biological activities, including antineoplastic potential. Here, six new PPAPs, named garcixanthochymones F–K (**3**, **5**, **7**, **8**, **11,** and **15**), together with nine known analogues were isolated from the fruits of *Garcinia xanthochymus*. Their structures were elucidated based on the spectroscopic data, including UV, HRESIMS, and NMR, and quantum chemical calculations. All the isolated PPAPs were tested for anti-proliferative activity against four human tumor cell lines, including SGC7901, A549, HepG2, and MCF-7. Most of the PPAPs possessed high anti-proliferative activity with IC_{50} values in the range of 0.89 to 36.98 μM, and significant apoptosis was observed in MCF-7 cells exposed to compounds **2** and **5**. Besides, docking results showed that compounds **2** and **5** could strongly combine with the Src homology 2 (SH2) domain of STAT3 via hydrogen bond and hydrophobic interaction, which is one of the key oncogenes and crucial therapeutic targets. Furthermore, compounds **2** and **5** efficiently downregulated the expression of p-STAT3^{Tyr705} and pivotal effector proteins involved in oncogenic signaling pathways of MCF-7 cells.

Keywords: polycyclic polyprenylated acylphloroglucinols; *Garcinia xanthochymus*; anti-proliferative; STAT3; apoptosis

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1. Introduction

Cancer is set to become a major cause of morbidity and mortality in the coming decades in every region of the world. By 2030, the number of cancer cases is projected to increase to 24.6 million, and the number of cancer deaths to 13 million [1]. Due to the inevitable defects of surgery, radiotherapy, and chemotherapy for cancer treatment, insights into the role of molecular targeted therapy have made natural products an attractive tool for cancer therapies which interfere with specific molecules [2].

The signal transducer and activator of transcription (STAT) family of proteins are cytoplasmic proteins with Src homology 2 (SH2) domains that function as transcription factors, responding to cytokines and growth factors [3]. Among the members of the STAT family, STAT3 has received the greatest attention since it is involved in various oncogenic signaling pathways. Once the SH2 domain is phosphorylated upon Tyr705 by Janus-like kinase (JAKs) and c-Src kinase, STAT3 forms homodimers that translocate to the nucleus and trigger the transcription of target genes involved in anti-apoptosis, angiogenesis, and invasion/migration [4,5].

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A characterized saponin extract of *Panax japonicus* suppresses hepatocyte EMT and HSC activation *in vitro* and CCl_4-provoked liver fibrosis in mice: Roles of its modulatory effects on the Akt/GSK3β/Nrf2 cascade

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ABSTRACT

Background and purpose: Liver fibrosis constitutes a pathologic condition resulting in a series of advanced liver diseases. Oleanane-type saponins are distinctive active constituents in the medicinal plant *Panax japonicus* C. A. Mey (*P. japonicus*). Herein, we assessed protective effects of a characterized saponin extract of rhizomes of *P. japonicus* (SEPJ) on hepatocyte EMT and HSC activation *in vitro* and liver fibrosis in mice. We also investigated molecular mechanisms underlying the hepatoprotective activity of SEPJ.

Methods: EMT of AML-12 hepatocytes was evaluated by observing morphology of cells and quantifying EMT marker proteins. Activation of LX-2 HSCs was assessed via scratch assay, transwell assay, and EdU-incorporation assay, and by quantifying activation marker proteins. Liver fibrosis in mice was evaluated by HE, SR, and Masson staining, and by measuring related serum indicators. Immunoblotting and RT-PCR were performed to study mechanisms underlying the action of SEPJ.

Results: SEPJ inhibited TGF-β-induced EMT in AML-12 hepatocytes and activation of LX-2 HSCs. SEPJ elevated Akt phosphorylation at Ser473 and GSK3β phosphorylation at Ser9 in these cells, giving rise to a descent of the catalytic activity of GSK3β. These events increased levels of both total and nuclear Nrf2 protein and upregulated expressions of Nrf2-responsive antioxidative genes. In addition, enhanced phosphorylation of Akt and GSK3β acted upstream of SEPJ-mediated activation of Nrf2. Knockdown of Nrf2 or inhibition of Akt diminished the protective activity of SEPJ against TGF-β in both AML-12 and LX-2 cells. Our further *in vivo* experiments revealed that SEPJ imposed a considerable alleviation on CCl_4-provoked mouse liver fibrosis. Moreover, hepatic Akt/GSK3β/Nrf2 cascade were potentiated by SEPJ. Taken together, our results unveiled that SEPJ exerted protective effects against fibrogenic cytokine TGF-β *in vitro* and ameliorated liver fibrosis in mice. Mechanistically, SEPJ regulated the Akt/GSK3β/Nrf2 signaling which subsequently enhanced intracellular antioxidative capacity.

Conclusions: SEPJ inhibits hepatocyte EMT and HSC activation *in vitro* and alleviates liver fibrosis in mice. Modulation of the Akt/GSK3β/Nrf2 cascade attributes to its hepatoprotective effects. Our findings support a possible application of SEPJ in the control of liver fibrosis.

Introduction

Liver fibrosis, characterized by abnormal depositions of fibrous connective tissue in livers, is a pathologic situation that may result in a series of advanced liver diseases (Bataller and Brenner, 2005; Parola and Pinzani, 2019). In hepatocytes, TGF-β provokes EMT. Augmented

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Abbreviations: Akt, Protein kinase B; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CAT, catalase; CCl_4, Carbon tetrachloride; ELISA, Enzyme linked immunosorbent assay; EMT, Epithelial-to-mesenchymal transition; FACS, Flow cytometry analysis; GCLC, Glutamate-cysteine ligase catalytic subunit; GSH, Glutathione; GSK3β, Glycogen synthase kinase 3β; HA, Hyaluronic acid; HE, Hematoxylin-eosin; HO-1, Heme oxygenase-1; HPLC, High performance liquid chromatography; HSCs, Hepatic stellate cells; HyP, Hydroxyproline; MDA, Malonaldehyde (MDA); NQO1, NAD(P)H: Quinone oxidoreductase 1; Nrf2, Nuclear factor erythroid 2-related factor 2; *P. japonicus*, *Panax japonicus* C. A. Mey; P-Akt, Phosphorylated Akt at Ser473; P-GSK3β, phosphorylated GSK3β at Ser9; PC III, type III procollagen; ROS, Production of reactive oxygen species; SiRNA, Small interference RNA; SR, Sirius red; TGF-β, Transforming growth factor-β1; UPLC/HRMS, Ultra performance liquid chromatography-tandem mass spectrometry.

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Methylgerambullin derived from plant *Glyccsmis pentaphylla (Retz) correa.* Mediates anti-hepatocellular carcinoma cancer effect by activating mitochondrial and endoplasmic reticulum stress signaling and inhibiting AKT and STAT3 pathways

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common fatal malignant tumors. *Glycosmis pentaphylla* is used by traditional medical practitioners worldwide to treat various diseases. We isolated and identified a chemical component with potential anti-hepatocellular carcinoma (HCC) effects. Methylgerambullin is a sulfur containing amine and has significant antihepatoma activity in vitro and in vivo. Methylgerambullin was significantly cytotoxic to HCC cells and induces apoptosis in HCC cells. In addition, methylgerambullin is able to inhibit the growth of transplanted tumors in nude mice without significant toxicity. Regarding the anti-cancer mechanism of methylgerambullin, treatment with methylgerambullin increased the expression of caspase-3, caspase-9 and Bax in vitro and in vivo and reduce the expression of B-cell lymphoma-2 (Bcl-2). Simultaneously, methylgerambullin can also affect ERS-related proteins, inhibit Protein Kinase B (Akt) activity, cause dephosphorylation of downstream Bad, and inhibit the expression of the Signal Transducer and Activator of Transcription 3 (STAT3) protein to inhibit HCC cells proliferation. Overall, these results suggest that methylgerambullin can inhibit HCC cells proliferation by inducing mitochondrial apoptosis, activating ERS signaling pathways and inhibiting the Akt and STAT3 pathways.

1. Introduction

Among all diseases, cancer is the second leading cause of human death after heart disease and the leading cause of death in developing countries (Siegel et al., 2019). Liver cancer is not only one of the most common cancers worldwide but is also one of the deadliest cancers, with a low survival rate (18%); thus liver cancer is a serious threat to human health (Starley et al., 2010). Among the different putative treatment strategies, chemotherapy is the most reliable option for the treatment of HCC (Anwanwan et al., 2020). At present, more than 60% of anticancer drugs were derived from plants. For thousands of years, natural products have been the main source of medicines and have made great contributions to the maintenance of human health (Banerjee et al., 2017; Singh et al., 2017; Li et al., 2019). For example, Zhenjian Zhuo et al. reported that ailanthone had potent antineoplastic activity against HCC (Zhenjian et al., 2015).

Glycosmis pentaphylla is a plant that belongs to the Rutaceae family. It is often called Vananimbuka in Sanskrit and Paanal in Malayalam. In

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Abbreviations: HCC, hepatocellular carcinoma; BCA, Bicinchoninic acid; DMEM, Dulbecco's modified eagle medium; dUTP, 2′-Deoxyuridine 5′-Triphosphate; ECL, Electrochemiluminescence; FITC, Fluorescein Isothiocyanate; GRP78, Glucose-regulated protein 78; MMP, Matrix metalloprotein; MTT, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; PBS, Phosphate buffer saline; PI, Propidium iodide; PVDF, Polyvinylidene fluoride; SDS-PAGE, Sodium dodecyl sulfate polyacrylamide gel electropheresis; STAT3, Signal transducers and activators of transcription 3; TBST, Western Blot wash and incubation buffer with tween; TUNEL, Terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling assay.

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Carboxymethyl chitosan microspheres loaded hyaluronic acid/gelatin hydrogels for controlled drug delivery and the treatment of inflammatory bowel disease

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Inflammatory bowel disease

ABSTRACT

A major drawback of oral treatment of inflammatory bowel disease (IBD) is the non-specific distribution of drugs during long-term treatment. Despite its effectiveness as an anti-inflammatory drug, curcumin (CUR) is limited by its low bioavailability in IBD treatment. Herein, a pH-sensitive composite hyaluronic acid/gelatin (HA/GE) hydrogel drug delivery system containing carboxymethyl chitosan (CC) microspheres loaded with CUR was fabricated for IBD treatment. The composition and structure of the composite system were optimized and the physicochemical properties were characterized using infrared spectroscopy, X-ray diffraction, swelling, and release behavior studies. In vitro, the formulation exhibited good sustained release property and the drug release rate was 65% for 50 h. In vivo pharmacokinetic experiments indicated that high level of CUR was maintained in the colon tissue for more than 24 h; it also played an anti-inflammatory role by evaluating the histopathological changes through hematoxylin and eosin (H&E), myeloperoxidase (MPO), and immunofluorescent staining. Additionally, the formulation substantially inhibited the level of the main pro-inflammatory cytokines of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) secreted by macrophages, compared to the control group. The pharmacodynamic experiment showed that the formulation group of CUR@gels had the best therapeutic effect on colitis in mice. The composite gel delivery system has potential for the effective delivery of CUR in the treatment of colitis. This study also provides a reference for the design and preparation of a new oral drug delivery system with controlled release behavior.

1. Introduction

Incidences of inflammatory bowel disease (IBD), a gastrointestinal mucosal immune response disorder, are increasing annually, all over the world. Once it occurs, it is difficult to cure, leading to heavy burden on public health care. IBD can be divided into ulcerative colitis (UC) and Crohn's disease, which is characterized by chronic recurrent intestinal ulceration, accompanied by diarrhea and other symptoms [1]. Ulceration can affect the entire gastrointestinal tract and is significantly related to the risk of colorectal cancer [2]. Currently, there is no standard treatment for the disease; therefore, patients with IBD must take drugs for life [3]. Drugs such as mesalazine, antibiotics, immunosuppressants, corticosteroids, and nonsteroidal anti-inflammatory drugs, are associated with adverse reactions such as nausea, headache, and diarrhea [4]. Due to the advantages of patient compliance, convenience, and cost-effectiveness, the oral route is the most popular drug delivery method [5]. However, oral drugs for IBD lesions face various challenges, such as the complex gastrointestinal environment, difficulties of long-distance transportation, and non-specific drug distribution in the gastrointestinal tract [6].

Due to the complexity and diversity of the gastrointestinal environment, in order to design and prepare an optimal oral delivery system to transport colitis drugs, many physiological and pathological factors need to be considered. These factors include gastrointestinal transit time, acid-base balance of the gastrointestinal site, thickness of the mucosa, pathological and structural characteristics of the inflammatory site, microbial number, and metabolic activity. Additionally, the safety, cost-effectiveness, and biocompatibility of the vehicle materials must be ensured. Due to the unfavorable conditions to which traditional oral preparations for the treatment of colitis are subjected [7], a high dosage is usually required, which results in severe toxicity and side effects [8,9]. In addition, new formulations, such as liposomes and particulate systems, are limited by poor stability, drug leakage, and low entrapment efficiency. The hydrogel delivery system is well known for its special physical properties, such as good biocompatibility, controlled degradation, and drug protection function [10]. Due to its porous structure, it is not only a suitable vehicle for the loading and delivery of

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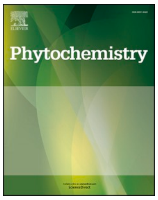

Sesquiterpenes with diverse skeletons from histone deacetylase inhibitor modified cultures of the basidiomycete *Cyathus stercoreus* (Schwein.) De Toni HFG134

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10,11-*Seco*-illudalane
14(11 → 10)*abeo*-illudalane
Antibacterial activity

ABSTRACT

Epigenetic modifiers are proved to be effective specialized products-mining tools by rationally regulating the gene expression of fungal biosynthetic pathways. Chemical investigation on the histone deacetylase inhibitor (HDI) vorinostat (also known as SAHA)-modified cultures of the basidiomycete *Cyathus stercoreus* (Schwein.) De Toni (Nidulariaceae) led to the isolation of nine previously undescribed sesquiterpenes, and four previously described ones. The structures of the nine undescribed compounds were determined by extensive NMR spectroscopic analysis, HRESIMS analysis, as well as ECD and NMR calculations. Notably, the isolated sesquiterpenes are exclusive or overproduced from the epigenetic modified cultures compared to the negative control cultures. Additionally, the skeleton types of the isolated sesquiterpenes include protoilludalane, illudalane, 1,11-*seco*-protoilludalane, 10,11-*seco*-illudalane, and 14(11→10)*abeo*-illudalane. It is noteworthy that the 14(11→10)*abeo*-illudalane skeleton is reported for the first time. Cystercorodiol A, 4-*O*-acetylcybrodol, cystercorotone, and cybrodol showed weak inhibitory activity against the bacterium *Escherichia coli* ATCC25922 with the inhibitory rates 34.7%, 33.0%, 32.3%, and 29.6% at the concentration 200 μM, respectively. This study suggested that epigenetic modifiers are also an effective tool for specialized metabolite-mining in basidiomycetes.

1. Introduction

The basidiomycetes are mainly fruiting body-forming fungi that usually thrive in summer. The seasonally growing mushrooms made them mysterious to the public and have attracted much attention from the natural product research community (Chen and Liu, 2017; Kou et al., 2021; Sofrenić et al., 2021; Tang et al., 2019a; Zhang et al., 2020, 2021). However, the specialized metabolite research on the mushroom is restricted by the culture technology or difficulty in collecting enough amount of fruiting body samples. Most of the mushrooms remain uncultivatable in normal laboratory culture conditions, such as the fungi from the genera *Tricholoma*, *Boletus*, and *Termitomyces* (Chang, 2006). The cumulative efforts in recent years on mushroom natural product research have proved that mushrooms are prolific sources of pigments (Zhou and Liu, 2010), alkaloids (Jiang et al., 2011), terpenoids (Chen and Liu, 2017), and non-proteinogenic amino acids (Zhou et al., 2012).

Our laboratory has long been engaged in the chemistry and biology of molecules originated from mushrooms collected from wild forests or cultured in laboratory conditions (Chen and Liu, 2017). An intriguing phenomenon is that the wild mushroom fruiting bodies produced different types of specialized metabolites compared with its corresponding lab cultivated mycelia. For example, the forest-collected medicinal mushroom *Irpex lacteus* is rich in triterpenoids with various skeletons, while its lab-made liquid cultures are mainly sesquiterpenes (Chen et al., 2020; Tang et al., 2018, 2019a, 2019b; Wang et al., 2020). It is reasonable that in wild conditions, the mushrooms are facing stressful conditions from the air humidity, light intensity, land nutrition, while in routine lab culture conditions, some of the factors are uncontrollable compared to the wild environment. We can differ that the transcription levels of some biosynthetic gene clusters are distinct of these two conditions (Sipos et al., 2017). Therefore, it is attractive to mining the compounds in lab conditions by economic methods before genome mining.

Histone deacetylase (HDAC) is a group of enzymes that remove the

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A novel visual sensing method based on Al@AuNCs for rapid identification of Chrysanthemum morifolium from different origins

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ABSTRACT

As a traditional and authentic Chinese medicinal material, Chrysanthemum morifolium (CM) has an excellent pharmacological effect. However, it is not easy to trace its origin at present, especially through visualization methods. Herein, Au nanoclusters (AuNCs) were successfully synthesized and combined with Al3 + to form Al@AuNCs complexes through the aggregation-induced fluorescence enhancement (AIE) effect, which was used to construct a visual sensor for the rapid identification of CM. Further studies revealed that 3-hydroxylflavonoid derivatives in CM actively competed with AuNCs for Al3 + through an excited-state intramolecular proton transfer (ESIPT) effect during the recognition process and flavonoids could effectively quench the fluorescence of AuNCs. Consequently, CM of different origins could produce fluorescence of various colors from red to green to produce a rapid visual differentiation effect. Finally, using the PLSDA method in chemometrics, it was proven that the accuracy of CM recognition can be increased from 93.10% and 46.15–100%.

1. Introduction

Chrysanthemum is a perennial herb belonging to Compositae and chrysanthemum genus. As one of China's top ten famous flowers, chrysanthemum has been cultivated and used for food and medicine for more than 3000 years [1,2]. According to modern scientific research, chrysanthemum is rich in a variety of flavonoids, organic acids, fatty acids, and polysaccharides with various pharmacologic actions. In traditional Chinese medicine theory, long-term consumption of chrysanthemum products involves scattering cold, expelling wind, clearing away heat and toxin, calming the liver, and brightening eyes causing that chrysanthemum has been widely used as a food supplement, medicine, and herb tea for hundreds of years [3–11]. It's recorded in Chinese Pharmacopoeia (2015) that as a national geographical marker in China, Chrysanthemum morifolium (CM) is one of the "eight flavors of Zhejiang", which is a relatively representative authentic medicinal material produced in Tongxiang, Jiaxing, Zhejiang province. Due to the influence of environmental factors such as soil, water, and climate in Tongxiang, CM is used more medicinally. The content of organic acid and flavonoids is generally higher than other chrysanthemum varieties. Therefore, it is more prominent in curative effect and regarded as the best variety in chrysanthemum, which leads to its considerable economic value. Furthermore, Chinese Pharmacopoeia (2015) have shown that the type and content of organic acids (chlorogenic acid, etc.), 3-hydroxyflavone derivatives (quercetin, kaempferol, etc.), and other flavonoids (acanthine, apigenin, etc.) rich in chrysanthemum are closely related to the origin of chrysanthemum, especially 3-hydroxyflavone derivatives and chlorogenic acid [12,13]. At present, the origin of CM is increasingly extensive, not limited to the authentic production area of Jiaxing City, Zhejiang Province, resulting in different types and proportions of compounds contained in chrysanthemum, which is reflected in the uneven quality and curative effect of CM [14]. However, the appearance, color, and aroma of CM from different origins are incredibly similar, which is the reason why it is difficult for ordinary consumers to directly identify the geographical origin of CM from its physical form. Therefore, it has high practical value and great practical significance to establish a visual sensing method for rapid and accurate identification of the origin of CM.

In recent years, quite a few researchers have identified the origin of

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Integrative Analysis of Metabolome and Transcriptome Identifies Potential Genes Involved in the Flavonoid Biosynthesis in *Entada phaseoloides* Stem

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Entada phaseoloides stem is known for its high medicinal benefits and *ornamental* value. Flavonoids are one of the *main active constituents* in *E. phaseoloides* stem. However, the regulatory mechanism of flavonoids accumulation in *E. phaseoloides* is lacking. Here, phytochemical compounds and transcripts from stems at different developmental stages in *E. phaseoloides* were investigated by metabolome and transcriptome analysis. The metabolite profiling of the oldest stem was obviously different from young and older stem tissues. A total of 198 flavonoids were detected, and flavones, flavonols, anthocyanins, isoflavones, and flavanones were the main subclasses. The metabolome data showed that the content of acacetin was significantly higher in the young stem and older stem than the oldest stem. Rutin and myricitrin showed significantly higher levels in the oldest stem. A total of 143 MYBs and 143 bHLHs were identified and classified in the RNA-seq data. Meanwhile, 34 flavonoid biosynthesis structural genes were identified. Based on the expression pattern of structural genes involved in flavonoid biosynthesis, it indicated that flavonol, anthocyanin, and proanthocyanin biosynthesis were first active during the development of *E. phaseoloides* stem, and the anthocyanin or proanthocyanin biosynthesis branch was dominant; the flavone biosynthesis branch was active at the late developmental stage of the stem. Through the correlation analysis of transcriptome and metabolome data, the potential candidate genes related to regulating flavonoid synthesis and transport were identified. Among them, the MYBs, bHLH, and TTG1 are coregulated biosynthesis of flavonols and structural genes, bHLH and transporter genes are coregulated biosynthesis of anthocyanins. In addition, the WDR gene TTG1-like (AN11) may regulate dihydrochalcones and flavonol biosynthesis in specific combinations with IIIb bHLH and R2R3-MYB proteins. Furthermore, the transport gene protein TRANSPARENT TESTA 12-like gene is positively regulated the accumulation of rutin, and the homolog of ABC transporter B family member gene is positively correlated with the content of flavone acacetin. This study offered candidate genes involved in flavonoid biosynthesis, information of flavonoid composition and

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Cloning and Functional Characterization of the Polyketide Synthases Based on Genome Mining of *Preussia isomera* XL-1326

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Fungal polyketides (PKs) are one of the largest families of structurally diverse bioactive natural products biosynthesized by multidomain megasynthases, in which thioesterase (TE) domains act as nonequivalent decision gates determining both the shape and the yield of the polyketide intermediate. The endophytic fungus *Preussia isomera* XL-1326 was discovered to have an excellent capacity for secreting diverse bioactive PKs, i.e., the hot enantiomers (±)-preuisolactone A with antibacterial activity, the single-spiro minimoidione B with α-glucosidase inhibition activity, and the uncommon heptaketide setosol with antifungal activity, which drive us to illustrate how the unique PKs are biosynthesized. In this study, we first reported the genome sequence information of *P. isomera*. Based on genome mining, we discovered nine transcriptionally active genes encoding polyketide synthases (PKSs), Preu1–Preu9, of which those of Preu3, Preu4, and Preu6 were cloned and functionally characterized due to possessing complete sets of synthetic and release domains. Through heterologous expression in *Saccharomyces cerevisiae*, Preu3 and Preu6 could release high yields of orsellinic acid (OA) derivatives [3-methylorsellinic acid (3-MOA) and lecanoric acid, respectively]. Correspondingly, we found that Preu3 and Preu6 were clustered into OA derivative synthase groups by phylogenetic analysis. Next, with TE domain swapping, we constructed a novel "non-native" PKS, Preu6-TE_{Preu3}, which shared a very low identity with OA synthase, OrsA, from *Aspergillus nidulans* but could produce a large amount of OA. In addition, with the use of Preu6-TE_{Preu3}, we synthesized methyl 3-methylorsellinate (synthetic oak moss of great economic value) from 3-MOA as the substrate, and interestingly, 3-MOA exhibited remarkable antibacterial activities, while methyl 3-methylorsellinate displayed broad-spectrum antifungal activity. Taken together, we identified two novel PKSs to biosynthesize 3-MOA and lecanoric acid, respectively, with information on such kinds of PKSs rarely reported, and constructed one novel "non-native" PKS to largely biosynthesize OA. This work is our first step to explore the biosynthesis of the PKs in *P. isomera*, and it also provides a new platform for high-level environment-friendly production of OA derivatives and the development of new antimicrobial agents.

Keywords: *Preussia isomera*, genome mining, fungal polyketides, polyketide synthase, heterologous expression, orsellinic acid derivatives

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marine drugs

Article

A Fucan Sulfate with Pentasaccharide Repeating Units from the Sea Cucumber *Holothuria floridana* and Its Anticoagulant Activity

Zimo Ning, Pin Wang, Zhichuang Zuo, Xuelin Tao, Li Gao, Chen Xu, Zhiyue Wang, Bin Wu *, Na Gao * and Jinhua Zhao

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Abstract: A fucan sulfate (HfFS) was isolated from the sea cucumber *Holothuria floridana* after proteolysis-alkaline treatment and purified with anion-exchange chromatography. The molecular weight (Mw) of HfFS was determined to be 443.4 kDa, and the sulfate content of HfFS was 30.4%. The structural analysis of the peroxidative depolymerized product (dHfFS-1) showed that the primary structure of HfFS was mainly composed of a distinct pentasaccharide repeating unit $\text{-[L-Fuc}_{2S4S}\text{-}\alpha(1,3)\text{-L-Fuc-}\alpha(1,3)\text{-Fuc-}\alpha(1,3)\text{-L-Fuc}_{2S}\text{-}\alpha(1,3)\text{-L-Fuc}_{2S}\text{-}\alpha(1,3)\text{-]}_n\text{-}$. Then, the "bottom-up" strategy was employed to confirm the structure of HfFS, and a series of fucooligosaccharides (disaccharides, trisaccharides, and tetrasaccharides) were purified from the mild acid-hydrolyzed HfFS. The structures identified through 1D/2D NMR spectra showed that these fucooligosaccharides could be derivates from the pentasaccharide units, while the irregular sulfate substituent also exists in the units. Anticoagulant activity assays of native HfFS and its depolymerized products (dHf-1~dHf-6) in vitro suggested that HfFS exhibits potent APTT-prolonging activity and the potencies decreased with the reduction in molecular weights, and HfFS fragments (dHf-4~dHf-6) with Mw less than 11.5 kDa showed no significant anticoagulant effect. Overall, our study enriched the knowledge about the structural diversity of FSs in different sea cucumber species and their biological activities.

Keywords: sea cucumber; fucan sulfate; pentasaccharide; oligosaccharide; chemical structure; anticoagulant

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1. Introduction

Fucan sulfate (FS) is a kind of sulfated polysaccharide rich in L-fucose, which is mainly found in brown algae and marine invertebrates, including sea cucumbers and sea urchins. FSs have been widely studied and used in food, pharmaceutical, and cosmetic fields for their various biological functions, such as antidiabetic, antiobesity, antiviral [1], anti-inflammatory [2], anticoagulation [3], antitumor, antioxidation [4], and immune regulation activities [5]. These activities are usually highly dependent on physiochemical properties and the structures of FS, such as molecular weight (Mw), sulfate content, sulfated position, structural sequence, and chain conformation at a molecular level [3]. In particular, FSs from sea cucumbers are usually linear polysaccharides mainly consisting of α-L-fucose residues linked by (1,3), (1,4), and (1,2) glycosidic bonds, and the sulfated patterns are usually observed as 2-O-, 3-O-, 4-O-, and 2,4-di-O-sulfates. At present, many FSs from invertebrates consist of defined repeating units (Scheme 1). For example, FSs from *Holothuria fuscopunctata*, *Thelenota ananas*, and *Stichopus horrens* are constructed through a single type of glycosidic linkage, mainly with one type of sulfated α-L-fucose residue [6]. Other FSs are composed of tetrasaccharide repeating units [7], such as FSs from *Acaudina molpadioides* [8], *Holothuria tubulosa* [9], *Isostichopus badionotus* [10], and *Pearsonothuria*

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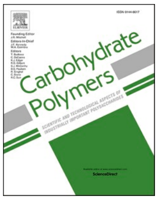

Peroxidative depolymerization of fucosylated glycosaminoglycan: Bond-cleavage pattern and activities of oligosaccharides

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A B S T R A C T

Peroxidative depolymerization is often used to elucidate the structure and structure-activity relationship of fucosylated glycosaminoglycan (FG), while the selectivity of bond cleavage and structural characteristics of the resulting fragments remain to be confirmed. Here, the FG from *Stichopus variegatus* (SvFG) was depolymerized by H_2O_2, and a series of yielded mono- and oligo-saccharides were purified. Almost all the non-reducing ends of oligosaccharides were D-GalNAc$_{4S6S}$, suggesting that GlcA-β1,3-GalNAc$_{4S6S}$ linkage was preferentially cleaved. The model reactions showed the glycosidic bond of uronate was more susceptible than those of *N*-acetyl hexosamine and fucose, which should be due to bond energy of the anomeric C—H. The reducing ends of oligosaccharides include C4–C6 saccharic acid and GalNAc or GalNAcA, which should be derived from the oxidation of the reducing end. A hexasaccharide with tartaric acid exhibited increased anti-iXase activity, suggesting the oxidation of reducing end did not impair the anti-iXase activity of FG-derived oligosaccharides.

1. Introduction

Polysaccharides are complex biomacromolecules and the structure elucidation is of great significance in the study of their biological functions. Chemical depolymerization methods have been established to produce low-molecular-weight products and oligosaccharides from polysaccharides (Amicucci et al., 2020), which are usually employed in structure analysis and structure-activity relationship studies. In particular, as a universal chemical method, peroxidative depolymerization has been widely applied to the structural analysis of complex polysaccharides (Amicucci et al., 2020). However, the peroxidative reaction could not only cleave the glycosidic linkages, but also the C—C bond of free vicinal diol, and the newly formed reducing end residues could be oxidized (Chen et al., 2021; Li, Yuan, et al., 2021; Panagos, Thomson, Bavington, & Uhrín, 2012; Vismara et al., 2010). Thus, the resulting products possess various termini, which would be a limitation for precise structural analysis and oligosaccharide purification by chromatographic methods.

Fucosylated glycosaminoglycan (FG) is a unique highly branched glycosaminoglycan (GAG) from sea cucumbers and possesses a chondroitin sulfate (CS) backbone composed of repeating disaccharide units of *N*-acetyl galactosamine (GalNAc) and glucuronic acid (GlcA) (Mourão et al., 1996; Xu, Zhou, Liu, Chen, & Wang, 2022). Peroxidative depolymerization has been used to produce the low-molecular-weight product from native FG, which could be employed for the structure elucidation of native FG and structure-activity evaluation (Panagos et al., 2014; Wu et al., 2015; Yoshida, Minami, Nemoto, Numata, & Yamanaka, 1992). However, the preference for glycosidic bond cleavage in FG during peroxidative depolymerization and the structural characteristics of the depolymerized products remain unclear. Recently, we studied the structures of a series of oligosaccharides released from HfFG (an FG from *Holothuria fuscopunctata*) by peroxidative depolymerization, and proposed the possible glycosidic bond cleavage mechanism of FG (Chen et al., 2021), suggesting that the β1,3 linkages between GlcA and GalNAc in the backbone of FG were preferentially cleaved. Interestingly, the disaccharides and trisaccharides possessed distinct dicarboxylic acid structures at the reducing end (Chen et al., 2021; Panagos et al., 2014). In addition to the reduction of Mw and oxidation of the reducing end, the depolymerized fragments could maintain the primary structures including the distinctive fucose branches and the sulfated substitution pattern as that in native FG. Nevertheless, the cleavage of glycosidic bond in FG by peroxidative method with different fucosyl

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The preparation of high-quality water-soluble silicon quantum dots and their application in the detection of formaldehyde†

Xiaoling Xu, Shiyao Ma, Xincai Xiao, Yan Hu and Dan Zhao*

This paper reports the synthesis of water-soluble fluorescence silicon quantum dots (Si QDs) through a hydrothermal route with urea propyl triethoxysilane (UPTES) as the source of silicon and sodium citrate as the deoxidizer. The UPTES was for the first time reported as the source of silicon. The preparation process is simple and green, and the prepared Si QDs exhibit high quantum yields, which would be ideal as a low-toxic material in biochemical applications. In addition, the prepared QDs emit excellent and stable fluorescence in a wide range of pH values (2–14), and show strong tolerance to salt and several common organic reagents, overcoming the weak anti-interference ability of traditional QDs and thus ensuring them as satisfactory candidates for biochemical detection. Using the prepared QDs as fluorescence probes, formaldehyde has been successfully detected in aqueous phase and acetonitrile through an electron transfer mechanism. The detection method is simple, sensitive and strongly anti-interfering, providing a new way for detecting formaldehyde in different solvents and expanding the potential applications of water-soluble low-toxic QDs in biochemical detection.

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1. Introduction

The great development of water-soluble quantum dots (QDs) has shown their immense potential in biological imaging,[1,2] drug delivery systems[3] and detection.[4,5] Apparently, their biological safety is still a hot topic.[6] Si QDs have attracted more attention due to their good biocompatibility, environmental-friendliness, inexpensive raw materials and richness in their synthesis methods.

The common methods of preparing Si QDs can be classified into two types: two-step synthesis and one-step synthesis. The two-step synthesis procedures include liquid reduction methods,[7] photochemical etching methods,[8] high temperature pyrolysis methods[9] and plasma synthesis.[10] The universally-used silicon sources in two-step synthesis methods are silica powder, silicon halides, silicon Zintl salt (*i.e.* ASi_x, A = Na, K, Mg *etc.*), or silicon oxides,[11] leading to poor water-solubility of the prepared Si QDs and inferior stability caused by easy oxidation tendency. Therefore, further modification is used to solve these problems,[12,13] which would cause attendant problems like decreased fluorescence intensity of prepared QDs,[14] aggregation of QDs in alkaline conditions[15] and the time consuming synthesis process.[16,17]

On the other hand, the one-step synthesis methods contains microwave method,[19] ultraviolet radiation method[2] and hydrothermal route.[4,5,20–22] Hydrothermal route requires no complicated and plentiful equipment, and is environmental friendly and convenient in operation, making it an appropriate method for Si QDs preparation. However, most of the fluorescence emissions of Si QDs prepared by hydrothermal route are blue, which can be easily interfered by tissue scatter and auto-fluorescence. Some team has already overcome the problem by coupling dye on the surface of Si QDs to make QDs suitable for biological imaging.[18]

The characteristics of the silicon source would greatly affect the synthesis factors of QDs. Recently, silicon sources for hydrothermal route are quite limited and the proposed synthesis process often take too long time (160–180 °C, 16–20 h).[4,5] Filtering proper silicon sources would be significant to the shortening of interaction time, the simplification and efficiency of synthesis process. In addition, it has been proposed that silicon quantum dots synthesised by the silicon source containing two nitrogen atoms (such as *N*-[3-(trimethoxysilyl) propyl]ethylenediamine) possess higher quantum yield[35] when compared with those prepared by APTMS, indicating that the proper nitrogen content of silicon sources will enhance the quality of prepared Si QDs. Therefore, it is necessary to develop a new silicon source containing two nitrogen atoms optimally. In addition, the diversity of silicon sources can also enriches the surface groups of Si QDs and thus extends their applications in the field of detection and analysis.

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Chemical constituents from *Sophora tonkinensis* and their glucose transporter 4 translocation activities

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ABSTRACT

Bioassay-guided phytochemical investigation of the EtOAc fraction (ST-EtOAc) from the roots of *Sophora tonkinensis* resulted in the isolation of a new compound 6a*R*,11a*R*-1-hydroxy-4-isoprenyl-maackiain (**1**), along with 12 known compounds (**2**–**13**). The structure of the new compound was established by 1D and 2D NMR, MS data and circular dichroism analysis. Polyprenylated flavonoids **6**–**9** and **11**–**13** increased GLUT-4 translocation by the range of 1.35–2.75 folds. Sophoranone (**8**) exerted the strongest activity with 2.75 folds GLUT-4 translocation enhancement at the concentration of 10 μM. This is the first report of the GLUT-4 translocation activity of the plant *Sophora tonkinensis*.

Diabetes Mellitus (DM) is a metabolic disorder with symptoms of high blood sugar and many other complications.[1] 90% patients worldwide have type 2 diabetes (T2DM) which is resulted from a loss of glucose homeostasis or insulin resistance.[2] The costs to prevent and treat T2DM and its associated complications have become global health and economic burdens.[3,4] This problem is particularly prevalent in China due to its rapid economic development, improved survival rate from communicable diseases, and the genetic susceptibility.[5]

GLUT-4, one of the 13 sugar transporter proteins, is highly expressed in adipose tissue and skeletal muscle and catalyzes hexose transport across cell membranes.[6] The protein also mediates glucose removal from the circulation and regulates glucose homeostasis.[7,8] Given its role in sugar regulation, GLUT-4 has been used as an important target for anti-diabetic drug discovery.

In this study, a cell-based GLUT-4 translocation system was established using L6 recombinant GLUT-4. Confocal imaging technique was used to quantify the translocation activity. The extracts and fractions from 800 traditional Chinese medicines (TCMs) were screened against GLUT4 translocation.[9–12] One EtOAc fraction (ST-EtOAc) from the roots of *Sophora tonkinensis* exerted a promising stimulatory effect on GLUT-4 translocation. Bioassay-guided phytochemical investigation on the active ST-EtOAc led to the isolation of a new compound, 6a*R*,11a*R*-1-hydroxy-4-isoprenyl-maackiain (**1**), along with 12 known flavonoids.

S. tonkinensis, a traditional medicine used for the treatment of asthma, allergic dermatitis, gastrointestinal hemorrhage, chronic bronchitis, acute pharyngolaryngeal infections and throat inflammation, was collected from Jingxi County, Guangxi Zhuang Autonomous Region, China, in June 2012. A specimen (No. SC0060) of this plant has been deposited in the Herbarium of South-Central University for Nationalities, Wuhan, China. The roots of the plant were triturated and then extracted sequentially by maceration with *n*-hexane, EtOAc, methanol successively. The EtOAc fraction was subjected to repeated flash chromatography on silica gel, MCI gel CHP20P and Sephadex LH-20, followed by C_{18} reverse phase HPLC to afford a new compound, 6a*R*,11a*R*-1-hydroxy-4-isoprenyl-maackiain (**1**, 8 mg), with an isoflavanone conjugate skeleton, as well as 12 known compounds (**2**–**13**) (Fig. 1). The known compounds were identified as trifolirhizin (**2**),[13] trifolirhizin-6″-monoacetate (**3**),[13] maackiain (**4**),[14] medicarpin (**5**),[15] 7,4′-dihydroxy-6,8-diprenylflavanone (**6**),[16] glabrol (**7**),[17] sophoranone (**8**),[18] sophoranochromene (**9**),[18] quercetin (**10**),[19] 6,8-diprenylkaempferol (**11**),[20] 2-(2′,4′-dihydroxyphenyl)-8,8-dimethyl-10-(3-methyl-2-butenyl)-8H-pyrano[2,3-*d*]chroman-4-

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ORIGINAL ARTICLE

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Anti-diabetic activity of stigmasterol from soybean oil by targeting the GLUT4 glucose transporter

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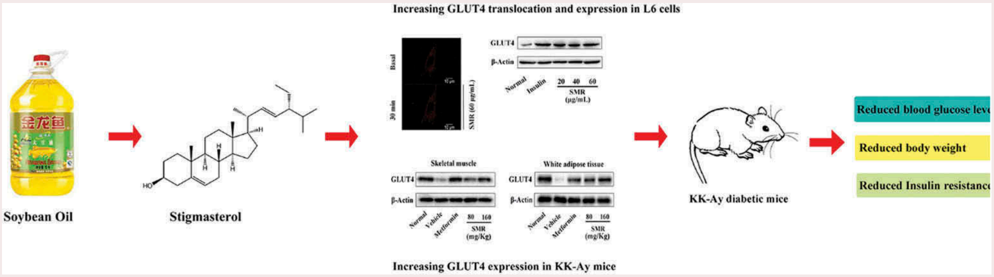
ABSTRACT

The present study investigated the anti-diabetic activity and potential mechanism of stigmasterol (SMR), which is a kind of phytosterols derived from the edible soybean oil *in vitro* and *in vivo*. SMR displayed a mild GLUT4 translocation activity by 1.44-fold in L6 cells. L6 cells were treated with different concentration of SMR, showing significant effects on the enhancing glucose uptake. SMR administrated orally to the KK-Ay mice significantly alleviated their insulin resistance and oral glucose tolerance with reducing fasting blood-glucose levels and blood lipid indexes such as triglyceride and cholesterol. Moreover, the GLUT4 expression in L6 cells, skeletal muscle and white adipose tissue had been also enhanced. In this paper we conclude that, stigmasterol seems to have potential beneficial effects on the treatment of type 2 diabetes mellitus with the probable mechanism of targeting GLUT4 glucose transporter included increasing GLUT4 translocation and expression.



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Introduction

Diabetes mellitus (DM) is one of most common chronic metabolic diseases in almost all countries across the world. It occurs either when the pancreas does not produce enough insulin or when the body cannot effectively utilize the insulin that is produced [1]. Excessive blood glucose, which is often seen as the main characteristic of DM, is sometimes accompanied by lipids and protein metabolism disorder [2]. With the rapid development of society and changes in people's lifestyle, DM has become the third biggest threat to human health after cardiovascular and neoplastic diseases, according to the World Health Organization (WHO) [3]. There are two types of diabetes: type 1 diabetes (insulin-dependent) and type 2 diabetes (non-insulin-dependent). The most common form is type 2 diabetes mellitus (T2DM), which up to 90% of diagnosed DM patients have [4].

T2DM is a progressive disease and its typical clinical manifestations include a gradual decline in glycemic control caused by insulin resistance (IR) and β cell functional deterioration [5]. The primary cause of T2DM is obesity-driven IR in the liver, white adipose tissue (WAT), and skeletal muscle, combined with the relative insufficient secretion of insulin by pancreatic β cells [6]. At present, the available drugs for T2DM fall into four general categories: insulin, insulin

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Fine classification and untargeted detection of multiple adulterants of *Gastrodia elata* BI. (GE) by near-infrared spectroscopy coupled with chemometrics

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Adulterations and geographical origins are two essential quality factors of foods and herbs. In this work, the authentication of a traditional Chinese herb, *Gastrodia elata* BI. (GE), against artificial frauds and fine classification of geographical origins, was performed using near-infrared (NIR) spectroscopy and chemometrics. Class models of representative and authentic GE samples collected from different geographical origins were developed using one-class partial least squares (OCPLS) for untargeted detection of 4 common exogenous adulterants, including taro starch, sweet potato starch, potato starch and *Polygonatum sibiricum* powder. Fine classification of GE samples from 14 geographical origins was performed using a new large-class-number classification strategy, interval-combination one-versus-one partial least squares discriminant analysis (IC-OVO-PLSDA). Different data preprocessing methods were investigated to improve the classification accuracy of models. As a result, OCPLS with second-order derivative (D2) spectra could detect 1.0% (w/w) or higher levels of 4 different adulterants and obtain a sensitivity of 0.9107. For fine classification of geographical origins, a total classification accuracy of 0.9250 was achieved by IC-OVO-PLSDA with standard normal variate (SNV) spectra. The study demonstrates the potential of using NIR combined with chemometrics for the authentication of pure GE against multiple adulterants and fine classification of geographical origins.

Introduction

Gastrodia elata BI. (GE), under the name of "Tian Ma", has been an important and widely used traditional Chinese medicine (TCM) for centuries.[1] GE is also used in other Asian countries, such as Korea and Japan.[2] It is considered to have various medicinal effects, such as anticonvulsant, analgesic and sedative effects,[3,4] and has been prescribed for the treatments of headaches, epilepsy, dizziness, rheumatism, neuralgia, paralysis, hypertension and other neurological and nervous disorders.[5] Intensive chemical and pharmacological research studies have been performed to isolate and identify its bioactive compounds and derivatives, including gastrodin, WSS25 (a sulfation product derived from the polysaccharide WGEW), vanillin, γ-aminobutyric acid (GABA), *p*-hydroxybenzyl alcohol (HBA), and others.[6] Tian Ma has also been widely used as a functional ingredient and supplement in cosmetics, foods, and beverages.[7–9]

According to the Chinese Pharmacopoeia (edition 2010), the quality control of GE is mainly based on the analysis of gastrodin and GE polysaccharides.[5,10] However, for economic reasons, in the domestic market, it is profitable to make fraudulent and adulterated GE preparations, such as powders or extracts, by adding some cheaper materials with similar appearances. Sometimes certain active components of GE are also added. It is hard to detect such frauds by traditional analytical methods focused on analyzing only a few marker compounds. Therefore, untargeted analytical techniques[11] are needed for quality control of GE against a range of known or/and unknown adulterants or frauds. Untargeted analysis can be achieved using chemometric class modeling techniques,[12–14] which can be trained using one-class representative objects (*e.g.*, a pure and authentic herb) based on the measured analytical signals. Because adulterations will cause new variations of analytical signals, the authenticity of a new object could be predicted using the class model by determining whether it should be accepted or rejected by the target class. Class modeling techniques are also called one-class classifiers to

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Non-targeted Detection of Multiple Frauds in Orange Juice Using Double Water-Soluble Fluorescence Quantum Dots and Chemometrics

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Abstract

The feasibility of a highly sensitive "turn-off" fluorescent probe of double quantum dots (QDs) combined with chemometrics was investigated for untargeted screening of extraneous adulterants in pure orange juice (OJ), including sucrose syrup and artificial fruit powder. Pure and adulterated OJ samples were characterized by their different quenching patterns of the two separate and strong fluorescent peaks generated by the double QDs followed by chemometrics analysis. Class models of pure OJ samples ($n = 117$) obtained from pressing newly harvested oranges were developed using one-class partial least squares (OCPLS) based on different signal preprocessing methods, including smoothing, taking second-order derivatives (D2) and standard normal variate (SNV) transformation. As a result, D2-OCPLS model could detect at 5.0% (*w*/*w*) of sucrose syrup and 2.0% (*w*/*w*) of artificial fruit powder in pure OJ with a sensitivity (the rate of true positives) of 97.8% and specificity (rate of true negatives) of 77.0%. In conclusion, the proposed fluorescence probe with double QDs has been demonstrated to have potential for applications in rapid and sensitive screening of adulterants in OJ, which also implies promising applications to untargeted analysis of other water-soluble food samples.

Keywords Orange juice · Double quantum dots · Beverage fraud · One-class partial least squares (OCPLS) · Untargeted detection

Introduction

The fruit juice industry is among the most important agricultural businesses associated with fruit cultivation. Production of fruit juices and extraction of essence concentrates in fruits allows consumption of many perishable and seasonal fruits during all year (Gómez-Ariza et al. 2005). Recently, interest in fruit juices as functional foods is increasing because they are believed to reduce the risks of many chronic and degenerative diseases (Szymczycha-Madeja et al. 2014; Cuny et al. 2008; Sørensen et al. 2007). According to the European Fruit Juice Association (AIJN), the total consumption of fruit juices (including 100% juices and nectars) amounted to 38,473 million liters in 2015 (Kamiloglu 2018). A great variety of fruits including apple, peach, and grape, has been used to produce commercial fruit juices, among which orange juice (OJ) remains the most produced and most widely consumed (Robards and Antolovich 1995; Garcia-Wass et al. 2000; Ammari et al. 2015).

With increasing market demands of fruit juices, economically motivated adulteration has been a common practice and raised severe public concerns. According to a big-data study from 1980 to 2010 (Moore et al. 2012), fruit juices are among the top 5 types of foods that are the most susceptible to adulterations and frauds. The most commonly practiced types of fraud concerning fruit juice are the addition of sugar or water and substitution of the named fruit with a cheaper variety (Garcia-Wass et al. 2000; Abad-García et al.

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Isopimarane diterpenes from the rice fermentation of the fungicolous fungus *Xylaria longipes* HFG1018

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A B S T R A C T

Xylongoic acids A–C, three isopimarane diterpene derivatives were isolated from the rice cultures of *Xylaria longipes* HFG1018, a fungicolous fungus isolated from the fruiting bodies of the wood-decay and medicinal fungus *Fomitopsis betulina*. The structures of the isolated compounds were determined by extensive analysis of NMR and HRESIMS data.

1. Introduction

Fungicolous fungi are a large group of organisms that are associated with other fungi. The science community has a long history understanding of the fungicolous fungi from two centuries ago since the ascomycete *Cladobotryum agaricina* has been found to have mycoparasitic activity with the mushroom *Agaricus* sp. (Sun et al., 2019). However, the definition of fungicolous fungi has long been ambiguous until a comprehensive definition has been given in recent years. The relationships between the fungicolous fungi and the host vary from symbiotic, mycoparasitic, and saprotrophic to neutral (Jeffries, 1995). Most fungicolous species are host-specific, except for some destructive mycoparasites, such as *Arthrobotrys oligospora*, *Clonostachys rosea*, and *Trichoderma viride* (Krauss et al., 2013). The specific roles of fungicolous fungi in guest-host binary biosystem made them intriguing targets for researchers, at least from the secondary metabolite aspect. However, the secondary metabolites of the fungicolous fungi have remained as largely underexplored resources, with only several cases reported (Chen et al., 2020b, c; Han et al., 2017; Zhao et al., 2018).

The fungus *Fomitopsis betulina* (former name *Piptoporus betulinus*) is a wood decaying fungus that grows exclusively on birch trees and is widely distributed in Northern Hemisphere. It is also a folk medicine used as antiparasitic and antimicrobial agents and staunching wound bleeding in Russia, Poland, and other Baltic countries (Grundemann et al., 2020). In a project aiming to explore the secondary metabolites from *F. betulina* as potential drug leads, a fresh fruiting body cube of this fungus was inoculated on the potato-dextrose-agar plate. However, the survival fungus was *Xylaria longipes* instead of *F. betulina* by molecular identification (Chen et al., 2020b,c). Notably, the fungus *X. longipes* is a fruiting body-forming ascomycete also known as “dead moll’s fingers” (Li et al., 2019a,b). The strain we obtained represented the first time which it was found as a fungicolous fungus.

Previous studies on the secondary metabolites on the liquid culture of this strain resulted in the isolation of eighteen 18- or 19-nor-isopimarane diterpenes with significant immunosuppressive activity and devoid of cytotoxicity (Chen et al., 2020c), and two diterpenes with unusual bicyclo [2.2.2]octane moieties (Chen et al., 2020b). As ongoing research to fully explore the secondary metabolome of this fungicolous fungus, the rice culture has been chemically investigated. We herein report the isolation, structural elucidation of three isopimarane diterpenes, including one diterpene glycoside from the rice fermentation of *X. longipes* (Fig. 1).

2. Results and discussion

Compound **1** was isolated as white powder. The molecular formula was determined to be $C_{20}H_{32}O_5$ according to the HRESIMS analysis. The 1D NMR spectra (Table 1) displayed signals which are ascribable to three methyl singlets (δ_H 0.81, 0.94, 1.21), seven methylenes (one is oxygenated), four methines (two are oxygenated), three sp^3 quaternary carbons, a tri-substituted double bond, a carboxylic group at δ_C 178.7. The data are reminiscent of a typical diterpene skeleton which showed similarity to those of hymatoxin L (Chen et al., 2020b), an isopimarane diterpene isolated from the same fungus. Detailed analysis of the 2D NMR spectra of **1** and comparison of the data with those of hymatoxin L allowed to assign the planar structure and relative configuration. The significant HMBC correlations from H_3-20 (δ_H 0.94, s) to C-1 (δ_C 79.7), C-5 (δ_C 52.2), C-9 (δ_C 59.9), C-10 (δ_C 44.1) helped to assign a hydroxy group at C-1 (Fig. 2). The key HMBC correlations from H_3-18 (δ_H 1.21, s) to C-3 (δ_C 36.4), C-4 (δ_C

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Review

Recent Advances about the Applications of Click Reaction in Chemical Proteomics

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Abstract: Despite significant advances in biological and analytical approaches, a comprehensive portrait of the proteome and its dynamic interactions and modifications remains a challenging goal. Chemical proteomics is a growing area of chemical biology that seeks to design small molecule probes to elucidate protein composition, distribution, and relevant physiological and pharmacological functions. Click chemistry focuses on the development of new combinatorial chemical methods for carbon heteroatom bond (C-X-C) synthesis, which have been utilized extensively in the field of chemical proteomics. Click reactions have various advantages including high yield, harmless by-products, and simple reaction conditions, upon which the molecular diversity can be easily and effectively obtained. This paper reviews the application of click chemistry in proteomics from four aspects: (1) activity-based protein profiling, (2) enzyme-inhibitors screening, (3) protein labeling and modifications, and (4) hybrid monolithic column in proteomic analysis.

Keywords: click reaction; chemical proteomics; activity-based protein profiling; hybrid monolithic column

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1. Introduction

Proteomics is a kind of omics which studies the protein composition, distribution and changing rules in cells, tissues or organisms. Essentially, it refers to the macroscale study of protein characteristics, including protein expression level, post-translational modification, small molecule–protein interaction and so on [1]. Research on the proteome cannot only provide the material foundation for the law of the activities of life, but also provides a theoretical foundation and solutions to elucidate and conquer numerous types of mechanisms of illness [2]. Traditional proteomic methods and analytical approaches have not been able to elucidate the complete network of interactions and modifications that proteins may undergo, nor do they evaluate protein activity or functional state in native environments. Therefore, those challenges emerged have sparked shared interests between chemists and biologists. To conquer these, a myriad of chemical proteomics methods have been developed, among which click chemistry can overcome the limitations of the biological proteome methods, identifying the binding targets in cells and tissues.

Click chemistry was first put forward by K B Sharpless in 2001 [3] which provides a quick and reliable synthesis method for different molecules to offer a range of reactivities, orthogonality and utility in various applications. Click chemistry is characterized by good chemical selectivity, favorable solvent compatibility, diverse modularization, minimum synthesis requirements and high yield, upon which it considerably reduces the effect of sensor incorporation on protein activity and reveals the structure and functionality of proteins. Click reactions commonly comprise of copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC), strain-promoted azide-alkyne cycloaddition (SPAAC), and inverse-electron-demand Diels–Alder (IEDDA) reaction and Staudinger ligation (Figure 1) [4]. In

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Formal [2+2+2] Cycloaddition Reaction of 1,3,5-Triazinanes with diethyl acetylene dicarboxylate: Approach to Tetrahydropyrimidines

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An unprecedented [2+2+2] cycloaddition reaction of 1,3,5-triazinanes with diethyl acetylene dicarboxylate is disclosed. This catalyst free reaction provided an efficient and mild approach to synthesize a variety of functionalized tetrahydropyrimidines in moderate to excellent yields (up to 99% yield). Preliminary mechanistic investigation has been conducted to elucidate the reaction process.

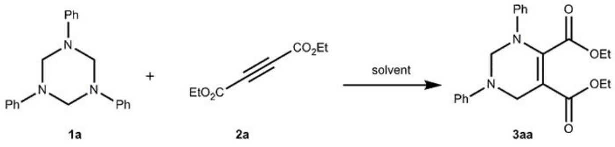
Nitrogen-containing heterocycles are of great interest in synthetic and medicinal chemists because of the diverse biological activities in pharmaceuticals and agrochemicals.[1] Among them, tetrahydropyrimidines, a six membered heterocyle containing two nitrogen atoms, represents an important structural motif, which is widely founded in natural products, functional materials and pharmaceutically active compounds. For example, the manzacidins, A, B, and C, are bioactive constituents isolated from Okinawan sponge, *Hymeniacidon* sp (Figure 1).[2] Polymers with functionalized tetrahedronpyrimidines in the backbone have unique fluorescence.[3] Tetrahydropyrimidin-2-ones were reported to be efficient HIV protease inhibitors.[4] In addition, tetrahydropyrimidines containing an amino acid unit have gained much attention due to their various properties such as muscarinic agonist activity,[5] antiviral[6] and inflammatory activity.[7]

Despite the importance of the tetrahydropyrimidine, limited approaches for the synthesis of tetrahydropyrimidine have been developed. The traditional methods are somewhat limited due to multistep reaction, tedious operation and low yields.[8] In fact, multicomponent cycloaddition reactions of electron-deficient alkynes with various nucleophilic nitrogen resources are one of the most effective and economic approaches for the synthesis of tetrahydropyrimidines. For example, Das reported a multicomponent reaction for the synthesis of tetrahydropyrimidine staring from nitro compounds and alkynes.[9] Jiang developed a one-pot quaternary components reaction to synthesize multisubstituted pyrimidine analogues containing α- and β-amino acid blocks (Scheme 1a).[10] [4+2] Cycloaddition reaction of azetidines with nitriles was also reported to be an efficient access to the tetrahydropyrimidines (Scheme 2a).[11] In addition, Sun[12] and Hashmi[13] reported the [2+2+2] cycloaddition reaction of 1,3,5-triazinanes with allenes and ynamides for the synthesis of tetrahydropyrimidines in the presence of gold species, respectively.

On the other hand, cycloaddition reaction via Huisgen's 1,4-dipoles generated from nucleophilic addition of nitrogen atoms such as imine, pyridine, quinoline and isoquinoline to electron-deficient alkynes has been demonstrated to be successful methods to access nitrogen-containing heterocycles.[14] In this context, on the basis of our interests in the triazinanes chemistry[15] and biologically active nitrogen-containing heterocycles synthesis, [16] we envisioned that nucleophilic 1,3,5-triazinanes should react with electron-deficient alkynes to form Huisgen's 1,4-dipoles, which further finish the cyclization to synthesize highly functionalized tetrahydropyrimidine in the presence of in situ generated *N*-phenylformaldimine. Herein, we wish to report our success in this [2+2+2] cycloaddition reaction for the synthesis of biologically promising tetrahydropyrimidines under transition metal free conditions.

We initiated our investigation with the reaction of 1,3,5-triphenyl-1,3,5-triazinane **1a** and diethyl but-2-ynedioate **2a** in $CHCl_3$ at 30 °C. As shown in Table 1, the reaction was performed smoothly and the corresponding cycloadduct **3aa** was obtained

Table 1. Optimization of reaction conditions.[a,b]



Entry	Solvent	T [°C]	*t* [h]	Yield
1	$CHCl_3$	30	80	85
2	DCE	30	80	34
3	DCM	30	80	37
4	Chlorobenzene	30	75	65
5	MeCN	30	80	80
6	EtOH	30	96	74
7	$CHCl_3$	50	60	88
8[c]	$CHCl_3$	50	72	48

[a] The reactions were performed with **1a** (0.2 mmol), **2a** (0.2 mmol) in solvent (2.0 mL). [b] Isolated yields. [c] 0.14 mmol **1a** was used.

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Research Article

One-Step Synthesis of High-Quality Water-Soluble CdSe Quantum Dots Capped by *N*-Acetyl-L-cysteine *via* Hydrothermal Method and Their Characterization

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Novel water-soluble CdSe quantum dots (QDs) have been prepared with *N*-acetyl-L-cysteine as new stabilizer through a one-step hydrothermal route. The influence of experimental conditions, including reaction time, molar ratio of reactants, and pH value, on the luminescent properties of the obtained CdSe QDs has been systematically investigated. The characterization of as-prepared QDs was carried out through different methods. In particular, we realized qualitative and semiquantitative studies on CdSe QDs through X-ray photoelectron spectroscopy and electron diffraction spectroscopy. The results show that the as-prepared CdSe QDs exhibit a high quantum yield (up to 26.7%), high stability, and monodispersity and might be widely used in biochemical detection and biochemical research.

1. Introduction

Quantum dots (QDs) are nanomaterials usually composed of II–VI or III–V elements [1]. The unique optical properties caused by their small diameters (1–10 nm) lead to their promising applications in biochemistry detections [2], biological labeling [3], cell imaging *in vivo* [4], solar battery [5], and electronic equipment [6].

Among QDs made up of II–VI group elements, CdSe QDs have attracted broad interests due to their fluorescence emission in visible light range [7]. Though selenium and telluride are both VI group elements, the spectra properties of the prepared CdSe QDs are much worse than those of CdTe QDs, because those CdSe QDs with sulphydryl compounds (such as thioglycolate and cysteine) as stabilizers possess low quantum yields (QYs) and wide emission full width at half maximum (FWHM) (>100 nm) [8]. Since synthesis method and the used stabilizer would greatly affect the optical properties of prepared QDs, the studies on the choice of stabilizer during the synthesis process of water-soluble QDs have been widely reported [8], including thiomalic acid, thioglycolate, *N*-(2-mercaptopropionyl)glycine, glutathione, and L-cysteine. The reports on *N*-acetyl-L-cysteine (NAC) as the stabilizer during the synthesis, however, have not been seen in literature. NAC is known as an antioxidant and impurity removal reagent and can be used to protect cells from oxidation and QDs induced cytotoxicity [9, 10]. Additionally, it possesses good water-solubility, is nonvolatile and inodorous, have excellent biocompatibility, and is friendly to the environment and its users. The commonly employed methods for direct synthesis of QDs in aqueous solution are reflux method [11–13] and microwave radiation method [14–16]. These methods, however, have obvious weaknesses: the reflux method requires long reaction time and the prepared QDs have low QYs and wide FWHM, while the microwave radiation method requires complex synthesis equipment, which greatly limits their practical applications. The hydrothermal route [17] is a newly developed hydrothermal route for direct synthesis of water-soluble QDs in an airtight reaction vessel (autoclave) under high pressure and temperature. The high temperature (usually supercritical temperature or close to critical temperature) speeds up the growth of QDs, decreases the surface defects, and thus reduces the probability of fluorescence quenching induced by irradiative decay and improves the fluorescence efficiency of prepared QDs [9]. Compared with core/shell CdSe/CdS QDs

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RESEARCH

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Immunosuppressive effects of a novel potassium channel toxin Ktx-Sp2 from Scorpiops Pocoki

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Abstract

Background: The cDNA Library of venomous animals could provide abundant bioactive peptides coding information and is an important resource for screening bioactive peptides that target and regulate disease-related ion channels. To further explore the potential medicinal usage of the transcriptome database of Scorpiops Pocoki's venom gland, this research identified the function of a new potassium channel toxin Ktx-Sp2, whose gene was screened from the database by sequence alignment.

Results: The mature peptide of Ktx-Sp2 was obtained by genetic engineering. Whole-cell patch-clamp experiment showed that Ktx-Sp2 peptide could effectively block three types of exogenous voltage-gated potassium channels—Kv1.1, Kv1.2 and Kv1.3, among which, the blocking activity for Kv1.3 was relatively high, showing selectivity to some extent. Taking Jurkat T cells as the cell model, this study found that Ktx-Sp2 peptide could also effectively block endogenous Kv1.3, significantly reduce the free calcium concentration in Jurkat T cells, inhibit the activation of Jurkat T cells and reduce the release of inflammatory cytokines IL-2, showing a strong immunosuppressant effect.

Conclusions: This study further proves that the transcriptome database of the Scorpiops Pocoki venom gland is an important resource for discovery of novel bioactive polypeptide coding genes. The newly screened Kv1.3 channel blocker Ktx-Sp2 expanded the range of leading compounds for the treatment of autoimmune diseases and promoted the development and application of scorpion toxin peptides in the field of biomedicine.

Keywords: Scorpiops Pocoki, Kv1.3 channel, Genetic engineering, Immunosuppression, IL-2

Introduction

Scorpion is one of the oldest species on earth. It has a great diversity and distributes widely in major terrestrial ecosystems. According to incomplete statistics, there are about 20 families, 208 genera and 2231 species of scorpion [1]. When hunting, a pair of venom glands in the tail of a scorpion release neurotoxic venom to paralyze or kill its prey. The venom is extremely important for the survival of the scorpion. Scorpion venom has complex components, including protein and non-protein components. The non-protein components mainly contain mucopolysaccharides, lipids, inorganic salts, nucleotides, free amino acids and biological amines. In contrast, the protein part is more abundant, not only including certain amount of phosphatase, hyaluronidase, metalloproteinase and other enzymes, but also bioactive peptides which selectively act on many kinds of ion channels [2]. With the increasing abundance of high-throughput screening technologies, researches on the composition, structure and function of scorpion venom are also

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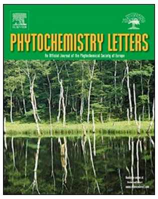

Cytotoxic polyketides from endophytic fungus *Phoma bellidis* harbored in *Ttricyrtis maculate*

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A B S T R A C T

Four new polyketides, namely bellidisins A-D (**1**-**4**), were isolated from rice fermentation extract of endophytic fungus *Phoma bellidis*, along with three known compounds pinolidoxin (**5**), 5,6-epoxypinolidoxin (**6**), and 2-epi-herbarumin II (**7**). Their structures and absolute configurations were determined by 1D and 2D NMR, HRESIMS and ECD calculation. Their cytotoxicity was evaluated against human cancer cell lines HL-60, A549, SMMC-7721, MCF-7, and SW480. Compound **4** showed significant cytotoxicity on these five cell lines with IC_{50} value ranged from 3.40 to 15.25 μM, which is stronger than cisplatin (4.86–27.70 μM).

1. Introduction

Phoma species are known as widely distributed pathogens, endophytes or soil fungi (Rai et al., 2014; Orlandelli et al., 2015). They can produce diverse secondary metabolites including polyketides, cyclic lipodepsipeptides, alkaloids, and fatty acids, with cytotoxic, neuraminidase inhibitory, squalene synthase inhibitory, antimicrobial, phytotoxic, or HIV-1 reverse transcriptase inhibitory activities (Arora et al., 2016; Bi et al., 2016; Graupner et al., 2003; Herath et al., 2009; Ondeyka et al., 2006; Tan et al., 2018; Zhang et al., 2012).

As the continuum of the research on diverse bioactive compounds from endophytic fungi harbored in medicinal plants (Li and Lou, 2018; Wang et al., 2016), *P. bellidis* was isolated from the healthy leave tissue of medicinal plant *Tricyrtis maculata* which is used for the treatment of blood stasis, asthma, and mental stress (Yan et al., 2017). From the ethyl acetate extract of the rice fermentation of *P. bellidis*, one novel decanolide-derivated polyketide (**1**), and three new decanolides (**2**-**4**) were identified by extensive spectroscopic characterization methods, along with three known compounds, namely pinolidoxin (**5**) (Evidente et al., 1993), 5,6-epoxypinolidoxin (**6**) (Evidente et al., 1993), and 2-epi-herbarumin II (**7**) (Cimmino et al., 2012) (Fig. 1). Diverse bioactivities of this type of decanolides were reported previously, including phytotoxic, antibacterial, and antitumoral activities (García-Fortanet et al., 2005; Sun et al., 2012). In order to discover promising anticancer agents, the cytotoxicity of these isolated compounds was evaluated against five human cancer cell lines.

2. Results and discussion

The molecular formula of compound **1** was determined as $C_{19}H_{28}O_7$ by HRESIMS at *m/z* 367.1761 [M-H]- (calcd for $C_{19}H_{27}O_7$, 367.1762), indicating six degrees of unsaturation. The ^1H NMR spectrum of **1** showed the typical signals of a sorbyl group at δ_H 5.82 (1H, d, 15.4, H-14), 7.27 (1H, dd, 15.4, 9.8, H-15), 6.23 (1H, dd, 15.3, 9.8, H-16), 6.20 (1H, dq, 15.3, 5.2, H-17) and 1.89 (3H, dd, 5.2, H-18), one methoxyl group at δ_H 3.49 (3H, s), and one triple methyl peak at δ_H 0.87 (3H, t, 7.3, H-12) (Table 1). The ^{13}C NMR spectrum of **1** associated with HSQC and DEPT experiments indicated one methyl, one methoxyl, four methenes, five methines, one carbonyl, and one aliphatic quaternary carbon, beside the signals of the sorbyl group (Table 2). In ^1H-^1H COSY experiment, three proton spin-spin systems were confirmed, as depicted in Fig. 2. The HMBC experiment showed correlations between H-6/C-7, H-8/C-7, H-2/C-1, H-3/C-1, H-6/C-1, and 1-OH/C-3 (Fig. 2). According to the mentioned information, the planar structure can be determined as showed in Fig. 2. To deduce the relative configuration of **1**, the ROESY experiment was performed with nuclear Overhauser effects (NOE) observed between H-2/1-OH, 1-OH/H-9, H-6/H-8, and H-8/H-10. Furthermore, the coupling constant between H-6 and H-5 is 10.5 Hz, indicating they are both axial bonds. Therefore, the relative configuration was determined as showed in Fig. 1. ECD calculation of **1** was performed on B3PW91-D3/6-31 G(d) level of theory to identify the absolute configuration. The calculated ECD curve of the 1*R*,2*S*,5*R*,6*R*,8*R*,9*R* enantiomer showed similar tendency to the

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Diastereoselective [3 + 3] cycloaddition reaction of 2-arylideneindan-1,3-diones with β-naphthols: Efficient assemble of immunosuppressive pentacyclic chromanes

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ABSTRACT

A base promoted diastereoselective formal [3 + 3] cycloaddition reaction of 2-arylideneindan-1,3-diones with β-naphthols towards the synthesis of functionalized pentacyclic indeno[1,2-*b*]chromen-(4b*H*)-ones has been developed. This methodology is appreciated in terms of diastereoselectivity and mild conditions. In addition, the immunosuppressive assay indicates that one of the products has selective inhibition on *T*-cell proliferation (IC_{50} value of 8.73 μM).

In the past few decades, great progress has been made in the synthesis of biologically active complex molecular structure via cycloaddition reactions. Functionalized chroman complexes represent a privileged structural motif that is found in a broad range of biologically active natural products [1] (e.g., carpanone [2] and (+)-machaeriol [3]) and pharmaceutically active compounds [4], such as (−)-nabilone, which is used as an antiemetic and analgesic agent [5], CB1 full agonist [6] and GPR40 receptor antagonist [7] (Fig. 1). Particularly, the polycyclic chroman cores are recurring structural motifs in natural product comprising (e.g., (-)-siccanin) [1,8]. Owing to the importance of chroman framework, the construction of this privileged skeleton and its analogues has attracted considerable attention, and several elegant strategies have been developed [9]. However, most prepared chroman scaffolds are bicyclic and tricyclic chromans [9,10]. In sharp contrast, the development of efficient methods for construction of functionalized polycyclic chromans has received much less attention and still remained challenging. For selected example, the Wu group described the C(sp3) −H bond functionalization of benzo[*c*]oxepines via C—O bond cleavage/Michael additinon/annulation reaction for the synthesis of multisubstituted chromans [11]. Wang's group achieved the $FeCl_3$-catalyzed cascade reaction of indoles and o-hydroxychalcones for the assembly of indole-bridged polycyclic chromans [12]. The Lin group developed the cascade reaction of azomethine imines and 2-benzalidene-1,3-indanediones to generate the structurally complex polycyclic bridged chroman framework [13]. Schneider reported the Brønsted acid catalyzed intramolecular oxa-Diels-Alder reaction of ortho-quinone methides with dienophiles to construct dihydrochromenochromenes.[14] Recently, a Fe(III)-catalyzed diastereoselective Friedel-Crafts alkylation/ hemiketalization/lactonization cascade has been established for the synthesis of polycyclic bridged 2-chromanol lactones by Kontham [15]. Despite these elegant examples, the development of synthetic method to construct the structurally attractive and biologically important polycyclic chroman framework from readily available starting material is still demanded.

During the past decades, due to the 1C,3O-bisnucleophilic reactivity, β-naphthols have emerged as powerful and versatile building blocks in a variety of [3 + n] cycloaddition reactions with biselectrophilic compounds for the synthesis of various biologically active heterocycles [16]. On the other hand, since the widely application of immunosuppressive agents in organ transplantation and immunity-associated disorders, the past half century has witnessed the fast progress of this research field, especially, the development of selective immunosuppressive drugs [17]. As our continuous research in discovery of novel immunosuppressants

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New cytochalasan alkaloids and cyclobutane dimer from an endophytic fungus *Cytospora chrysosperma* in *Hippophae rhamnoides* and their antimicrobial activities

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ABSTRACT

Three new cytochalasan alkaloids, cytochrysins A-C (**1**–**3**), and a new cyclobutane dimer, cytospodimer A (**4**), along with three known compounds (**5**–**7**), were isolated from the solid culture of *Cytospora chrysosperma*, an endophytic fungus isolated from *Hippophae rhamnoides*. Their structures were determined by a combination of spectroscopy and single-crystal X-ray crystallography. Compound **1** showed significant antibacterial activity against multi-drug resistant *Enterococcus faecium* with an MIC value of 25 μg/mL, and compound **3** against methicillin-resistant *Staphylococcus aureus* with an MIC value of 25 μg/mL.

Endophytic fungi are a group of microorganisms, which live in the internal tissues of plants and form mutualistic symbiotic relationship with host plants [1,2]. Due to the special ecological environment, they have the capability to produce structurally diverse and biologically active secondary metabolites, and have been considered as a promising source for novel natural bioactive compounds with the potential application in medicine, agriculture, and food industry [3–8].

At present, due to the abuse of antibiotics, an increasing number of new clinical drug-resistant bacteria has been created all over the world. Terrifyingly, traditional antibiotics have no effect on these drug-resistant bacteria. Therefore, the investigation of new antibiotics for these bacteria is urgent [9–12]. As part of our program to search for new biologically active secondary metabolites from endophytic fungi, *Cytospora chrysosperma* (HYQZ-931) was isolated from the desert plant *Hippophae rhamnoides*. To the best of our knowledge, the chemical constituents of *C. chrysosperma* have not been reported. In this study, we investigated the chemical constituents of this fungus cultivating in rice medium with malt extract broth (MEB), resulting in the isolation of three new cytochalasan alkaloids, cytochrysins A–C (**1**–**3**), and a new cyclobutane dimer, cytospodimer A (**4**), along with three known compounds (**5**–**7**). Herein, we report the fermentation, isolation, structure elucidation, and antimicrobial activity of these compounds.

Compound **1** was obtained as a colorless crystal. Its molecular formula was determined to be $C_{25}H_{37}NO_4$ based on the positive HRESIMS ion peak at m/z 416.2794 $[M+H]^+$ (calcd for $C_{25}H_{38}NO_4$, 416.2795), which indicated eight degrees of unsaturation. The IR spectrum of **1** showed an absorption band at 3323 cm^{-1} assignable to a hydroxy group and a strong carbonyl absorbance at 1695 cm^{-1}. The ^1H NMR data (Table 1) indicated the presence of five methyls (δ_H 0.92, 0.94, 1.17, 1.19, 1.79), one olefinic proton (δ_H 5.51). Meanwhile, its ^{13}C NMR data (Table 2) in conjunction with DEPT data revealed 25 carbon signals, corresponding to one ketone carbonyl carbon (δ_C 213.4), one amide carbon (δ_C 176.4), two olefinic carbons (δ_C 141.4, 128.7), two quaternary carbons (δ_C 83.0, 66.0), nine methines including one oxygenated carbon

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Synthesis of N-acetyl-L-cysteine-capped ZnCdSe quantum dots *via* hydrothermal method and their characterization

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Abstract

Compared with the most studied green-red emitting (530–650 nm) quantum dots (QDs), the preparation of short-wavelength-emitting QDs remains difficult. Besides, one of the representative short-wavelength QDs materials, ZnCdSe, has a shortcoming of high content of toxic cadmium metal. In this paper, we report the synthesis of high-quality water-soluble ZnCdSe QDs via optimized one-step hydrothermal method with a new thiol as ligand, within a short time of 65 min. The emission wavelength of prepared QDs is tunable in the range of 425–540 nm by merely controlling the molar ratio of Cd:Zn or Se:Zn, and the quantum yield reaches 35%. More importantly, the maximum Cd:Zn molar ratio has been reduced to 0.04:1.0, much lower than that reported in the literature (0.5:1.0), resulting in excellent biological compatibility of prepared QDs and thus their promising applications in biological fields. Moreover, the transmission electron microscopy was employed to examine the effect of Cd:Zn ratio on the size of prepared ZnCdSe QDs, which were also characterized by x-ray photoelectron spectroscopy and electron diffraction spectroscopy.

S Online supplementary data available from stacks.iop.org/STAM/15/055001/mmedia

Keywords: ZnCdSe, QDs, NAC, hydrothermal route

1. Introduction

Quantum dots (QDs) have received considerable attention over the last few decades, because of their distinguished roles in fundamental studies and technical applications [1–6]. Especially, compared with quantum well (active material in ZnSe-based materials lasers) [7], QDs possess many obvious advantages, including higher differential gain, lower threshold current density, and higher temperature stability [8]. Unfortunately, the binary systems do not work well for the synthesis of the QDs with emission in the short wavelength spectral region from 420 to 500 nm, which is of technological interest for the preparation of QDs-based blue light-emitting devices and white-light generation [9]. For example, the CdSe QDs can emit fluorescence in the blue-green spectral range, but the fluorescence in the blue spectral region requires small particle size (smaller than 2 nm) for such a wide band gap [10], which would lead to the instability problem [11]. Even though wider band-gap materials such as CdS and ZnSe can also be used to prepare blue-emitting QDs theoretically, their photoluminescence (PL) properties are also not very stable in practice [12]. Recent advances in synthesis have led to the exploration of ternary QDs [9] through adjusting the constituent stoichiometries of alloyed semiconductors [11].

ZnSe-based materials have been regarded as the most promising candidates of light emitting and laser diodes in the blue-green spectral region [13, 14], and ZnSe-based colloidal ternary alloy QDs, such as ZnCdSe [9–12, 15–18], ZnMnSe [19, 20] and ZnCuSe [21], have been widely investigated.

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Gynura procumbens Reverses Acute and Chronic Ethanol-Induced Liver Steatosis through MAPK/SREBP-1c-Dependent and -Independent Pathways

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ABSTRACT: The present study aimed to evaluate the hepatoprotective effect and mechanism of action of *Gynura procumbens* on acute and chronic ethanol-induced liver injuries. Ethanol extract from *G. procumbens* stems (EEGS) attenuated acute ethanol-induced serum alanine aminotransferase levels and hepatic lipid accumulation. Therefore, EEGS was successively extracted by petroleum, ethyl acetate, and *n*-butyl alcohol. The results showed that the *n*-butyl alcohol extract was the active fraction of EEGS, and hence it was further fractionated on a polyamide glass column. The 60% ethanol-eluted fraction that contained 13.6% chlorogenic acid was the most active fraction, and its effect was further evaluated using a chronic model. Both the *n*-butyl alcohol extract and the 60% ethanol-eluted fraction inhibited chronic ethanol-induced hepatic lipid accumulation by modulating lipid metabolism-related regulators through MAPK/SREBP-1c-dependent and -independent signaling pathways and ameliorated liver steatosis. Our findings suggest that EEGS and one of its active ingredients, chlorogenic acid, may be developed as potential effective agents for ethanol-induced liver injury.

KEYWORDS: *Gynura procumbens, chlorogenic acid, alcoholic liver disease, steatosis, MAPK, SREBP-1c*

■ INTRODUCTION

Alcohol has long been identified as a major risk factor for liver diseases. Sustained excessive drinking of alcohol can lead to the development of alcoholic liver disease (ALD), which refers to a broad range of liver injury, including steatosis, alcoholic hepatitis, fibrosis, and cirrhosis.[1] Globally, approximately 70% of alcohol-related mortalities are directly attributed to hepatic disease,[2] and 4% of human deaths are related to ALD, which seriously affects patients' quality of life and places a huge burden on health care systems.[3,4] The development of ALD is a complex process that involves a multitude of signal pathways, and the mechanism behind ALD is still not well understood. Although multiple attempts have been made to improve patient outcome, we have yet to find a reliable treatment, except for alcohol abstinence.[1] During the past decades, less toxic multi-targeting herbs have attracted considerable attention as potential therapeutic candidates against ALD.[5]

Gynura procumbens (Lour.) Merr., a traditional food and herb, enthusiastically used in Southeast Asia, possesses a wide range of pharmacological properties, such as reducing blood glucose and lipids levels,[6] possessing anti-liver cancer activity,[7] and relieving hepatotoxicity and other ALD-associated symptoms.[8,9] As a new food material recommended by the National Health and Family Planning Commission of China in 2012, *G. procumbens* became a popular vegetable and folk medicine. People in southern and central China like planting *G. procumbens* in their yards. However, until now, very little was known about its active ingredients or pharmacologic mechanisms. In the current study, we performed in vivo experiments to screen the active fraction(s) from *G. procumbens* for protective effects against ethanol-induced liver steatosis and further elucidate its probable mechanisms.

The progression of ethanol-induced liver steatosis, an early stage in the development of ALD, is a multi-factorial and multi-step process that involves multiple metabolic pathways. Acetyl-coenzyme A carboxylase (ACC), which converts acetyl-CoA to malonyl-CoA, is the committed step of the fatty acid synthesis.[10] Fatty acid synthase (FAS) is another key enzyme that catalyzes fatty acid synthesis. The expression of genes required for fatty acid and lipid production, including *ACC* and *Fasn*,[11,12] are positively regulated by a master regulator of lipid homeostasis, sterol regulatory element binding protein 1c (SREBP-1c). Previous studies have proven that SREBP-1c activation in ALD is directly influenced by AMP-activated protein kinase (AMPK)[13] and mitogen-activated protein kinases (MAPKs).[1,14,15] AMPK is a protein kinase that inhibits lipid synthesis through phosphorylation and inactivates key lipogenic genes such as *SREBP-1* and *ACC*.[13] Meanwhile, MAPKs are also the protein kinases that inhibit SREBP-1c through phosphorylation.[15] Because *G. procumbens* affects lipids metabolism and SREBP-1c plays a predominant role in alcohol-induced hepatic steatosis,[16] we focused on the pathways upstream and downstream of SREBP-1c to elucidate the

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Isoliensinine, a Bioactive Alkaloid Derived from Embryos of *Nelumbo nucifera*, Induces Hepatocellular Carcinoma Cell Apoptosis through Suppression of NF-*κ*B Signaling

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Supporting Information

ABSTRACT: Isoliensinine (isolie) is an alkaloid produced by the edible plant *Nelumbo nucifera*. Here, we unveiled that isolie was able to provoke HepG2, Huh-7, and H22 hepatocellular carcinoma (HCC) cell apoptosis. Isolie decreased NF-*κ*B activity and constitutive phosphorylation of NF-*κ*B p65 subunit at Ser536 in HCC cells. Overexpression of p65 Ser536 phosphorylation mimics abrogated isolie-mediated HCC cell apoptosis. Furthermore, intraperitoneal injection of isolie inhibited the growth of Huh-7 xenografts in nude mice. Additionally, isolie given by both intraperitoneal injection and gavage diminished the proliferation of transplanted H22 cells in Kunming mice. Reduced tumor growth in vivo was associated with inhibited p65 phosphorylation at Ser536 and declined NF-*κ*B activity in tumor tissues. Finally, we revealed that isolie was bioavailable in the blood of mice and exhibited no detectable toxic effects on tumor-bearing mice. Our data provided strong evidence for the anti-HCC effect of isolie.

KEYWORDS: *Nelumbo nucifera, isoliensinine, hepatocellular carcinoma, apoptosis, NF-κB*

■ INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies and is the third most frequent cause of cancer-related mortality worldwide.[1] Surgical resection is considered to be the standard strategy for treatment of HCC. However, only a small proportion of HCC patients are eligible for surgical intervention, since HCC is often diagnosed in later stages due to the extended length of time it takes for HCC to begin and develop.[2] Therefore, the majority of HCC patients must rely on systemic chemotherapies. Though compounds such as sorafenib, 5-fluorouracil, and cisplatin are approved for clinical HCC treatment, they only provide limited benefit due to toxic side effects in patients and chemoresistance in HCC cells. Thus, it is imperative to discover and develop new chemotherapy reagents that are capable of inducing HCC cell death but have low or no toxic side effects in patients.

Nuclear factor *κ*B (NF-*κ*B) is a family of widely expressed and structurally related homo- or heterodimeric DNA-binding proteins that control the transcription of NF-*κ*B responsive genes and participate in a multitude of important biological processes.[3] Aberrant activation of NF-*κ*B is involved in the pathogenesis of HCC.[4] The heterodimer p65/p50 is a representative form of NF-*κ*B. Phosphorylation of the p65 subunit of NF-*κ*B is an important mechanism modulating NF-*κ*B activity. For instance, phosphorylation of p65 at Ser536 enhances NF-*κ*B transcriptional potential.[5] In cancer cells of different origins, such as myeloma cells, stomach cancer cells, and embryonic carcinoma cells, reduction of p65 phosphorylation at Ser536 is associated with cancer cell apoptosis induced by potential chemotherapeutic reagents.[6−8] However, the role of p65 dephosphorylation at Ser536 in HCC cell apoptosis remains to be fully elucidated.

In recent years, natural products have garnered a lot of attention from pharmaceutical researchers and clinicians owing to their efficiency, safety, and immediate availability.[9−11] During the past 30 years, more than 70% of the drugs approved by the U.S. Food and Drug Administration originated from natural products.[12] *Nelumbo nucifera* (*N. nucifera*), commonly known as lotus, is a well-known edible plant. Food related to *N. nucifera* is popular in some areas of East Asia, especially China. Embryos of *N. nucifera* contain structurally related bioactive alkaloids including liensinine, isoliensinine (isolie), and neferine (chemical structures shown in Figure 1A). In previous pilot studies in our lab, liensinine, isolie, and neferine were prepared from embryos of *N. nucifera* and tested for cytotoxic activity in a series of human HCC cell lines. Isolie displayed stronger cytotoxic activity on HCC cells compared to liensinine or neferine. Interestingly, the cytotoxic effect of isolie on untransformed hepatocytes, including human HL-7702 hepatocytes and primary mouse hepatocytes, was much lower than the cytotoxic effects of neferine or liensinine (Table 1). In the current study, we demonstrate that isolie provokes HCC cell apoptosis both in vitro and in vivo. Mechanistically, dephosphorylation of p65 at Ser536 which inhibits NF-*κ*B activity is a crucial molecular event mediating isolie-induced

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Synthesis and characterization of high-quality water-soluble CdMnTe quantum dots capped by *N*-acetyl-L-cysteine through hydrothermal method

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ABSTRACT

High-quality water-soluble Mn^{2+} doped CdTe quantum dots (QDs) with *N*-acetyl-L-cysteine (NAC) as capping reagent have been synthesized through hydrothermal route, allowing a rapid preparation time (<1 h), tunable emitting peaks (from 530 to 646 nm) and excellent quantum yields (approximately 50%). The influences of various experimental variables, including Mn-to-Cd ratio, Te-to-Cd ratio, pH value, and reaction time on the growth rate and luminescent properties of the obtained QDs have been systematically investigated. And the optimum reaction conditions (Cd:Mn:NAC:Te = 1.0:1.0:2.4:0.2, pH = 9.5, 35 min, 200 °C) are found out. The optical features and structure of the obtained CdMnTe QDs have been characterized through fluorescence spectroscopy, UV absorption spectroscopy and TEM. In particular, we realized qualitative, semi-quantitative and quantitative studies on the doping of Mn to CdTe QDs through XPS, EDS, and AAS. The actual molar ratio of Mn to Cd in CdMnTe QDs (551 nm) is 1.166:1.00, very close to the feed ratios (1:1).

1. Introduction

Because of their unique photophysical properties, water-soluble quantum dots (QDs) have been applied in many fields including biochemical detection [1], bio-labeling [2,3], solar cells [4] and cellular and in vivo imaging [5–7]. Among them, the CdE (E = S, Se, Te) quantum dots are one of the most commonly and widely used types in these fields. However, the heavy metal cadmium contained in these QDs is regarded as a hidden danger to the environment and organic system, raising concerns on safety of their biomedical applications [8]. Therefore, further efforts to reduce their toxicity and to improve their biological compatibility and fluorescence qualities have thus become urgent requirements. On this occasion, the appearance of doped semiconductor nanocrystals shows the potential to be a class of mainstream emissive materials due to their apparent merits in overcoming the toxicity and self-quenching problem of undoped QDs through their substantial ensemble stokes shift [9], narrower emission band, broad excitation band, and better photochemical stability [10]. Zhong and his co-workers [11] have successfully prepared high-quality $Zn_xCd_{1-x}Se$ nanocrystals by incorporating stoichiometric amounts of Zn and Se into pre-prepared CdSe nanocrystals. The photoluminescence (PL) properties (PL efficiency of 70–85%, FWHM = 22–30 nm) are comparable to those for the best reported CdSe-based QDs, and in particular, the alloy nanocrystals retain high luminescence (PL efficiency reaches over 40%) when dispersed in aqueous solutions.

Actually, the doped QDs are not new in the field, and many different doped QDs have already been reported in the literatures, such as $Zn_xCd_{1-x}Se$ [11–13], $Zn_xCd_{1-x}S$ [14], CdSeTe [15], and $Cd_xZn_{1-x}Te$ [16,17]. Compared to the ternary alloyed nanocrystals, Mn^{2+} doped II-VI semiconductor QDs can not only reduce the dosage of cadmium, but also possess remarkably intense photoluminescence due to the ${}^4T_1({}^4G) \rightarrow {}^6A_1({}^6S)$ transition [18]. These doped dots are as efficient as conventional ones, and possess some unique properties, including low cytotoxicity, high photostability, and reduced chemical sensitivity. These merits ensure them as ideal fluorescent labels for biological assays, cells and tissues imaging, and even in vivo investigations [19]. Besides, the long lifetime of $ZnS:Mn^{2+}$ nanocrystals (ca.1 ms) makes the luminescence readily distinguishable from the short-lifetimed background luminescence [10]. Moreover, the impurity states of Mn^{2+} has also played special role in affecting the electronic energy structures and transient probabilities in the doped QDs [20]. The dilute magnetic properties of Mn^{2+}-doped QDs renders $Cd_{1-x}Mn_xTe$ the most popular dilute magnetic semiconductor compounds owing to their high technological properties, the highest possible magnetic moment of the manganese 3d-shell and favorable

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Simultaneous determination of Repaglinide and Irbesartan in biological plasmas using micellar enhanced excitation-emission matrix fluorescence coupled with ATLD method

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A highly sensitive and selective 3D excitation-emission fluorescence method has been proposed to rapidly quantify the combined antidiabetics Repaglinide (Re) and Irbesartan (Ir) in rat and human plasmas with the aid of second-order calibration method based on alternating trilinear decomposition (ATLD) method. Re and Ir with weak fluorescence can be endowed with strong fluorescent property by changing the microenvironment in samples and improving the fluorescence quantum yield by using an appropriate micellar enhanced surfactant. The enhanced excitation-emission matrix fluorescence of Re and Ir can be accurately resolved and can simultaneously attain the optimal concentration even in the presence of a potentially strong intrinsic fluorescence from complex biological matrices, such as rat and human plasmas, by using the ATLD method, which completely exploits the "second-order advantage". The average recoveries of Re and Ir obtained from ATLD with the factor number of 3 (N=3) were 101.0%±4.3% and 99.1%±4.1% for rat plasma and 100.5%±5.4% and 97.1%±3.6% for human plasma. Several statistical methods, including Student's *t*-test, figures of merit, and elliptical joint confidence region, have been utilized to evaluate the accuracy of the proposed method. Results show that the developed method can maintain second-order advantage in simultaneous determinations of the weak fluorescent analytes of interest in different biological plasma matrices.

Repaglinide, Irbesartan, micellar enhanced fluorescence, alternating trilinear decomposition

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1 Introduction

To date, complications related to hyperglycemia and hypertension have become the leading causes of death worldwide. Hyperglycemia or high blood sugar is a condition in which an excessive amount of glucose circulates in blood plasma. Chronic levels of blood sugar exceeding 7 mmol L^{-1} can produce a wide variety of serious complications, including kidney damage, neurological disorders, cardiovascular diseases, retinal injury, or damage to feet and legs, over a period of several years [1–5]. Hypertension, which is also known as high blood pressure or arterial hypertension, is a chronic medical condition in which blood pressure in the arteries is elevated. Hypertension is one of the main causes of cardiovascular diseases and also exhibits complications,

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“Turn-off” fluorescent sensor for highly sensitive and specific simultaneous recognition of 29 famous green teas based on quantum dots combined with chemometrics

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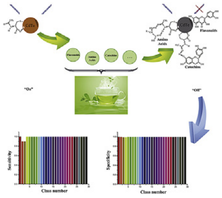
HIGHLIGHTS

- LCNC would bring new challenges to traditional classification methods.
- An excellent fluorescent probe QDs are designed for sensing various green teas.
- The fluorescent data array sensor is firstly developed to tackle LCNC.
- The new detection mode is superior to the conventional fluorescent method for LCNC.

GRAPHICAL ABSTRACT



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ABSTRACT

Fluorescent “turn-off” sensors based on water-soluble quantum dots (QDs) have drawn increasing attention owing to their unique properties such as high fluorescence quantum yields, chemical stability and low toxicity. In this work, a novel method based on the fluorescence “turn-off” model with water-soluble CdTe QDs as the fluorescent probes for differentiation of 29 different famous green teas is established. The fluorescence of the QDs can be quenched in different degrees in light of positions and intensities of the fluorescent peaks for the green teas. Subsequently, with aid of classic partial least square discriminant analysis (PLSDA), all the green teas can be discriminated with high sensitivity, specificity and a satisfactory recognition rate of 100% for training set and 98.3% for prediction set, respectively. Especially, the “turn-off” fluorescence PLSDA model based on second-order derivatives (2nd der) with reduced least complexity (LVs = 3) was the most effective one for modeling. Most importantly, we further demonstrated the established “turn-off” fluorescent sensor mode has several significant advantages and appealing properties over the conventional fluorescent method for large-class-number classification (LCNC) of green teas. This work is, to the best of our knowledge, the first report on the rapid and effective identification of so many kinds of famous green teas based on the “turn-off” model of QDs combined with chemometrics, which also implies other potential applications on complex LCNC

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Protective effect of luteolin on streptozotocin-induced diabetic renal damage in mice via the regulation of RIP140/NF-κB pathway and insulin signalling pathway

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ABSTRACT

Luteolin (LUT) is one of the most common flavonoids present in various fruits and vegetables. The effects of luteolin (LUT) on streptozotocin (STZ)-induced diabetic renal damage were investigated. LUT was orally administered at 10, 20 mg/kg/day for 4 weeks to streptozotocin-induced diabetic mice. Serum levels of uric acid, creatinine, triacylglycerol, total cholesterol, low density lipoprotein and blood urea nitrogen were measured. Urinary uric acid and creatinine were assayed. Serum insulin level and oral glucose tolerance test (OGTT) were determined. Kidney pathological changes were detected. Receptor-interacting protein 140 (RIP140)/nuclear factor κB (NF-κB) pathway and insulin signalling pathway were detected. LUT restored streptozotocin-induced insulin resistance, dyslipidaemia, hyperuricemia, and renal inflammatory cell infiltration in streptozotocin-induced mice. Furthermore, LUT inhibited RIP140/NF-κB pathway and improved the insulin signalling pathway in streptozotocin-induced renal damage in mice. Thus, the beneficial effect of LUT against diabetic nephropathy (DN) is related to its regulation of RIP140/NF-κB and insulin pathway.

1. Introduction

Diabetic mellitus is one of the most recognisable endocrine metabolic disorders fundamentally characterised by hyperglycaemia via the disruption of carbohydrate, fat and protein metabolism caused by insufficient secretion of endogenous insulin (WHO) (Chen et al., 2015a). An abnormally elevated blood glucose level contributes to inflammatory stress and formation of advanced glycation end products (AGE), which have been closely linked to diabetic complications (Ahmed, 2005). In particular, diabetics are at increased risk for several types of kidney disease, and the predominant cause of end-stage renal disease in this disorder is diabetic nephropathy (Selby et al., 1990). Prevention and treatment of diabetic nephropathy have become an important issue. It has been reported that insulin resistance plays a critical role in type 2 diabetes-induced renal damage (Gum et al., 2003). Moreover, insulin

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A Self-Assembled Oligopeptide as a Versatile NMR Alignment Medium for the Measurement of Residual Dipolar Couplings in Methanol

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Abstract: *Residual dipolar coupling (RDC) is a powerful structural parameter for the determination of the constitution, conformation, and configuration of organic molecules. Herein, we report the first liquid crystal-based orienting medium that is compatible with MeOH, thus enabling RDC acquisitions of a wide range of intermediate to polar organic molecules. The liquid crystals were produced from self-assembled oligopeptide nanotubes (AAKLVFF), which are stable at very low concentrations. The presented alignment medium is highly homogeneous, and the size of RDCs can be scaled with the concentration of the peptide. To assess the accuracy of the RDC measurement by employing this new medium, seven bioactive natural products from different classes were chosen and analyzed. The straightforward preparation of the anisotropic alignment sample will offer a versatile and robust protocol for the routine RDC measurement of natural products.*

Residual dipolar coupling (RDC) is a highly valuable structural parameter for biomacromolecules[1] as well as small organic molecules[2] with respect to constitution, conformation, configuration, and structural dynamics. The application of RDC for organic compounds has been significantly accelerated owing to the recent progress on the development of new pulse sequences, alignment media, and analysis methods.[3]

A prerequisite for RDC measurement is the availability of suitable alignment media for introducing the necessary anisotropy to the analytes. Two main classes of alignment media have been introduced for organic molecules, stretched polymer gels and lyotropic liquid crystalline (LLC) phases.[3e–h] Polymer gels have been widely applied for acquiring anisotropic NMR data, as various polymer-based media have been developed for different organic solvents.[4] Notably, Luy et al. proposed a robust cross-linked poly(ethylene oxide) (PEO) gel, which is until now the only orienting medium that covers a wide range of solvent compatibilities.[5] LLCs are another good option to align small molecules because of their excellent NMR spectroscopic properties and their ability to simultaneously align organic molecules. However, most of the LC phases for example, PBLG,[2c] polyguanidines,[6] polyisocyanates,[7] polyacetylenes,[8] polyisocyanopeptides[9] are only compatible with apolar solvents such as chloroform or a mixture of $CDCl_3$ with polar solvents,[10] while a few phases such as ACHC-rich β-peptides[11] and disodium cromoglycate[12] are compatible with water. In our previous work, we proposed a series of graphene oxide-based LLCs as orienting media for polar solvents such as dimethylsulfoxide (DMSO).[13] Nevertheless, to best of our knowledge, until now there is still no LC phase that is compatible with methanol (MeOH), which is a very frequently used solvent in natural product chemistry, as it is compatible with a wide range of molecule classes including alcohols, carboxylic acids, amines, and esters. Our aim was therefore to develop a new methanol-compatible LLC phase, which is stable at sufficiently low critical concentrations and can be produced easily in large scale.

Recently, self-assembled oligopeptides have attracted immense attention because of their potential applications in biomedicine, biomimetic materials, and nanotechnology.[14] Various hierarchical architectures, including nanofibrils, nanotubes, and nanowires, using peptide building blocks have been developed in the last few years.[14] Inspired by the filamentous Pf1 bacteriophage[15] and DNA-nanotubes[16] as excellent orientational ordering media in aqueous solution, we started our investigations on self-assembled peptides that are soluble in organic solvents. In fact, several oligopeptide-based anticancer drugs such as nafarelin, detirelix, and leuprolide, have been shown to form lyotropic liquid crystalline phases with β-sheet rod-like architecture.[17] More interestingly, Hamley and co-workers developed a peptide nanotube, which can form a nematic phase at 1 wt% concentration in methanol.[18] This self-assembled oligopeptide has the sequence of AAKLVFF, which was derived from a fragment of the amyloid β-peptide Aβ-(16–20), KLVFF, whose structure and properties have been systematically investigated. Furthermore, the self-assembly mechanism and the formation of a nematic phase in methanol of AAKLVFF

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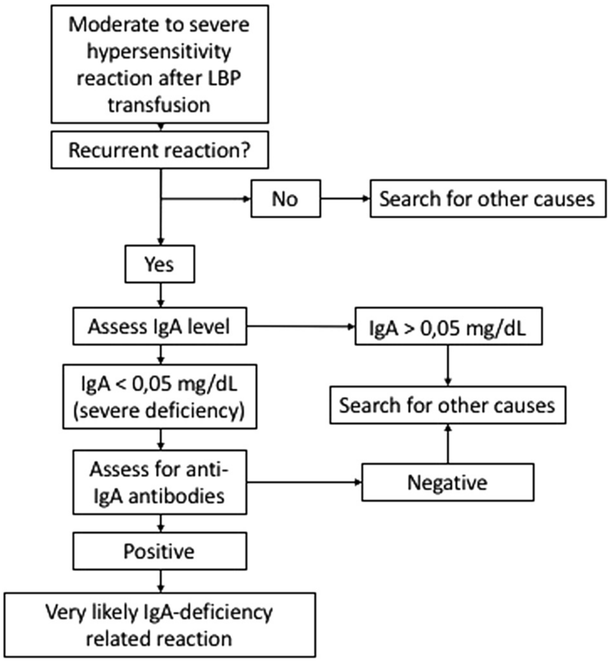

FIG 1. Diagnostic algorithm for IgA-deficiency–related reactions.

considered possible. Analysis of this large database thus indicates that HTR is a rare complication with a maximum frequency of 1 per 871,911 patients exposed.

The difficulty in confirming a diagnosis of IgA-related HTR should not be ignored: (1) IgA deficiency does not necessarily lead to sensitization; (2) IgA-related HTR is highly unlikely in a patient with detectable IgA. Risk has probably been overestimated in prevalence studies because the IgA threshold was too high; more sensitive IgA assays are needed; (3) although HTRs are usually considered to be IgG-mediated, any IgE-mediated sensitization that might occur will be missed by existing diagnostic protocols; (4) nonallergic mechanisms may be involved.[10] The current strategy of investigating a possible IgA deficiency in HTR cases is thus an expensive and not very efficient option and should be replaced by a new diagnostic algorithm (Fig 1). An alternative strategy might be to transfuse patients with recurrent ATRs with WRBC-PC or IgA-deficient fresh frozen plasma and investigate only refractory patients for IgA deficiency.

In conclusion, an HTR due to anti-IgA sensitization is exceptional. Only recurrent moderate-to-severe HTRs should be investigated for IgA deficiency and it will always be difficult to confirm the diagnosis.

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The antimicrobial peptide human beta-defensin 2 promotes itch through Toll-like receptor 4 signaling in mice

To the Editor:

Chronic skin inflammation is considered the most prominent feature for clinical diagnosis of psoriasis, a long-lasting autoimmune disease characterized by patches of red, itchy, and scaly skin. Besides skin inflammation, up to 84% of patients with psoriasis suffer from chronic itch, which significantly impairs quality of life.[1] Although recent exciting studies have identified a positive correlation between the intensity of psoriatic itch and the expression levels of nerve growth factor, neuropeptides, and many cytokines,[2] the molecular and cellular mechanisms underlying psoriatic itch are not fully understood.

In response to T_H1 or T_H17 cytokines, excessive antimicrobial peptides (AMPs) are locally released by rapidly differentiating psoriatic keratinocytes. Among them, human beta-defensin 2 (hBD2) is increased by nearly 400-fold in patients with severe psoriasis and serves as a biomarker for psoriasis activity.[3] Besides potent antimicrobial activity, hBD2 has diversified roles in regulating adaptive immunity, wound healing, and male fertility.[4] Interestingly, hBD2 also promotes inflammation by recruiting multiple types of immune cells through interacting with both C-C chemokine receptor type 2 (CCR2) and C-C chemokine receptor type 6 (CCR6) *in vitro*.[5,6] However, the role of hBD2 in itch sensation has not been determined. We therefore investigated whether hBD2 could elicit scratching in wild-type *C57BL/6J* mice. Strikingly, intradermal injections of hBD2 produced a robust scratching response in wild-type mice in a dose-dependent manner (Fig 1, *A* and *B*). In addition, murine beta-defensin 4, the hBD2 ortholog in mouse, and hBD3 could also elicit scratching in mice although the itch intensity varied among different AMPs (see Fig E1 in this article's Online Repository at www.jacionline.org), which provides a proof of concept that both human and mouse AMPs could serve as endogenous pruritogens.

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Detection of unexpected frauds: Screening and quantification of maleic acid in cassava starch by Fourier transform near-infrared spectroscopy

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One-class partial least squares (OCPLS)

ABSTRACT

Fourier transform near-infrared (FT-NIR) spectroscopy and chemometrics were adopted for the rapid analysis of a toxic additive, maleic acid (MA), which has emerged as a new extraneous adulterant in cassava starch (CS). After developing an untargeted screening method for MA detection in CS using one-class partial least squares (OCPLS), multivariate calibration models were subsequently developed using least squares support vector machine (LS-SVM) to quantitatively analyze MA. As a result, the OCPLS model using the second-order derivative (D2) spectra detected 0.6% (w/w) adulterated MA in CS, with a sensitivity of 0.954 and specificity of 0.956. The root mean squared error of prediction (RMSEP) was 0.192 (w/w, %) by using the standard normal variate (SNV) transformation LS-SVM. In conclusion, the potential of FT-NIR spectroscopy and chemometrics was demonstrated for application in rapid screening and quantitative analysis of MA in CS, which also implies that they have other promising applications for untargeted analysis.

1. Introduction

Cassava (*Manihot esculenta* Crantz) is an important food in tropical and subtropical regions, including Africa, Asia, Latin America and the Caribbean (Ampe, Sirvent, & Zakhia, 2001; Morales, Álvarez, & Sánchez, 2008). Cassava starch (CS) has been widely employed in food formulations for bread, cakes, biscuits, pasta, tapioca balls, and cassava noodles due to the specific characteristics, such as bland taste and flavor, high paste clarity, and lower amylase content compared with wheat, potato, and maize starches (Fiorda, Soares, Silva, Grosmann, & Souto, 2013; Raja, 1995; Shittu, Dixon, Awonorin, Sanni, & Maziya-Dixon, 2008). However, in 2013, a serious food safety scandal caused significant public concern in Taiwan and Singapore when an industrial substance, maleic acid (MA), was identified in popular snacks from meat balls to the tapioca "pearls" used in bubble tea (ANN, 2014). MA can cause acute kidney failure, but high concentrations were intentionally added to powdered CS to impart and improve chewiness of the starch. Similar to melamine (Filazi, Sireli, Ekici, Can, & Karagoz, 2012) and diethylhexyl phthalate (DEHP) (Yang, Hauser, & Goldman, 2013), MA is another emerging toxic and illegal food additive that was not included in routine analysis of CS before the scandal occurred.

Although analytical methods to detect MA in powdered CS were quickly developed after the scandal (Chen, Wu, & Wu, 2015; Tsai et al., 2015; Xu et al., 2013), it is still challenging to obtain a quick response and/or early warning signs of "unexpected" adulterants. Traditional mechanisms in response to food safety problems are less applicable because the analytical methods target known adulterants, or in other words, relevant analyses are only required and performed when an adulterant is discovered or suspected to exist. Because fraudulent new food and extraneous adulterants are constantly emerging, reliance on routine targeted analysis enables the control of food adulterations and fraudulent foods to be caught in a vicious cycle of "adulteration, scandal, targeted analysis, new adulterants, etc." (Xu, Yan, Cai, Wang, & Yu, 2013). To tackle such challenges, a new strategy of untargeted analysis has been proposed to

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RESEARCH ARTICLE

Diabetes Treatment

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Antidiabetic Activity of Ergosterol from *Pleurotus Ostreatus* in KK-A^y Mice with Spontaneous Type 2 Diabetes Mellitus

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Scope: The number of people with diabetes is increasing rapidly in the world. In the present study, the hypoglycemic activity and potential mechanism of ergosterol (ERG), a phytosterol derived from the edible mushroom *Pleurotus ostreatus* are investigated in vitro and in vivo.

Methods and results: ERG is isolated from *Pleurotus ostreatus* and identified by NMR spectra. The effects of ERG on the glucose uptake, glucose transporter 4 (GLUT4) translocation, GLUT4 expression, and the phosphorylation of AMPK, Akt and PKC in L6 cells are evaluated. ERG enhances glucose uptake and displays a GLUT4 translocation activity with up-regulating GLUT4 expression and phosphorylation of Akt and PKC in L6 cells. In vivo, antidiabetic activity of ERG is examined. The phosphorylation of Akt and PKC in different tissues from KK-A^y mice is assessed. ERG significantly improves insulin resistance and blood lipid indices while reducing fasting blood glucose levels and protecting pancreas and liver in the mice. Moreover, the phosphorylation of Akt and PKC is increased in different tissues.

Conclusion: The results suggest that ERG may be a potential hypoglycemic agent for the treatment of T2DM with the probable mechanism of stimulating GLUT4 translocation and expression modulated by the PI3K/Akt pathway and PKC pathway.

1. Introduction

Diabetes mellitus (DM) is an endocrine disease which occurs either when the pancreas does not produce enough insulin or when the body cannot effectively utilize the insulin it produces.[1] It elevated high blood glucose as the main characteristics, and accompanied by the metabolism disorder of glucose, lipids, and proteins. With the rapid growth of the incidence of DM, it has become the third disease which is a severe threat to human health following cardiovascular and neoplastic disease.[2] There are two types of diabetes: type 1 diabetes (insulin-dependent, T1DM) and type 2 diabetes (non-insulin-dependent, T2DM). Over 90% of patients with diabetes are non-insulin-dependent which is caused by insulin resistance and β-cell dysfunction.[1] Its typical clinical manifestation concludes excessive drink, excessive food, diuresis or sweet urine, and weight loss, and it is also characterized by lipid abnormalities.

Complications associated with T2DM include leg ulcers,[3] cardiovascular lesions,[4] diabetic nephropathy,[5] and retinopathy.[6] The disease can also result in vascular and microvascular damage, which can threaten the heart, brain, eyes, and peripheral nerves if blood glucose levels remain elevated for long periods of time.

Drugs currently available for the treatment of DM fall into four general categories: insulin; insulin secretagogues; insulin sensitizers; and prandial glucose regulators. However, many of these drugs can have serious adverse effects in patients with poor tolerance.[7] More effective and safer hypoglycemic agents are needed.

Natural plant remedies are showing an increasing trend in modern clinical medicine and have been applied as an alternative treatment for T2DM, with satisfactory efficacy and few side effects. Such remedies have gained increased attention because of their safe application.[8]

Phytosterols are a group of natural bioactive products mainly found in plants and have a similar structure to cholesterol, with no toxicity to humans and animals.[9] Studies have reported that phytosterols can significantly reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in the blood, and increase the index of high-density lipoprotein cholesterol (HDL-C)/LDL-C and HDL-C/TC.[10,11]

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Article

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Activity of Isoliensinine in Improving the Symptoms of Type 2 Diabetic Mice via Activation of AMP-Activated Kinase and Regulation of PPARγ

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Supporting Information

ABSTRACT: This study was designed to explore the effects and mechanism of isoliensinine (isolie) from embryos of *Nelumbo nucifera* on type 2 diabetes and dyslipidemia in vivo and in vitro. The in vitro study showed that isolie increased the GLUT4 translocation by 2.5-fold in L6 cells. Furthermore, after 4 weeks of treatment, the in vivo biochemical study indexes revealed that isolie had a positive effect on decreasing serum insulin level (42.2 ± 5.10 vs 55.7 ± 6.33 mU/L, $P < 0.05$) and reducing fast blood glucose (9.4 ± 1.5 vs 18.7 ± 2.3 mmol/L, $P < 0.001$) and body weight (37.8 ± 2.9 vs 46.9 ± 5.4 g, $P < 0.05$) compared with the KK-Ay model mice. Isolie treatment led to significant increases in GLUT4 proteins (~2.7-fold in skeletal muscle and ~2.4-fold in WAT) and phosphorylated AMP-activated protein kinase (~1.4-fold in skeletal muscle, ~3.1-fold in WAT, and ~2.3-fold in liver). However, isolie caused a significant decrease in lipogenesis protein expressions of PPARγ and SREBP-1c, and decreased the activity of ACC by increasing the phospho-ACC level. Our findings showed that isolie has the potential to alleviate type 2 diabetes associated with hyperlipidemia in KK-Ay mice. Regulation of GLUT4, SREBP-1c, PPARγ, AMPK phosphorylation, and ACC phosphorylation is implicated in the antidiabetic effects of isolie.

KEYWORDS: *isoliensinine, type 2 diabetes, hyperlipidemia, glucose transporter 4, p-AMPK*

INTRODUCTION

In 2015, according to the International Diabetes Federation (IDF) programs, it was estimated that there were 415 million adult people with diabetes across the world, and this number is expected to rise to 642 million by 2040.[1] Around 97% of these diabetic patients will have type 2 diabetes mellitus (T2DM).[2] T2DM is a progressive disease whose clinical manifestation is a gradual decline in glycemic control caused by β cell functional deterioration over time and increased associated risk of microvascular and macrovascular complications.[3] The primary cause of T2DM is obesity-driven insulin resistance in the liver, white adipose tissue (WAT), and skeletal muscle, combined with insufficient secretion of insulin by pancreatic β cells to overcome this resistance.[4] Although the strategies currently available for T2DM management have achieved great effects, the tolerability and significant mechanism-based side effects are still unignorable.[5] Therefore, looking for new drugs to prevent and treat T2DM is becoming an urgent problem that must be solved.

Elevating the activity of glucose transporter 4 (GLUT4) can be a promising strategy for controlling obesity-related insulin resistance.[6,7] GLUT4 is a glucose transporter expressed primarily in adipose and muscle tissues.[8] Reduced GLUT4 expression and abnormal GLUT4 translocation are tightly associated with decreased glucose uptake in skeletal muscles in patients with insulin resistance.[9,10] AMP-activated protein kinase (AMPK) is an important regulator of the GLUT4; metformin is a commonly used antidiabetic drug which has been demonstrated to increase GLUT4 expression and translocation through activating AMPK pathway.[11,12] In this way, compounds capable of enhancing the expression or translocation of GLUT4 may be suitable agents for controlling T2DM.

Natural products are gaining an increasing amount of attention from pharmaceutical researchers and clinicians because of their efficiency, safety, and immediate availability.[13,14] Over the past 30 years, more than 70% of drugs approved by the U.S. Food and Drug Administration originated from natural products.[15] To look for potential hypoglycemic agents from natural products, a cell-based GLUT4 translocation assay system using stable L6 myotubes expressing pIRAP-mOrange cDNAs was established to screen potential antidiabetic plants extracts, fractions, and individual natural compounds by evaluating their effects on GLUT4 translocation.[16,17] During the screening of a plant extract library (800 biotas) on GLUT4 translocation, we found that the total alkaloids from embryos of *Nelumbo nucifera* displayed a promising positive activity on GLUT4 translocation.

N. nucifera is commonly known as lotus, and it is a well-known edible plant. Foods and dietary supplements derived from *N. nucifera* are very popular in China.[18] Embryos of *N. nucifera* have been long used in Chinese herbal medicine for the prevention of arrhythmia, insomnia, hypertension, spermatorrhea, cardiac action, and hyperpyrexia.[19,20] The main active components in the total alkaloids from embryos of *N. nucifera* are liensinine, isoliensinine (isolie), and neferine (Figures 1A and 1B). Alkaloids are one of the most important active ingredients in natural medical

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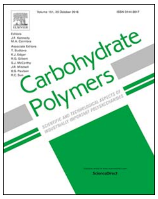

Digestibility of fucosylated glycosaminoglycan from sea cucumber and its effects on digestive enzymes under simulated salivary and gastrointestinal conditions

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N-Acetyl-D-Galactosamine (PubChem CID: 35717)
Alpha-D-glucose (PubChem CID: 79025)
L-Fucose (PubChem CID: 17106)
D-Galactose (PubChem CID: 6036)
Acarbose hydrate (PubChem CID: 129837378)
Sodium Alginate (PubChem CID: 5102882)
Orlistat (PubChem CID: 3034010)
Heparin (PubChem CID: 772)

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ABSTRACT

The digestibility of fucosylated glycosaminoglycan (FG) and its effects on digestive enzymes were investigated using an in vitro digestion model. Results showed that the molecular weight and the reducing sugar content of FG were not significantly changed, and no free monosaccharides released from FG were detected after the salivary, gastric and intestinal digestion, indicating that both the backbone and the sulfated fucose branches of FG are resistant to be cleaved in the saliva and gastrointestinal tract environments. Furthermore, FG can dose-dependently inhibit digestive enzymes such as α-amylase, pepsin and pancreatic lipase in different degrees under the simulated digestion conditions due to the sulfate and carboxyl groups. These physiological effects of FG may help control the postprandial glucose concentration and have the potential in the prevention or treatment of reflux disease and obesity. The findings may provide information on the digestibility and beneficial physiological effects of FG as a potential natural product to promote human health.

1. Introduction

Polysaccharides derived from natural products have showed many biological functions such as anti-hyperlipidemia, anti-hyperglycemia and antithrombotic activities following oral administration; however, how the biomacromoleculars exert their activities in gastrointestinal tract is still a puzzle (Fonseca & Mourão, 2006; Wu et al., 2016; Zhao et al., 2012). Therefore, digestion of bioactive polysaccharides and their effects on gastrointestinal related physiological functions have received increasing attention among researchers in recent years (Chen et al., 2016).

Sea cucumbers, belonging to Echinodermata, Holothuroidea, are marine invertebrates found in most benthic marine habitats across the world. These animals have been a traditional tonic food in Asian countries such as Japan, Korea, Philippines and China for centuries as they contain high level of nutritional contents including vitamins, minerals, proteins and polysaccharides (Katzman & Jeanloz, 1969). Fucosylated glycosaminoglycan (FG), one of the polysaccharides from the body wall of sea cucumbers, has shown many pharmacological activities including antitumor, anti-hyperlipidemia, anti-hyperglycemia, antivirus, anti-inflammatory, anticoagulant and antithrombotic activities (Pomin, 2014). The activities were greatly affected by its molecular size and sulfated fucose (Fuc) branched units, which has been confirmed by the literature and our previous studies (Chen et al., 2013; Wu et al., 2012; Zhao et al., 2013). Intriguingly, recent studies also showed that FG can increase the content of probiotics bacteria in vitro in achieving health-enhancing effect and exert antithrombotic and anti-hyperlipidemic effects by the oral routes to experimental animals (Fonseca, Sucupira, Oliveira, Santos, & Mourão, 2017; Fonseca & Mourão, 2006; Liu, Ko, & Hu, 2002; Wei et al., 2017; Wu et al., 2016).

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“Turn-off” fluorescent sensor based on double quantum dots coupled with chemometrics for highly sensitive and specific recognition of 53 famous green teas

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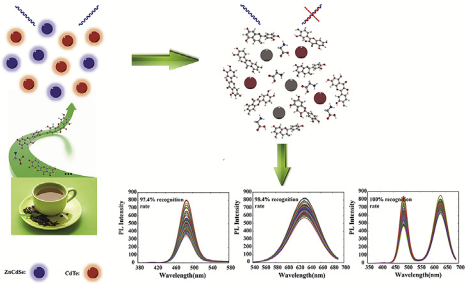
HIGHLIGHTS

- The double QDs fluorescent data array sensor is firstly developed to tackle LCNC.
- The new detection mode is superior to the conventional fluorescent method and single fluorescent probe QDs method for LCNC.
- The new double QDs detection mode gives satisfactory and 100% recognition rate in the LCNC system.

GRAPHICAL ABSTRACT



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ABSTRACT

Fluorescent “turn-off” sensors based on double quantum dots (QDs) has attracted increasing attention in the detection of many materials due to their properties such as more useful information, higher fluorescence efficiency and stability compared with the fluorescent “turn-off” sensors based on single QDs. In this work, highly sensitive and specific method for recognition of 53 different famous green teas was developed based on the fluorescent “turn-off” model with water-soluble ZnCdSe-CdTe double QDs. The fluorescence of the two QDs can be quenched by different teas with varying degrees, which results in the differences in positions and intensities of two peaks. By the combination of classic partial least square discriminant analysis (PLSDA), all the green teas can be discriminated with high sensitivity, specificity and a satisfactory recognition rate of 100% for training set and 100% for prediction set, respectively. The fluorescent “turn-off” sensors based on the single QDs (either ZnCdSe QDs or CdTe QDs) coupled with PLSDA were also employed to recognize the 53 famous green teas with unsatisfactory results. Therefore, the fluorescent “turn-off” sensors based on the double QDs is more appropriate for the large-class-number classification (LCNC) of green teas. Herein, we have demonstrated, for the first time, that so many kinds of famous green teas can be discriminated by the “turn-off” model of double QDs combined

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Chlorogenic acid methyl ester exerts strong anti-inflammatory effects *via* inhibiting the COX-2/NLRP3/NF-κB pathway

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The objective of this study was to investigate the anti-inflammatory effect of chlorogenic acid methyl ester (CME) and the molecular mechanism involved, through using non-infectious inflammation and infectious inflammation animal models as well as lipopolysaccharide (LPS)-stimulated mouse macrophage RAW264.7 cell models. Our results demonstrated that CME markedly inhibited ear swelling, paw swelling and granuloma swelling, and decreased intraperitoneal capillary permeability in non-infectious inflammation. Moreover, CME significantly alleviated the pathological damage of the lung tissue, reduced the levels of PGE2 and IL-1β in the serum and the protein expression levels of related-inflammatory factors in the lung tissue of LPS-induced mice with acute lung injury (ALI). In addition, CME affected the RAW264.7 cell cycle and inhibited the protein expressions of COX-2 and NLRP3 and prevented the phosphorylation of NF-κB p65 in RAW264.7 cells treated with LPS. These observations not only validated the anti-inflammatory effects of CME, but also revealed the underlying molecular basis, which involves the down-regulation of the expression of inflammatory factors and blockade of the COX-2/NLRP3/NF-κB signaling pathway.

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Introduction

Inflammation is a defensive response of the body to external inflammatory stimuli such as pathogens, lipopolysaccharide and viruses.[1] Inflammation can lead to symptoms including redness, swelling, heat, pain, and disruption of the structure and function of tissue.[2] Inflammation, commonly occurring in a variety of pathological processes, is complex and regulated by a number of inflammatory-related mediators whose excessive production leads to various acute and chronic inflammatory diseases such as acute lung injuries (ALI), cancer and even death.[3,4]

At present, the major anti-inflammatory drugs on the market are non-steroidal anti-inflammatory drugs (NSAIDs).[5] However, the clinical application of NSAIDs is severely limited by adverse reactions such as gastrointestinal bleeding, bronchospasm, thrombosis and renal failure.[6] In consideration of these side effects of NSAIDs, extensive efforts are being made to identify and develop natural products that can be used as anti-inflammatory agents.

Bolbostemma paniculatum (Maxim.) Franquet (BPF), a member of the genus *Bolbostemma* that has been used widely as edible and medicinal resources in China, is traditionally used as an antidote or anti-inflammatory or antitumor agent.[7] The purpose of this study was to characterize the anti-inflammatory activity of chlorogenic acid methyl ester (CME), an extract from BPF, and to explore the molecular pathways involved, using both *in vitro* and *in vivo* inflammation models. We found that CME could significantly inhibit the inflammatory reaction through modulating the mediators and the COX-2/NLRP3/NF-κB signaling pathway.

Materials and methods

Materials and reagents

Bulbs of BPF were collected in Enshi, Hubei Province, PR China, and identified by Dr Dingrong Wan's laboratory, School of Pharmaceutical Sciences, South-Central University for Nationalities, China. Voucher samples (No. SC-20150428) were

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Anti-diabetic activity of a polyphenol-rich extract from *Phellinus igniarius* in KK-Ay mice with spontaneous type 2 diabetes mellitus†

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The present study investigated the anti-diabetic activity and potential mechanisms of the polyphenol rich extract from *Phellinus igniarius* (PI-PRE) *in vitro* and *in vivo*. Four main phenolic compounds of PI-PRE were purified and identified as 7,8-dihydroxycoumarin, 3,4-dihydroxybenzalacetone, 7,3′-dihydroxy-5′-methoxyisoflavone and inoscavin C by the off-line semipreparative liquid chromatography-nuclear magnetic resonance protocol. *In vitro*, PI-PRE stimulated GLUT4 translocation by 2.34-fold and increased glucose uptake by 1.73-fold in L6 cells. However, the selective AMP-activated protein kinase (AMPK) inhibitor, compound C, completely reversed the PI-PRE-induced GLUT4 translocation. *In vivo*, KK-Ay mice treated with PI-PRE for four weeks had lower fasting blood glucose levels, as well as other blood–lipid indexes, compared with the vehicle control group. Mechanistic studies showed that the expressions of p-AMPKα and GLUT4 were significantly increased by treatment with PI-PRE in L6 cells. In KK-Ay mice, the expression of p-AMPKα was enhanced in the liver and skeletal muscle, and the expression of GLUT4 was increased in skeletal muscle. These findings suggest that PI-PRE possesses potential anti-diabetic effects including improving glucose tolerance, reducing hyperglycemia, and normalizing insulin levels. These effects are partly due to the activation of GLUT4 translocation *via* the modulation of the AMPK pathway.

Introduction

Diabetes mellitus (DM) is a serious chronic metabolic disorder that is prevalent worldwide.[1] Based on a study published by the World Health Organization (WHO), the incidence of diabetes mellitus has increased rapidly in recent years. Currently, there are approximately 347 million people suffering from diabetes, and 90–95% of all diabetes patients have type 2 diabetes mellitus (T2DM).[2,3] T2DM is a result of the ineffective use of insulin, or insulin resistance.[3] Chronic hyperglycemia syndrome, which is a common complication of T2DM, can result in conditions such as obesity, kidney failure, fatty liver, nerve damage, hyperlipidemia, hypertension, and cardiovascular diseases. According to previous reports, the number of diabetes patients in China increased to 96 million as of 2014.[2] Therefore, the development of strategies for the prevention and control of diabetes and its resulting complications is a growing need.

As a new trend in modern clinical medicine for the treatment of T2DM, functional fungi such as *Ganoderma lucidum*, *Poria cocos* Wolf, *Shiraia bambusicola*, *Inonotus obliquus*, and *Grifola frondos* have been attracting significant attention due to their efficacy and minimal side effects. These functional fungi have been reported to exhibit significant anti-diabetic effects.[4–8] Therefore, natural remedies from functional fungi show great potential for the prevention and treatment of T2DM.

Phellinus igniarius (L.) Quail, a well-known functional fungus commonly referred to as "Sanghuang" in China, is widely consumed as a tea preparation, as an adjunct therapy or a preventive measure.[9] It is a rich source of natural polyphenols, which has been used as a traditional functional food in the prevention or treatment of numerous diseases in Asia over the last two centuries.[10,11] In several folk recipes, it is used to treat stomach aches and arthritis. Recent studies have demonstrated that polysaccharides isolated from *P. igniarius* possess anti-inflammatory, anti-tumor, anti-oxidant, and α-glucosidase

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Anti-Proliferative and Anti-Inflammatory Lanostane Triterpenoids from the Polish Edible Mushroom *Macrolepiota procera*

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Supporting Information

ABSTRACT: This study features the isolation and identification of 12 lanostane-type triterpenoids, namely lepiotaprocerins A−L, **1−12**, from the fruiting bodies of the Poland-collected edible mushroom *Macrolepiota procera*. The structures and the absolute configurations of the new compounds were ambiguously established by extensive spectroscopic analyses, ECD calculation, and single-crystal X-ray diffraction analyses. Structurally, lepiotaprocerins A−F, **1−6**, are distinguished by the presence of a rare "1-en-1,11-epoxy" moiety which has not been previously described in the lanostane class. Biologically, lepiotaprocerins A−F, **1−6**, displayed more significant inhibitions of nitric oxide (NO) production than the positive control L-N^G-monomethyl arginine (L-NMMA) (IC_{50} 47.1 μM), and lepiotaprocerins G−L, **7−12**, showed various cytotoxicity potencies against a panel of human cancer cell lines. Compound **9** also displayed antitubercular activity against *Mycobacterium tuberculosis* H37Ra with a minimal inhibitory concentration (MIC) 50 μg/mL.

KEYWORDS: *Mushroom, Macrolepiota procera, lanostane triterpenoid, anti-inflammatory activity, cytotoxicity*

INTRODUCTION

According to the World Health Organization, cancer is the second leading cause of death worldwide, and was responsible for 8.8 million deaths in 2015.[1] Many cancers arise from infection, chronic irritation, and inflammation. Recent researches expanded the concept that inflammation is a critical component of tumor progression.[2,3] Therefore, anti-inflammatory therapy is efficacious toward early neoplastic progression and malignant conversion. A large number of scientific publications have shown that natural products from medicinal/edible mushrooms play a dominant role in the discovery of leads for the development of drugs for prevention and treatment of this disease.[4−6] Moreover, a meta-analysis of results of observational studies suggested that consumption of more mushrooms may be associated with decreased risk of breast cancer.[7]

The mushroom *Macrolepiota procera*, also called "parasol mushroom" due to its large fruiting body resembling a parasol, is widespread in temperate regions. In Europe, *M. procera* is a highly sought-after and popular item due to its large size fruiting bodies, frequent seasonal accessibility, and versatility in the kitchen. However, no reports have addressed the secondary metabolites of this kind of famous edible mushroom so far. As our continuous research aiming at discovery drug leads from edible mushroom, a chemical investigation on the constituents of the Poland-origin parasol mushroom *M. procera* was carried out. Herein, we report the isolation, structure elucidation, and biological evaluation of 12 lanostane triterpenoids, namely lepiotaprocerins A−L, **1−12**, from the fruiting bodies of *M. procera* (Figure 1).

MATERIALS AND METHODS

General Experimental Procedures. Optical rotations were measured by a JASCO P-1020 digital polarimeter (Horiba, Kyoto, Japan). A UV-2401PC UV−visible recording spectrophotometer (Shimadzu, Kyoto, Japan) was used to record the ultraviolet (UV) spectra. A Chirascan circular dichroism spectrometer (Applied Photophysics Limited, Leatherhead, Surrey, UK) was used to record the CD spectra. 1D and 2D NMR spectra were obtained on Bruker Avance III 600 MHz or Ascend 800 MHz spectrometers (Bruker Corporation, Karlsruhe, Germany). An Agilent 6200 Q-TOF MS system (Agilent Technologies, Santa Clara, CA) was used to acquire the HRESIMS data. A Waters AutoSpec Premier P776 MS system (Waters Corporation, Milford, MA) was used to acquire the HREIMS datum. An APEX II DUO spectrophotometer (Bruker AXS GmbH, Karlsruhe, Germany) was applied for performing the single-crystal X-ray diffraction experiment. Column chromatography (CC) was run on Sephadex LH-20 (Amersham Biosciences, Uppsala, Sweden) and silica gel (Qingdao Haiyang Chemical Co., Ltd., Qingdao, China). A Büchi Sepacore System (pump manager C-615, pump modules C-605, and fraction collector C-660) (Büchi Labortechnik AG, Flawil, Switzerland) was used to perform medium-pressure liquid chromatography (MPLC). It was equipped with a column (400 mm × 7.4 mm i.d., 40−75 μm, flow rate 40 mL/min) filled with Chromatorex C-18 (Fuji

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Liensinine suppresses STAT3-dependent HK2 expression through elevating SHP-1 to induce apoptosis in hepatocellular carcinoma cells *in vitro* and *in vivo*

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ABSTRACT

Liensinine is an alkaloid from the embryos of *Nelumbo nucifera* Gaertn. Here, we revealed that liensinine induces hepatocellular carcinoma (HCC) cell apoptosis. Accumulation of ROS participates in liensinine-induced apoptosis. Mechanically, liensinine inhibits the expression of hexokinase 2 (HK2) and metabolism of glucose through glycolysis. In addition, liensinine increases SHP-1 expression, impairs STAT3 transactivity, and declines the binding between STAT3 and HK2 promoter. Loss of function analysis revealed that upregulation of SHP-1 is a critical event mediating liensinine-induced inhibition of the STAT3/HK2 cascade. Moreover, knockdown of SHP-1 abrogates liensinine-provoked glycolysis inhibition, ROS generation, and subsequent cell apoptosis. Animal studies showed that liensinine induces transplanted H22 cell apoptosis *in vivo* with few toxic effects on the host. Consistent with the *in vitro* data, liensinine modulates the SHP-1/STAT3/HK2 axis *in vivo*. Our findings support considering liensinine as a novel functional food ingredient applied in clinical HCC treatment.

1. Introduction

Hepatocellular carcinoma (HCC), the most frequent type of intrahepatic cancer, is the fifth most common cancer and the third leading cause of mortality related with cancer worldwide (Di Poto et al., 2018). Surgical operation, chemotherapy, radiation, and liver transplantation are standard clinical treatments against HCC. Although surgical intervention is considered to be the most effective strategies, HCC is generally diagnosed in later stages, as a result of its extended initiation and progression times. Consequently, only a relatively limited proportion of HCC patients are eligible for surgery (Mittal et al., 2016), and the majority of them have to rely on systemic chemotherapies (Lyu et al., 2018). A series of compounds has been approved for HCC chemotherapy, including 5-fluorouracil (5-FU), sorafenib, and cisplatin, but their prognosis is often hampered by drug resistance of HCC cells and a range of toxic impacts on the patients. Therefore, it is still imperative to search for novel chemical entities for the chemotherapeutic treatment of HCC.

Aberrant reprogramming of glucose catabolism is a fundamental characteristic of HCC. In HCC cells, production of cellular energy is mainly driven by glycolysis, rather than oxidative phosphorylation, even in the presence of sufficient oxygen, leading to increased uptake of glucose and production of lactate. This phenotype confers a survival advantage on HCC cells by reducing the production of reactive oxygen species (ROS), a series of toxic byproduct of oxidative phosphorylation (DeBerardinis & Chandel, 2016; Lee et al., 2017). Previous studies revealed that suppression of glycolysis in HCC cells gives rise to surges of intracellular ROS and subsequent reduction of cell viability (Jin et al., 2017; Shen et al., 2013). These findings indicated that inhibition of glycolysis can be a feasible strategy in the treatment of HCC.

Signal transducer and activator of transcription (STAT) is a family of transcription factors participating in the regulation of many aspects of biological processes. Among this family, STAT3 has received more attentions than other members, since it is expected to be a pathway that connects inflammation to carcinogenesis (Kim, Yi, & Ye, 2016). In resting state, STAT3 are dephosphorylated at Tyr705 and located in cytoplasm. STAT3 can be phosphorylated by Janus kinases at Tyr705. Phosphorylated STAT3 undergoes dimerization and translocates to the nucleus in which it promotes the transcription of its responsive genes (Mohan et al., 2014). For instances, STAT3 is involved in the transcription initiation of hexokinase 2 (HK2) which is a rate-limiting enzyme catalyzing the first irreversible step of glycolysis (Jiang et al.,

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Abbreviations: HCC, hepatocellular carcinoma; HK2, hexokinase 2; ROS, Reactive oxygen species; SHP-1, SH2 domain-containing protein tyrosine phosphatase-1; STAT3, signal transducer and activator of transcription 3

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Tibetan medicine Kuan-Jin-Teng exerts anti-arthritic effects on collagen-induced arthritis rats via inhibition the production of pro-inflammatory cytokines and down-regulation of MAPK signaling pathway

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ARTICLE INFO

Keywords:
Tinospora sinensis (Lour.) Merr
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ABSTRACT

Background: The stems of *Tinospora sinensis* (Lour.) Merr commonly named “Kuan-Jin-Teng” in Chinese, have been used to treat rheumatoid arthritis as a Tibetan medicine.
Purpose: The effects of the EtOAc fraction of ethanolic extract from the stems of *T. sinensis* (KJT) on the pro-inflammatory cytokines and MAPK pathway were studied in collagen-induced arthritis (CIA) model.
Study design: Anti-arthritic activity of KJT was investigated in CIA model.
Methods: The chemical constituents of KJT were analyzed by LC-MS and HPLC. The CIA model was established with injecting the bovine CII emulsified in Freund's adjuvant in Wistar rats. Several doses of KJT (50.0, 100.0 and 200.0 mg/kg) were administrated via oral gavage to CIA rats daily for 4 weeks. The anti-arthritic activity of KJT was investigated by clinical arthritis scoring, paw swelling inspection and hyperalgesia measurement, as well as radiological and histological analysis in CIA rats. The impacts of KJT on the activation of MAPK pathway, production of pro-inflammatory cytokines (TNF-α, IL-1β and IL-17) in ankle joints, serum, and spleen in CIA rats were examined by western blot, immunohistochemical staining, ELISA, and quantitative real-time PCR respectively. Lastly, the effects of KJT on production of the nitric oxide (NO) and pro-inflammatory cytokines as well as the regulation of the phosphorylation of p38 and Erk were detected in lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophage cells.
Results: KJT significantly alleviated the paw swelling, hyperalgesia and arthritic severity, and reduced the synovial tissue proliferation and inflammatory cell infiltration in the CIA rats. Moreover, KJT suppressed the production of TNF-α, IL-1β, and IL-17 in ankle joints, serum, and spleen and reversed the up-regulation of the phosphorylation of p38 and Erk in CIA rats. KJT was also demonstrated to inhibit the production of NO and pro-inflammatory cytokines (TNF-α, IL-1β and IL-6), and phosphorylation of p38 and Erk in LPS-stimulated RAW264.7 cells.
Conclusion: These results suggest the mechanisms of KJT performing its anti-arthritis effect may be attributed to inhibiting the production of pro-inflammatory cytokines and down-regulating the MAPK signaling pathway.

Introduction

Rheumatoid arthritis (RA) as a chronic autoimmune disease mainly targets the synovial membrane, cartilage, and bone, and leads to reduced physical function and decreased quality of life (McInnes and Schett, 2011). The signs and symptoms of RA may typically result from synovitis, a direct development and progression of inflammatory response of the synovial membrane within joints (Mcinnes and

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Abbreviations: CIA, Collagen-induced arthritis; DMARDs, Disease-modifying anti-rheumatic drugs; Erk, Extracellular signal-regulated kinase; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinases; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NO, Nitric oxide; NSAIDs, Nonsteroidal anti-inflammatory drugs; RA, Rheumatoid arthritis

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γ-Oryzanol alleviates acetaminophen-induced liver injury: roles of modulating AMPK/GSK3β/Nrf2 and NF-κB signaling pathways†

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Acetaminophen (APAP) overdose is a major cause of drug-induced liver injury worldwide. Our current study was performed to assess the potential protective effects of γ-oryzanol (ORY) on APAP-induced liver injury in mice and explore the underlying molecular mechanisms. We unveiled that ORY alleviated the APAP-induced death of HL-7702 hepatocytes *in vitro* and liver injury in mice. Moreover, ORY promoted the nuclear translocation of Nrf2, increased the expressions of Nrf2-downstream antioxidative enzymes, including HO-1, NQO1, GCLC, and GCLM, and thereby restrained APAP-induced oxidative stress in hepatocytes. Moreover, ORY modulated the AMPK/GSK3β axis that acts upstream of Nrf2 in hepatocytes. Compound C, an inhibitor of AMPK, prevented the ORY-mediated activation of Nrf2 and protection against APAP toxicity in HL-7702 hepatocytes. Additionally, in the liver of mice receiving APAP, ORY suppressed the nuclear translocation of the NF-κB p65 subunit, downregulated the expressions of iNOS and COX-2, and reduced the levels of pro-inflammatory factors including TNF-α, IL-1β, IL-6, and NO. Taken together, our findings revealed that ORY is capable of ameliorating APAP-induced liver injury. The modulation of AMPK/GSK3β/Nrf2 and NF-κB signaling pathways is implicated in the hepatoprotective activity of ORY.

1. Introduction

Liver injury induced by drug abuse is becoming a major reason for worldwide clinical acute liver injury. Acetaminophen (APAP) is an approved and widely used antipyretic and analgesic drug, but overdose of APAP triggers acute liver injury or even fatal liver failure.[1,2] However, few effective treatments for APAP-provoked liver injury are available nowadays. Thus, there is an urgent need to identify new therapeutic or preventive agents for APAP detoxification.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor which is involved in the regulation of intracellular antioxidant reactions. Upon the occurrence of oxidative stress, Nrf2 translocates into the nucleus, interacts with the antioxidant response element located in promoters of Nrf2-responsive genes, and initiates their transcription.[3] Additionally, Nrf2 is also controlled by an array of upstream signals, including AMP-activated kinase (AMPK) and glycogen synthase kinase 3β (GSK3β).[4] Nrf2 boosts the transcription initiation of a series of antioxidant genes, including heme oxygenase-1 (HO-1), NAD(P)H dehydrogenase 1 (NQO1), as well as the catalytic and modified subunit of glutamate–cysteine ligase (GCLC and GCLM).[5] Elevated expressions of these enzymes are propitious to combat against intracellular oxidative stress arising from exogenous toxic substances or endogenously.[6,7] Previous studies unveiled that Nrf2-deficient mice are highly susceptible to the hepatotoxicity of APAP,[8,9] whereas mice with Nrf2 gain-of-function mutation are resistant to APAP-provoked liver injury.[10] Therefore, activation of Nrf2 can be a feasible strategy to ameliorate the hepatotoxicity of APAP.

More and more attention has been paid to natural compounds from food components as a potential resource of hepatoprotective agents.[11–13] γ-Oryzanol (ORY) is a mixture of ferulic acid esters with phytosterols isolated from rice bran oil.[14,15] Nowadays, ORY is mainly used in the treatment of autonomic dysfunction and menopausal syndrome clinically.[16] Moreover, ORY is also demonstrated to have the capacity of modulating metabolic syndrome, inhibiting oxidative stress, and delaying senescence.[17,18] In human embryonic kidney 293 cells, ORY dramatically activated Nrf2 and repressed H_2O_2-induced intracellular oxidative stress.[19] However, it remains poorly understood whether ORY is able to alleviate liver injury caused by APAP. Thus, this study was performed to evaluate the potential protective effects of ORY on APAP-induced liver injury and explore the underlying molecular mechanisms.

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Article

Precise Structure and Anticoagulant Activity of Fucosylated Glycosaminoglycan from *Apostichopus japonicus*: Analysis of Its Depolymerized Fragments

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Abstract: *Apostichopus japonicus* is one of the most economically important species in sea cucumber aquaculture in China. Fucosylated glycosaminoglycan from *A. japonicus* (AjFG) has shown multiple pharmacological activities. However, results from studies on the structure of AjFG are still controversial. In this study, the deaminative depolymerization method that is glycosidic bond-selective was used to prepare the depolymerized products from AjFG (dAjFG), and then a series of purified oligosaccharide fragments such as tri-, hexa-, nona-, and dodecasaccharides were obtained from dAjFG by gel permeation chromatography. The 1D/2D NMR and ESI-MS spectrometry analyses showed that these oligosaccharides had the structural formula of L-FucS-α1,3-D-GlcA-β1,3-{D-GalNAc$_{4S6S}$-β1,4-[L-FucS-α1,3-]D-GlcA-β1,3-}$_n$-D-anTal-diol$_{4S6S}$ (n = 0, 1, 2, 3; FucS represents Fuc$_{2S4S}$, Fuc$_{3S4S}$, or Fuc$_{4S}$). Thus, the unambiguous structure of native AjFG can be rationally deduced: it had the backbone of {-4-D-GlcA-β1,3-D-GalNAc$_{4S6S}$-β1-}$_n$, which is similar to chondroitin sulfate E, and each D-GlcA residue in the backbone was branched with a L-FucS monosaccharide at *O*-3. Bioactivity assays confirmed that dAjFG and nonasaccharides and dodecasaccharides from AjFG had potent anticoagulant activity by intrinsic FXase inhibition while avoiding side effects such as FXII activation and platelet aggregation.

Keywords: *Apostichopus japonicus*; fucosylated glycosaminoglycan; oligosaccharide; unambiguous structure; anti-Fxase

1. Introduction

Sea cucumber *Apostichopus japonicus* (or *Stichopus japonicus*) is widely distributed in the northwest Pacific, e.g., northern coast of China and almost all coastal areas of Japan, and has become one of the most popular sea cucumber species around the world due to its high value as a marine tonic [1]. Studies on this marine animal showed that it contains valuable nutrients, such as collagens, peptides, amino acids, sphingolipids, and polysaccharides [2]. Fucosylated glycosaminoglycan (FG) and fucan sulfate (FS) are the two main polysaccharides found in the body wall of sea cucumber. FG is a structurally distinctive glycosaminoglycan derivative containing fucose sulfate (FucS) branches found

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Inverse-Electron-Demand [4+2]-Cycloaddition of 1,3,5-triazinanes: Facile Approaches to Tetrahydroquinazolines

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. An unprecedented inverse-electron-demand [4+2] cycloaddition reaction of *in situ* generated aza-*o*-quinone methides with 1,3,5-triazinanes has been developed under mild conditions, providing an efficient and mild approach to synthesize tetrahydroquinazolines in high yields (up to 99%) with excellent functional group tolerance. This protocol represents the first example of inverse-electron-demand [4+2] cycloaddition reaction of 1,3,5-triazinanes.

Keywords: Inverse-Electron-Demand; [4+2] Cycloaddition reaction; 1,3,5-triazinanes; Aza-*o*-quinone methides; Tetrahydroquinazolines

Tetrahydroquinazoline and 2,3-dihydroquinazolin-4(1*H*)-one skeletons constitute important structural motifs in natural products (e.g., Luotonin A[1] and Anisotine[2]) and pharmaceutically active compounds (Figure 1) such as butyrylcholinesterase inhibitor,[3] CCKA antagonist (Asperlicin D),[4] and clinical drug non-small cell lung cancer inhibitor (Erlotinib).[5] Therefore, the development of novel methods to construct tetrahydroquinazolines is a high value goal due to their promising bioactivities.[6] Traditional approaches for the preparation of tetrahydroquinazoline derivatives are mainly limited to the routine condensation of various 2-(aminomethyl)anilines with aldehydes and ketones, only providing C2 substituted tetrahydroquinazolines.[7] To the best of our knowledge, however, the examples that can efficiently construct tetrahydroquinazolines are still limited.[8] Seidel developed a 1,6-hydrogen transfer based ring-fused aminals of nitrogen heterocycles to construct tetrahydoquinazolines (Scheme 1).[9] Recently, Sun and co-workers reported [4+2]-cycloaddition of copper-allenylidenes with hexahydro-1,3,5-triazines to access chiral tetrahydroquinazolines.[10] Despite these splendid advances, the development of novel approaches for the assembly of biologically promising tetrahydroquinazolines remains highly desirable and challenging.

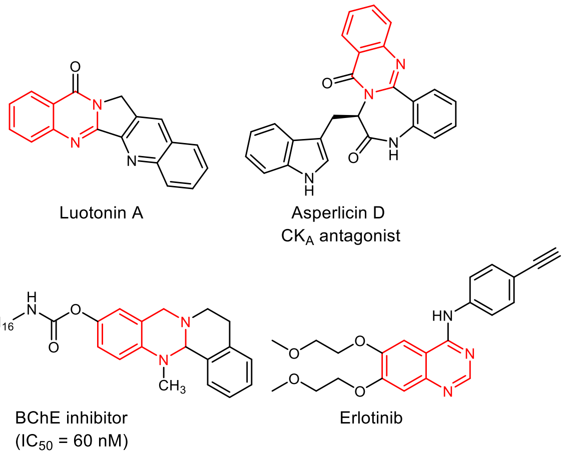

Figure 1. Examples of tetrahydroquinazoline and 2,3-dihydroquinazolin-4(1*H*)-one derivatives in bioactive compounds

1,3,5-triazinanes, first introduced by Reinfield in 1902,[11] were widely utilized as surrogate of corresponding *N*-aryl formaldimines in the aminomethylation reactions with various nucleophiles.[12] During the past a few years, 1,3,5-triazinanes have attracted increasing attention in the synthesis of *N*-containing compounds. For example, Krische described the hydroaminomethylation of allenes/dienes by using 1,3,5-triazinanes as the surrogate of formaldimines.[13] Subsequently, Feng[14] and Kang[15] reported the asymmetric Mannich reaction of 1,3,5-triazinanes, respectively. Besides the aminomethylation protocols, 1,3,5-triazinanes were also employed as dipolar adducts to synthesize *N*-containing heterocycles in various cycloaddition reactions such as [3+2] cycloaddition,[16] [2+2+2] cycloaddition,[17] [3+2+2] cycloaddition,[18]

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Fluorescence paper-based sensor for visual detection of carbamate pesticides in food based on CdTe quantum dot and nano ZnTPyP

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ARTICLE INFO

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Paper-based sensor
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Quantum dots
Nano porphyrin
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ABSTRACT

The needing of rapid and sensitive detection method for pesticides is increasing, to facilitate its detection without complicated instruments. Herein, a novel paper-based senor was developed for the visual detection of three carbamate pesticides (metolcarb, carbofuran, and carbaryl) based on CdTe quantum dots (QDs) and nano zinc 5, 10, 15, 20-tetra(4-pyridyl)-21*H*-23*H*-porphine (nano ZnTPyP) with a "turn-off-on" mode. This fluorescence sensing model could be applied in the highly selective and sensitive detection of carbamate pesticides both by fluorescence spectrometry or paper-based sensors. Based on the extracted RGB color values of paper, the partial least squares regression (PLSR) was used to accurately quantify the concentrations of carbamate pesticides in different food matrices (apple, cabbage and tea water). This method featured in high speed, low price and high accuracy, and provided a new strategy for the detection of food safety.

1. Introduction

China is a major agricultural country, but also a major manufacturer of pesticides. Carbamate pesticides, as kinds of insecticides and herbicides, are extensively used to eradicate agricultural pests to increase crop yields. The residues of carbamate pesticides have been frequently found in food and environmental stuff due to their widespread use (Berman et al., 2017). These residues can enter the human body through inhalation, intake and in contact with skin, leading to a series of serious harm such as headache, memory loss, proximal muscle weakness and anorexia etc. (Sahoo et al., 2018). Therefore, there is an increasingly urgent need to develop rapid and sensitive analytical methods for the detection of low concentration of carbamate pesticides in the daily-consumed food and drinking water.

In recent years, numerous efforts have been taken to develop effective approaches for the determination of pesticides in food or drinking water. Liquid/gas chromatography coupled with mass spectrometry (da Costa Morais, Collins, & Jardim, 2018; Lehmann, Oltramare, & De Alencastro, 2018), electrochemical analysis (Uniyal & Sharma, 2018) and enzyme-linked immunosorbent assay (ELISA) (Piao et al., 2009) are well-developed for the detection of pesticides. Although these approaches prove to be highly selective and sensitive and allow for the detection of pesticides in complex samples, they involve expensive instruments, complex sample pretreatment and the need for skilled operators. Therefore, the widespread use of these traditional methods has been limited. The emerging chemical and biological sensing methods have been successfully applied to the detection of pesticides due to their high sensitivity and short analysis time (Supharoek,

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Abbreviations: $CdCl_2$, cadmium chloride; CTAB, hexadecyl trimethyl ammonium bromide; DM, deltamethyrin; DDVP, 2,2-dichlorovinyldimethyl phosphate; ELISA, enzyme-linked immunosorbent assay; FRET, fluorescence resonance energy transfer; FT-IR, Fourier transform infrared; LOD, limit of detection; LVs, latent variables; Na_2TeO_3, Sodium tellurite; NAC, *N*-acetyl-L-cysteine; $NaBH_4$, sodium borohydride; PET, photo-induced electron transfer; PLSDA, partial least squares discriminant analysis; PLSR, partial least squares regression; QDs, quantum dot; RMSEC, root mean squared error of the calibration; RMSEP, root mean squared error of the prediction; RSD, relative standard deviation; TEM, transmission electron microscopy; Tris, 3-hydroxymethyl-methane; ZnTPyP, zinc 5, 10, 15, 20-tetra(4-pyridyl)-21H-23H-porphine

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Environmentally Friendly Protocol for 2,3-Difunctionlization of Indole Derivatives

Wen-Wu Sun,* Na Chen, Ting-Ting Wei, Guo-Jing You, Hao Yang, Ji-Kai Liu,* and Bin Wu*

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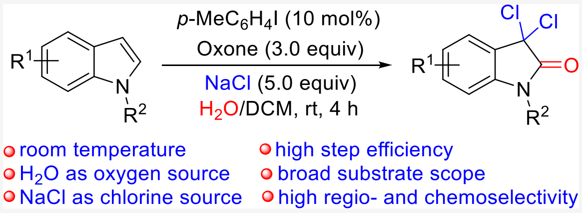
ABSTRACT: Environmentally friendly and highly regioselective C-3 dichlorination and C-2 oxidation of N-substituted indoles have been established using NaCl as a chlorine source and H_2O as an oxygen source. A series of 3,3-dichloro-2-oxindoles were obtained in moderate to excellent yields. The gram-scale synthesis and derivatization reaction were explored. The possible mechanism for this reaction was elucidated.



INTRODUCTION

3,3-Dihalo-2-oxindoles have been widely used in medicine and agriculture industries, and they are also important intermediates in organic synthesis.[1] Given the pharmaceutical relevance of this structural unit, the development of novel methodologies for the synthesis of 3,3-dichloro-2-oxindoles has attracted considerable attention from organic chemists in the past few years.[2] In 2005, Padwa reported a nucleophilic addition-[3,3]-sigmatropic rearrangement−cyclization reaction of vinyl sulfilimines with dichloroketene, producing diverse γ-lactam derivatives.[3] Murphy described (dichloroiodo)benzene ($PhICl_2$)-mediated *a*,*a*-dichlorination of isatin-3-*p*-tosylhydrazones or isatin-3-hydrazones, leading to the formation of 3,3-dichloroindolin-2-ones.[4] Phosphorus pentachloride (PCl_5),[1e,5] sulfonylchloride (SO_2Cl_2),[6] chlorosulfonic acid ($ClSO_3H$),[7] and tungsten(VI) chloride (WCl_6)[8] were used as chlorine sources for chlorination of isatins. The halogenation−decarboxylation of indolecarboxylic acids with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and phenyliodine diacetate (PIDA) was also achieved.[9] However, these transformations inherently required prefunctional substrates or highly toxic reagents. To address these issues, it is highly desirable to develop superior procedures for the construction of 3,3-dichloro-2-oxindoles from simple and readily available indoles.

In 2015, Finn reported only one example of the synthesis of 3,3-dichloro-2-oxindole from indole with NaN_3, NaClO, and AcOH.[10] Yu's group described hypervalent iodine-mediated chlorooxidation of indoles.[11] We recently demonstrated an efficient route to 3,3-dichloro-2-oxindoles from N-substituted indoles using $PhICl_2$ as an oxidation reagent and a chlorine source.[12] In 2017, our group employed aryliodide, selectfluor, and amine $(HF)_x$ to in situ generate $PhIF_2$ to synthesize 3,3-difluoro-2-oxindoles.[13] With our continuous interest in the synthesis of 3,3-dihalo-2-oxindoles, we herein report 4-iodotoluene-promoted water-phase C-3 dichlorination and C-2 oxidation of N-substituted indoles at room temperature. Compared with the previous reports, this method has several advantages: (1) water acts as an oxygen source and a solvent; (2) NaCl, an environmentally friendly reagent, is used as a chlorine source; (3) oxone, a nontoxic, cheap, and stable reagent, is used as an oxidant; and (4) the reaction conditions are mild and easy to operate.

RESULTS AND DISCUSSION

Our original idea was to develop a transition-metal-catalyzed $C(sp^2)$−H bond activation at the C-3 position of indoles with 2-aminopyrimidine as a directing group, but in the end, a metal-free synthetic strategy to oxindoles has been developed via the $PhICl_2$-mediated C-2 oxidation and C-3 dichlorination of N-substituted indoles.[12] In this project, we plan to further develop an easily handled aryliodide-catalyzed procedure for oxindole synthesis (Table 1). The desired product **2a** was obtained in 6% yield, along with 6% of **3a** in the presence of p-MeC_6H_4I (10 mol %) and oxone (1.1 equiv) (entry 1). Next, a series of cosolvents (DCM, DCE, MeCN, EtOAc, THF, MeOH, EtOH, CF_3CH_2OH, and AcOH) were screened (entries 2−10), giving rise to a slightly higher yield (15%) of **2a** when DCM was used. Increasing the loading of oxone led to a significant improvement of product **2a** in 85% yield (entries 11−13). The desired product **2a** was obtained in 83% when p-MeC_6H_4I was replaced by PhI (entry 14). Compound **3a** was the major product when the amount of NaCl decreased to 2.0 equiv. A slightly lower yield was obtained when KCl was used as the chlorine source (entry 17). Further attempts with other oxidants revealed that the performance of *m*-CPBA,

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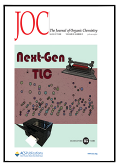

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Chrysanthemum ethanol extract induced loss of Kupffer cells *via* the mitochondria-dependent apoptotic pathway†

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Chrysanthemum has been viewed as an important traditional Chinese medicine (TCM) with a long history. Research studies indicated many potential pharmaceutical effects of chrysanthemum extract. However, hardly any investigation has been performed to describe its toxicity. In this study, acute application of chrysanthemum ethanol extract (CEE, 300 mg kg^{-1}) was found to induce apoptosis of hepatic Kupffer cells *in vivo*. CEE was also observed to induce apoptosis of RAW264.7 cells in a dose- and time-dependent manner. Further analysis using flow cytometry and western blotting revealed that CEE induced apoptosis of RAW264.7 cells *via* a mitochondria-dependent pathway. After a HPLC combined screening assay, we narrowed down the toxicity caused by the petroleum extract of CEE (CEE-PE, 66 μg mL^{-1}). *In vivo* effects of CEE-PE were also tested in mice. Additionally, nine potential toxic compounds were isolated and identified from CEE-PE. In all, we found that components with small polarities in CEE could induce apoptosis of Kupffer cells and macrophages *via* a mitochondrial dependent pathway, which might draw attention to the safety issues of everyday use of chrysanthemum.

Introduction

Chrysanthemum is the dried flower of *Chrysanthemum morifolium* (Ramat.), and has been viewed as an important traditional Chinese medicine (TCM) with a long history. According to the historical literature of TCM, chrysanthemum possessed "the taste" (a TCM term indicating the pharmacological characteristics of a certain medicine) of sweet and bitter, and had the effects of dispersing "liver wind" (a TCM term indicating a range of health conditions that occur suddenly in the liver), balancing "liver and eyesight", clearing "heat", and detoxifying.[1] Concurrent analysis of the components of chrysanthemum extract revealed that it contained flavonoids (including apigenin, luteolin, and quercetin), volatile oils (including mono- and sesqui-terpenes, their oxygen-containing derivatives, and aromatic compounds), organic acids (such as chlorogenic acids), polysaccharides (composed of galactose, glucose, mannose, and pectinose), and other minor components (vitamin C, selenium, and so on).[2,3] Modern pharmacological studies also suggested that chrysanthemum exhibited pharmaceutical functions such as cell protection,[4,5] and anti-colitis, anti-tumor,[6–8] anti-oxidation,[9] and anti-bacterial[10–13] effects. Moreover, the extract of chrysanthemum has been shown to be capable of preventing lipid accumulation in the liver.[14–16] Therefore, it has been widely used in medicines and everyday life in China.

For centuries, little was known about the potential side effects of chrysanthemum. A research in 2010 demonstrated that uptake of up to 15 g per kg body weight chrysanthemum extract does not cause any change to the main organs of rats.[17] However, as stated in the "*Materia Medica*", the historical literature of TCM, chrysanthemum should be cautiously used especially in patients with symptoms of "deficiency of Qi, cold in stomach, low appetite and diarrhea" (the description of symptoms in TCM referring to a lack of vital energy). As it has been stated in the theory of TCM that "liver" could be a primary target organ of chrysanthemum, we speculated that potential side effects, if any, would occur in the liver first. Fundamentally, the liver has been viewed as an indispensable hub for various physiological processes, including nutrient uptake and metabolism, sugar and lipid homeostasis, immune responses, and breakdown of xenobiotic compounds.[18] To accomplish these complex functions, many

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Paper-based sensor for visual detection of Ag^+ based on a “turn-off-on” fluorescent design

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ABSTRACT

A fluorescence paper-based sensor method by simply using thiomalic acid modified CdTe (TMA-capped CdTe) was proposed for visual detection of silver ions (Ag^+). Red-emission TMA-capped CdTe with a large amount of carboxyl groups on the surface could be combined with Ag^+ by electrostatic interaction, thus leading to the fluorescence quenching. It was found that the adding of amino acids contributed to fluorescence recovery by the leaving of Ag^+ on the surface of TMA-capped CdTe. Moreover, the more amino group, benzene and thiol group equipped in the structure of amino acid, the stronger fluorescence restoring of CdTe could be achieved. This fluorescence spectrometry method for Ag^+ showed low detection of limit with the value of 13.16 nmol/L, with no response to other heavy metals, which demonstrating its high sensitivity and high selectivity for Ag^+. More importantly, this paper-based sensor method combined with chemometrics could accurately identify and quantify different concentrations of Ag^+ in different complex matrices. This fast, economical, accurate and effective approach exhibited a new idea for the on-site detection of Ag^+, and was expected to be extended to the on-site detection of Ag^+ in biological and environmental fields.

1. Introduction

Thousands of tons of silver ions (Ag^+) are released into the environment through industrial waste and emissions every year. Through the accumulation of food chains, people can directly or indirectly consume foods and medicines contaminated by heavy metal. Ag^+ is designated as the most toxic and dangerous heavy metal contaminant [1], and because of its extensive application in industry, it poses a serious threat to the environment and human health. It is well known that Ag^+ can induce the generation of inactive thiol enzymes, and also bind to carboxyl, aminesand imidazolesgroups of various metabolites such as proteins with high molecular weight and metallothioneins, which do serious harm to human body [2,3]. Daily intake of Ag^+ can cause anemia, heart enlargement, growth retardation and degenerative changes in animals [4]. Human exposed to Ag^+ can trigger blood and urine silver excretion. Conventional analysis technologies, like inductively coupled plasma mass spectrometry (ICP-MS) and atomic absorption/emission spectroscopy [5,6], have been used to detect of trace heavy metals in water. However, these techniques require expensive instruments and complex sample preparation processes, resulting in limited application [5,6]. In contrast, spectroscopic methods, especially fluorescence spectroscopy, show unique potentials such as high selectivity, high sensitivity, and simple operation [7]. Fluorescence sensing methods based on “turn-off” or “turn-on” model have been widely employed for the detection of heavy metal ions [8]. Therefore, the selection of a suitable fluorescent probe is particularly important for the detection of heavy metal ions with high specificity and sensitivity.

Fluorescent nanomaterials have attracted the interest of researchers because they can be used in different fields such as chemical sensors, biosensors and biological imaging [10–12]. Among the fluorescent probes studied, quantum dots (QDs), as a kind of semiconductor nanocrystals, are obtained increasing attention due to its good stability, high biocompatibility, high quantum yield and low cytotoxicity [14].

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Dual-QDs ratios fluorescent probe for sensitive and selective detection of silver ions contamination in real sample

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ABSTRACT

Silver ions, as a commonly used industrial heavy metal, tends to deposit in the body and induce many diseases. In this work, modified CdTe QDs with green and red emission were synthesized to assemble dual-QDs, which could be efficient and selective utilized for Ag^+ determination through the electron transfer progress between surface functional group of dual-QDs and Ag^+, and the aggregation of Ag^+ on the surface of dual-QDs. Under the appropriate pH value and volume ratio, the interaction between the surface functional groups of assembled dual-QDs reduce the affinity of Hg^{2+} in this system. The fluorescent signal of dual-QDs simultaneously attenuation or enhancement in the same proportion remove the interference of Cu^{2+} and other metal ions. Therefore, this method can selectively detect Ag^+ without any masking agents. The linear region of detection was from 0 to 800 nmol/L ($R^2 > 0.998$), and low of detection (LOD) was 7.7 nmol/L, which could meet the corresponding standards of World Health Organization (WHO) and Environmental Protection Agency (EPA). This effective proposed dual-QDs ratios fluorescent probe has been applied to detect Ag^+ in real environment water, tea and *Citri Reticulatae Pericarpium* (CRP) water.

1. Introduction

With the rapid development of economic, science and technology, people's living standard has been greatly improved, however, it has also led to a series of environmental pollution problems, especially heavy metal pollution [1]. The release of heavy metals into the environment, even at low concentrations, will have serious harm on the surrounding environment and organisms [2]. According to the standards of the World Health Organization (WHO), presence of Ag^+ less than 0.05 ppm (0.05 g/mL) is safe for human body, any concentration above this could lead to various adverse health effects [3]. As is known to all, Ag^+, a rare but highly demanded and cost-effective metal catalyst, which is widely used in jewelry, pharmaceuticals, biomedicine, electronic equipment, photography, imaging and other industries [5–9]. However, researchers have shown that Ag^+ can damage the activity of enzymes and combine with various metabolites such as amine, imidazole and carboxyl, causing serious consequences to environmental safety and human health [10–12]. Therefore, to design and develop a simple, quick, sensitive and selective method to detect Ag^+ is of great significance for the environmental safety and human health.

Conventional methods including inductively coupled plasma atomic emission spectrometry, voltammetry, flame atomic absorption, ion-selective electrodes (ISEs) and electrochemical method, are extensively used to detect Ag^+ [13–17]. However, these methods have various shortcomings which often require complicated operation procedures, large sample volumes, sophisticated instrumentation, time-consuming analysis, specialized skills and interfered from closely related metal ions [18,19]. Spectroscopic method, especially fluorescence, has attracted great attentions because of its high sensitivity, selectivity, simplicity and does not use any expensive instrument or complicated operations and detection procedures [20]. In addition, it has been found that the detection of heavy metal ions by fluorescence method can well solve the shortcomings of other detection methods [21].

With the rapid development of nanometer science and technology, fluorescent nanomaterials have unique advantages in the design of various fluorescent sensors [22]. Quantum dots (QDs) are semiconductor nanomaterials which received considerable attention because of its unique properties, such as narrow and symmetry emission spectrum, wide excitation spectrum, relatively high quantum yield, large stokes shift effectively, good selectivity, high sensitivity and superior photochemical stability [23–25]. Particularly, some efforts have devoted to

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Article

Sesquiterpenoids from Cultures of the Basidiomycetes *Irpex lacteus*

Meng Wang, Jiao-Xian Du, Yang Hui-Xiang, Quan Dai, Ya-Pei Liu, Juan He, Yi Wang, Zheng-Hui Li, Tao Feng,* and Ji-Kai Liu*

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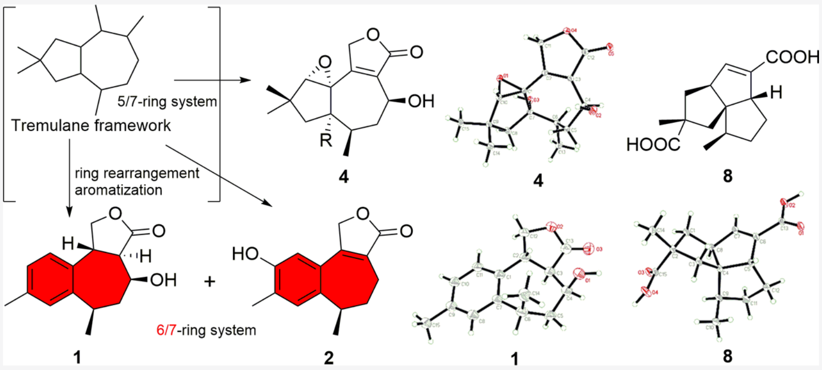

ABSTRACT: Eight previously undescribed sesquiterpenoids, tremutins A–H (**1**–**8**), together with three known ones (**9**–**11**), were isolated from cultures of the basidiomycetes *Irpex lacteus*. Structures of the new compounds together with absolute configurations were elucidated on the basis of extensive spectroscopic methods, as well as single-crystal X-ray diffractions and equivalent circulating density calculations. Compounds **1** and **2** possess an unusual 6/7-fused ring system that might be derived from a tremulane framework. Compounds **3**–**7** and **9**–**11** are tremulane sesquiterpenoids of which **4** and **5** are the first tremulane examples with a 1,2-epoxy moiety to be reported. Compounds **6**, **7**, **10**, and **11** possess weak activities to several human cancer cell lines. Compound **8** shows a weak inhibitory effect on NO production with a half maximal inhibitory concentration (IC_{50}) value of 22.7 μM. Compound **1** inhibits the lipopolysaccharide (LPS)-induced proliferation of B lymphocyte cells with an IC_{50} value of 22.4 μM, while **2** inhibits concanavalin A (Con A)-induced T cell proliferation and LPS-induced B lymphocyte cell proliferation with IC_{50} values of 16.7 and 13.6 μM, respectively.

Sesquiterpenoids are arguably the most abundant classes of natural products from both plants and microbes.[1] The rearrangements of the highly malleable 15 carbons resulted in a number of diverse backbones. Meanwhile, abundant structural variations led to diverse bioactivities. For instance, the potent antimalarial drug artemisinin from *Artemisia* plants,[2] is one of the most significant sesquiterpenoids. Irofulven,[3] a semi-synthetic derivative of illudin S from the mushroom *Omphalotus illudens*,[4] has been extensively investigated in numerous clinical trials and displayed significant activity against ovarian, prostate, and gastrointestinal cancers including hepatocellular tumors.[5−8]

Among numerous backbones of sesquiterpenoids, the tremulane-type sesquiterpenoids, featuring a 5/7 bicyclic carbon skeletal array, were first isolated in 1993 from the aspen tree rotting fungus *Phellinus tremulae*.[9] Over the last 10 years, tremulane-type sesquiterpenoids have been found from several fungal species including *Phellinus igniarius*, *Ceriporia lacerate*, *Conocybe siliginea*, and *Irpex lacteus*.[10−17] *I. lacteus* is a pathogenic wood-decaying fungus belonging to the family Polyporacea.[18] Its crude polysaccharide fraction has long been used as a traditional Chinese medicine for the treatment of chronic glomerulonephritis in clinic.[19] Our previous chemical investigations on the liquid fermentation of this fungus reported irlactins A–D that featured a novel 6/6 backbone, as well as a series of tremulane sesquiterpenoids.[16,17] Later, studies on the fruiting bodies reported a new skeletal triterpenoid irpexolidal with a 6/5/6/5 backbone.[20] Inspired by structural and bioactivity diversities, a further chemical study on this fungus following a large-scale fermentation in rice medium was performed. As a result, eight new sesquiterpenoids, tremutins A–H (**1**–**8**), together with three known tremulane sesquiterpenoids (**9**–**11**), were isolated from cultures of *I. lacteus* in rice medium. Their structures with the absolute configurations were elucidated by extensive

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Environmentally Friendly Protocol for 2,3-Difunctionlization of Indole Derivatives

Wen-Wu Sun,* Na Chen, Ting-Ting Wei, Guo-Jing You, Hao Yang, Ji-Kai Liu,* and Bin Wu*

Cite This: *J. Org. Chem.* 2020, 85, 10143−10151 Read Online

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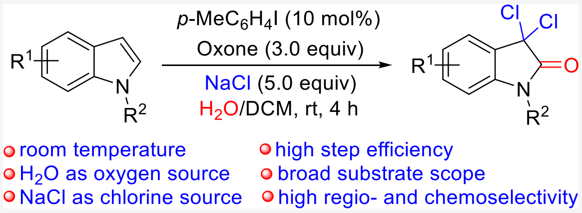
ABSTRACT: Environmentally friendly and highly regioselective C-3 dichlorination and C-2 oxidation of N-substituted indoles have been established using NaCl as a chlorine source and H_2O as an oxygen source. A series of 3,3-dichloro-2-oxindoles were obtained in moderate to excellent yields. The gram-scale synthesis and derivatization reaction were explored. The possible mechanism for this reaction was elucidated.



■ INTRODUCTION

3,3-Dihalo-2-oxindoles have been widely used in medicine and agriculture industries, and they are also important intermediates in organic synthesis.[1] Given the pharmaceutical relevance of this structural unit, the development of novel methodologies for the synthesis of 3,3-dichloro-2-oxindoles has attracted considerable attention from organic chemists in the past few years.[2] In 2005, Padwa reported a nucleophilic addition-[3,3]-sigmatropic rearrangement−cyclization reaction of vinyl sulfilimines with dichloroketene, producing diverse γ-lactam derivatives.[3] Murphy described (dichloroiodo)benzene ($PhICl_2$)-mediated *a*,*a*-dichlorination of isatin-3-*p*-tosylhydrazones or isatin-3-hydrazones, leading to the formation of 3,3-dichloroindolin-2-ones.[4] Phosphorus pentachloride (PCl_5),[1e,5] sulfonylchloride (SO_2Cl_2),[6] chlorosulfonic acid ($ClSO_3H$),[7] and tungsten(VI) chloride (WCl_6)[8] were used as chlorine sources for chlorination of isatins. The halogenation−decarboxylation of indolecarboxylic acids with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and phenyliodine diacetate (PIDA) was also achieved.[9] However, these transformations inherently required prefunctional substrates or highly toxic reagents. To address these issues, it is highly desirable to develop superior procedures for the construction of 3,3-dichloro-2-oxindoles from simple and readily available indoles.

In 2015, Finn reported only one example of the synthesis of 3,3-dichloro-2-oxindole from indole with NaN_3, NaClO, and AcOH.[10] Yu's group described hypervalent iodine-mediated chlorooxidation of indoles.[11] We recently demonstrated an efficient route to 3,3-dichloro-2-oxindoles from N-substituted indoles using $PhICl_2$ as an oxidation reagent and a chlorine source.[12] In 2017, our group employed aryliodide, selectfluor, and amine $(HF)_x$ to in situ generate $PhIF_2$ to synthesize 3,3-difluoro-2-oxindoles.[13] With our continuous interest in the synthesis of 3,3-dihalo-2-oxindoles, we herein report 4-iodotoluene-promoted water-phase C-3 dichlorination and C-2 oxidation of N-substituted indoles at room temperature. Compared with the previous reports, this method has several advantages: (1) water acts as an oxygen source and a solvent; (2) NaCl, an environmentally friendly reagent, is used as a chlorine source; (3) oxone, a nontoxic, cheap, and stable reagent, is used as an oxidant; and (4) the reaction conditions are mild and easy to operate.

■ RESULTS AND DISCUSSION

Our original idea was to develop a transition-metal-catalyzed $C(sp^2)$−H bond activation at the C-3 position of indoles with 2-aminopyrimidine as a directing group, but in the end, a metal-free synthetic strategy to oxindoles has been developed via the $PhICl_2$-mediated C-2 oxidation and C-3 dichlorination of N-substituted indoles.[12] In this project, we plan to further develop an easily handled aryliodide-catalyzed procedure for oxindole synthesis (Table 1). The desired product **2a** was obtained in 6% yield, along with 6% of **3a** in the presence of *p*-MeC_6H_4I (10 mol %) and oxone (1.1 equiv) (entry 1). Next, a series of cosolvents (DCM, DCE, MeCN, EtOAc, THF, MeOH, EtOH, CF_3CH_2OH, and AcOH) were screened (entries 2−10), giving rise to a slightly higher yield (15%) of **2a** when DCM was used. Increasing the loading of oxone led to a significant improvement of product **2a** in 85% yield (entries 11−13). The desired product **2a** was obtained in 83% when *p*-MeC_6H_4I was replaced by PhI (entry 14). Compound **3a** was the major product when the amount of NaCl decreased to 2.0 equiv. A slightly lower yield was obtained when KCl was used as the chlorine source (entry 17). Further attempts with other oxidants revealed that the performance of *m*-CPBA,

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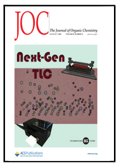

Research Article

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Rapid detection of five pesticide residues using complexes of gold nanoparticle and porphyrin combined with ultraviolet visible spectrum

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Abstract

BACKGROUD: Pesticides are widely used to control insect infestation and weeds in agriculture. However, concerns about the pesticide residues in agricultural products have been raised in recent years because of public interest in health and food quality and safety. Thus, rapid, convenient, and accurate analytical methods for the detection and quantification of pesticides are urgently required.

RESULTS: A nanohybrid system composed of gold nanoparticles (AuNPs) and tetrakis(*N*-methyl-4-pyridiniumyl) porphyrin (TMPyP) was used as an optical probe for the detection and quantification of five pesticides (Paraquat, Dipterex, Dursban, methyl thiophanate and Cartap). The method is based on the aggregation effect of pesticides on the carboxyl group modified by AuNPs. Subsequently, with the help of particle swarm optimization-optimized sample weighted least squares-support vector machine (PSO-OSWLS-SVM), all the pesticides could be successfully quantified. In addition, partial least squares discriminant analysis (PLS-DA) was applied and the five pesticides were satisfactorily recognized based on data array obtained from the ultraviolet visible (UV-visible) spectra of AuNP–TMPyP complex. Furthermore, the quantitative and qualitative analysis of the five pesticides could be also achieved in the complex real samples, in which all the relative standard deviations (RSDs) were less than 0.3‰ and all the linear absolute correlation coefficients were more than 0.9990. Furthermore, recognition rate of the training set and the prediction set based on multiplicative scatter correction (MSC), or second-order derivative (2nd derivative) UV-visible spectra in PLS-DA model could reach 100%.

CONCLUSION: This method was successfully applied for the rapid and accurate determination of multicomponent pesticide residues in real food samples.

Supporting information may be found in the online version of this article.

Keywords: AuNP–TMPyP complex; nanometer effect; chemometrics; pesticides detection

INTRODUCTION

Pesticides are widely used to control insect infestation and weeds in agriculture, as well as various pests and disease carriers in houses, malls, offices, and streets.[1-4] Concerns about pesticide residues in agricultural products associated with their exposure (for example, after the application of herbicides, insecticides, and antiseptic substances) have been raised in recent years because of increasing health concerns and public interest in food quality and safety.[5,6] Everyday foodstuffs, such as vegetables, fruits, teas, and even traditional Chinese herbs, can contain pesticide residues because pesticides are often used to improve the visual aspect, as well as profitability, in the agricultural industry.[7-10] Studies have shown that in addition to acute poisoning,[11,12] long-term consumption of food containing excessive pesticide residues is one of the main risks leading to developmental delay in the fetal nervous system and the development of Alzheimer's disease.[13,14] Widely used identification and quantification of pesticides are

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Research Article

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A novel fluorescence sensing strategy based on nanoparticles combined with spectral splicing and chemometrics for the recognition of *Citrus reticulata* 'Chachi' and its storage year

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Abstract

BACKGROUND: The fluorescence sensing method has been increasingly applied in food quality control because it is fast and sensitive. However, its application in quality evaluation is challenging. Using Citri Reticulatae Pericarpium (CRP; dried mandarin orange peel) as an example, we developed a simple and low-cost fluorescence sensing strategy based on nanoparticles combined with spectral splicing and chemometrics for quality evaluation. This method can recognize *Citrus reticulata* 'Chachi' (CRC) from other CRP cultivars and further identify the storage year.

RESULTS: Nanogold particles and cadmium telluride quantum dots were selected as nanosensors and mixed with aqueous extracts of CRP separately to produce fluorescence quenching spectra. Then, a simple spectral splicing procedure was applied to obtain spliced spectra comprising different combinations of the self-fluorescence and fluorescence quenching spectra of CRP samples. With the aid of partial least-squares discriminant analysis, the new strategy achieved recognition rates of 100% in distinguishing CRC samples from other CRP samples, as well as recognition rates of 100% for the training set and 98.04% for the prediction set in the discrimination of the storage year of CRC. The recognition mechanism is dominated by interactions between the nanoparticles and the fluorescent components in the CRP samples, but other components also have concurrent effects.

CONCLUSIONS: This novel fluorescence sensing strategy not only provides a new tool for the quality evaluation of CRC but also has good prospects for the authentication and traceability of other foods and herbs. Crucially, the developed method is convenient, simple and effective.

Supporting information may be found in the online version of this article.

Keywords: fluorescence nanosensor; spectral splicing; *Citrus reticulata* 'Chachi'; quality evaluation; chemometrics

INTRODUCTION

Citri Reticulatae Pericarpium (CRP), which is made from the dried peel of mandarin oranges, has been used as a kind of popular tea, snack, traditional spice and flavoring for centuries. More recently, CRP has been developed into a variety of functional foods.[1] The cultivars of CRP mainly are divided into *Citrus reticulata* 'Chachi' (CRC) which is produced in Xinhui County (Guangdong Province, China) and *Citrus reticulata* Blanco (CRB) which grows in other geographical locations. CRC is the most famous cultivar of CRP and is often considered to have better fragrance and pharmacological effects.[2]

It is believed that the aging of CRC has an effect on its quality, and a common saying is 'the longer the CRC is stored, the higher is the quality'.[3,4] As a result, the cost of CRC is higher than that of CRB and older CRC is much more expensive than younger CRC. However, the morphologies of CRC, aged CRC and CRB are similar, thereby making discrimination difficult. In China, because of high demand, the CRP market suffers from significant food fraud,

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Chemical constituents and their cytotoxicities from mushroom *Tricholoma imbricatum*

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Triterpenoids
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ABSTRACT

Two undescribed triterpenes, tricholimbrins A and B, three undescribed steroids, tricholimbrins C–E, one undescribed 4-chromanone derivative, along with 27 known compounds were isolated from fruiting bodies of the mushroom *Tricholoma imbricatum*. Tricholimbrins A and B are two polycyclic triterpenoids with a carbon degradation, while tricholimbrin C is a ring-rearranged steroid containing an aromatic moiety that might be derived from an ergosterol. Isocyathisterol, 3*β*,15*α*-dihydroxyl-(22*E*,24*R*)-ergosta-5,8(14),22-trien-7-one, demethylincisterol A_3, and volemolide showed cytotoxicities to six human cancer cell lines. 3*β*-Hydroxyl-(22*E*,24*R*)-ergosta-5,8,22-trien-7,15-dione and 3*β*-hydroxyl-(22*E*,24*R*)-ergosta-5,8,22-trien-7-one showed preferable cytotoxicities against HL-60 while chaxine C and volemolide showed preferable cytotoxicities against A-549, with IC_{50} values less than 10 μM.

1. Introduction

Tricholoma is a genus of agaric fungus with large and fleshy fruiting bodies, classified in the family Tricholomataceae of the Division Basidiomycotina. The genus comprises about more than 200 species growing throughout the world, of which about 90 species were recorded in China up to date (Deng et al., 2004). Our previous chemical research of *Tricholoma* fungi revealed a series of structurally diverse terpenoids and steroids, such as triterpenoids terreolides A–F (Yin et al., 2014) and saponaceolides H–S (Feng et al., 2015; Yin et al., 2014) and meroterpenoids terreumols A – D (Yin et al., 2013) from *Tricholoma terreum* (Schaeff.) P. Kumm., novel terpenoids tricholopardins A and B (Feng et al., 2019) from *Tricholoma pardinum* (Pers.) Quél, and novel ergosterol derivatives matsutakone and matsutoic acid (Zhao et al., 2017) from *Tricholoma matsutake* (S. Ito & S. Imai) Singer. In addition to the complex compounds, the previous studies also proved that many *Tricholoma* terpenoids exhibited significant bioactivities. For instance, terreumols A, C, D and saponaceolide Q showed certain cytotoxic activities to several human cancer cell lines (Feng et al., 2015; Yin et al., 2013). Tricholopardins A and B displayed significant anti-inflammatory activities (Feng et al., 2019). Moreover saponaceolides B and M were identified as mushroom toxins that increased serum creatine kinase levels in mice (Yin et al., 2014). Of the isolates, the total syntheses of terreumols A and C have been completed (Frichert et al., 2016) to solve the structural problem of their unique 5/6/7 trioxaspiroketal system.

Tricholoma imbricatum (Fr.) P. Kumm. is an ectomycorrhizal fungus with a wide distribution in Sichuan, Shanxi, Gansu, and Qinghai provinces of China. As inspired by the properties of *Tricholoma* natural products, a phytochemical study on the fruiting bodies of *T. imbricatum* led to the isolation of two 5,5-*cis*-fused cyclic lactone-containing lanostane triterpenes with a carbon degradation tricholimbrins A (**1**) and B (**2**), one ring-rearranged ergosterol derivative tricholimbrin C (**3**), one highly conjugated ergosterol tricholimbrin D (**4**), one new ergosterol tricholimbrin E (**5**), a new 4-chromanone (**6**), together with 27 known compounds (Fig. 1). The structures with absolute configurations were elucidated by extensive MS and NMR spectroscopic methods, as well as the single crystal X-ray diffraction, optical rotation and ECD calculations. All compounds were evaluated for their cytotoxicities against six human cancer cell lines including HL-60, SMMC-7721, A-549, MCF-7, SW480, and K562. This paper reports the isolation, structural elucidation, and cytotoxicities of these isolates.

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Acid-promoted synthesis and photophysical properties of substituted acridine derivatives†

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A simple and efficient synthetic protocol for the preparation of acridinium esters and amides through the cyclization and esterification or amidation of isatins with alcohols or amines as nucleophiles in the presence of CF_3SO_3H is established. A series of polycyclic acridine derivatives bearing large π-conjugated systems were obtained in high yields, including some key intermediates for the synthesis of biologically active molecules. The photophysical properties of these synthesized acridines were investigated, demonstrating that the sulfur heterocyclic acridine **9w** was obtained in a high quantum yield.

Introduction

Acridine derivatives exhibit many biological activities, exemplified by compounds **1–6** in Fig. 1, and have therefore been attracting the attention of organic chemists.[1,2] Due to their importance in human health care and many other applications, significant effort has been devoted to developing efficient synthetic methodologies for the preparation of acridine derivatives over the past few decades.[3] Most methods for the synthesis of acridines involve several types of ring closure reactions, including the reaction of arynes with a number of partners, such as 2-aminoaryl ketones and hydrazones.[4] The cross-coupling reactions of aromatic amines or azide compounds with suitable partners have provided various substituted acridines under catalysis by Pd or Rh.[5] The intramolecular electrophilic cyclization of diphenylamine-2-carbonyls or 2,6-diaryl-3,5-dialkynylpyridines has also led to the formation of acridines.[6] A thermal rearrangement reaction of indazolium salts afforded 9-amino-substituted acridines.[7] Although there are some reports on the synthesis of acridine-9-carboxylic acids by the treatment of isatin with a base, both substrate scope and functional group tolerance are very limited.[8] Here, we report an efficient, one-step synthetic method to synthesize various 9-ester or amide substituted acridines from commercially available isatins in the presence of an acid promoter. Furthermore, to explore their potential applications in materials science, the photophysical properties of these synthesized acridines were investigated.

Results and discussion

We first examined the reaction of 1-phenylisatin **7a** in the presence of 2.0 equivalents of $BF_3 \cdot Et_2O$ in MeOH at 100 °C for 36 h. To our delight, the methyl acridine-9-carboxylate **9a** was obtained in 10% yield (Table 1, entry 1), and its structure was unambiguously confirmed by X-ray diffraction analysis.[9] We then investigated the solvent effect on the reaction and found that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was the best solvent (Table 1, entries 2–5). When the amount of $BF_3 \cdot Et_2O$ was increased to 5.0 equivalents, the yield of product **9a** increased from 40% to 54% (Table 1, entries 5 and 6). Next, we tested some other Lewis acids in the reaction. All three Lewis acids ($Al(OTf)_3$, *p*-$TsOH \cdot H_2O$ and CF_3SO_3H) promoted the reaction. The reaction in the presence of 7.0 equivalents of *p*-$TsOH \cdot H_2O$ or 2.0 equivalents of CF_3SO_3H afforded the acri-

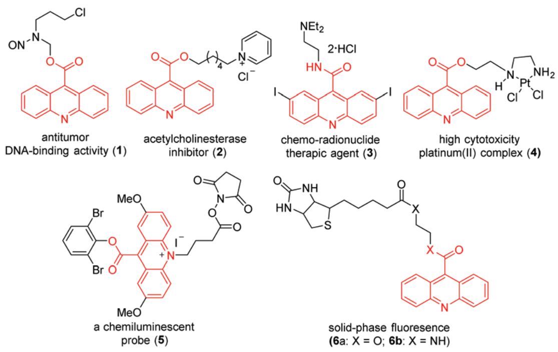

Fig. 1 Biologically active compounds with acridinium ester and amide derivatives.

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† Electronic supplementary information (ESI) available: All experimental details, details of chemical synthesis, additional figures, tables and crystallographic data. CCDC 1960437 and 1968988. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob01824d

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Diterpenes with bicyclo[2.2.2]octane moieties from the fungicolous fungus *Xylaria longipes* HFG1018†

He-Ping Chen,[a,b] Jing Li,[a,b] Zhen-Zhu Zhao,[c] Xinyang Li,[d] Shui-Lin Liu,[a] Qing-Yuan Wang[a] and Ji-Kai Liu*[a,b]

Xylarilongipins A (1) and B (2), two diterpenes each with an unusual cage-like bicyclo[2.2.2]octane moiety, along with their biosynthetic precursor hymatoxin L (3), were isolated from the culture broth of the fungicolous fungus *Xylaria longipes* HFG1018 inhabiting in the medicinal fungus *Fomitopsis betulinus*. The structures and absolute configurations of the three compounds were established by extensive spectroscopic analysis and single-crystal X-ray diffraction analysis. Xylarilongipin A (1) displayed moderate inhibitory activity against the cell proliferation of concanavalin A-induced T lymphocytes and lipopolysaccharide-induced B lymphocytes with IC_{50} values of 13.6 and 22.4 μM, respectively. Additionally, the biosynthetic pathways for compounds 1–3 are discussed. This work not only corroborates the structure of the 9,16-cyclo-(18-nor-)isopimarane skeleton by single-crystal X-ray diffraction analysis for the first time, but also provides new insights into the biosynthetic origin of the unusual diterpene skeletons.

Introduction

Fungicolous fungi are a large group of organisms that colonize in other fungi and have parasitic, symbiotic, saprophytic, or even neutral relationships with the host. Fungicolous fungi sometimes cause serious diseases to cultivated mushrooms, which decrease their yield and quality.[1] The genus *Xylaria* is a group of ascomycetous fungi commonly growing on dead wood and always forming black stroma. The anamorphs of this genus of fungi are always found as plant endophytes, which are reported to be a rich source of natural products.[2] *Xylaria longipes*, an inedible fungus commonly known as "dead moll's fingers", was found to distribute in Europe, Asia, and North America. However, the secondary metabolite profiles of this kind of fungus were underexplored for a long time until several papers concerning its phytochemical studies were published recently and the reported structures xylaridines A–D have aroused great attention for natural product mining from this fungus.[3,4] Amongst the structures, xylaridine A possesses a 5/6/6/5/5 fused polycyclic system with a unique 2-azaspiro[4.4]nonane scaffold, while xylaridines C and D possess a centred thiopyran ring.

Diterpenoids are a family of terpenoids with various skeletons from plants, fungi, and marine organisms. Compared with the extensive examples of polyketide compounds from the order Xylariales, the diterpenes are relatively a small group with only two types of skeletons, the isopimaranes and sordarins, reported until now.[5] As a continuous program to explore natural products with promising activity from fungi, the culture broth of the fungus *X. longipes* which was isolated from the fruiting bodies of the medicinal mushroom *Fomitopsis betulinus* was chemically investigated. As a result, a new type of diterpene named xylarilongipin A (**1**) (Fig. 1), which was found to harbour an unusual 18-nor-9,16-cyclo-isopimarane skeleton, along with two biosynthetic congeners, xylarilongipin B (**2**) and hymatoxin L (**3**) (Fig. 1), were isolated and characterized. Herein, we report the isolation, structural elucidation, feasible

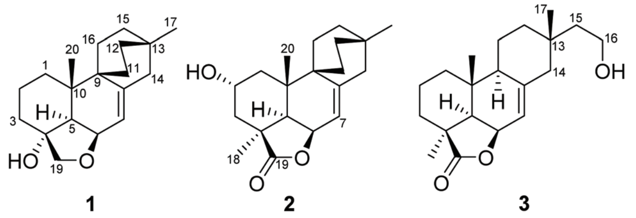

Fig. 1 Structures of compounds **1–3**.

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† Electronic supplementary information (ESI) available: The 1D & 2D NMR, MS, and crystallographic data of compounds 1–3. CCDC 1963364, 1963365 and 1977046. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob00220h

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A novel thioctic acid-carbon dots fluorescence sensor for the detection of Hg^{2+} and thiophanate methyl via S-Hg affinity

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ABSTRACT

Mercury ions and thiophanate methyl (TM), are common contaminants present in the environment and food products. These contaminants cause neurovirulence and carcinogenicity effect on the human body. Herein, thioctic acid-carbon dots (SCDs) was synthesized and applied in a fluorescent “turn-off–on” probe to detect Hg^{2+} and TM. The presence of other common metal ions and pesticides did not affect the response of the developed sensor. Further investigation revealed that the fluorescent “turn-off–on” model were static, wherein the “turn-off” was induced by an electron transfer effect, while the “turn-on” was caused by the formation of TM-Hg complexes. Under optimal conditions, the fluorescence sensor method exhibited limits of detection as low as 33.3 nmol/L and 7.6 nmol/L for Hg^{2+} and TM, respectively. The developed sensor was designed to detect Hg^{2+} and TM in real tap water, grape juice and Citri Reticulatae Pericarpium (CRP) water samples.

1. Introduction

Due to the rapid industrialization and economic development, considerable attention has been directed toward heavy metal and pesticide pollution. In particular, the formation of mercury (Hg) and thiophanate-methyl (TM) residues should be extensively investigated because these contaminants severely affect the human health and environment (Chowdhury, Mazumder, Al-Attas, & Husain, 2016; Li, Sun, Pu, & Jayas, 2017). In addition, there are serious concerns regarding Hg and TM contamination in the food industry, resulting in an overall loss of credibility and economic frustration. Hg contamination can arise from natural and industrial sources such as volcanic eruptions, fossil fuels, and mining, and the Hg contaminants can spread through the water, air, soil, and food products (Yang, Peng, Han, Song, & Wang, 2020). Exposure to Hg largely occurs via the consumption of Hg-contaminated agricultural, aquatic, and other food products, causing a variety of reproductive, physiological and biochemical abnormalities (Guo, Kang, Liang, & Zhang, 2020). Hg may exist in its elemental state, or as organic/ inorganic salts in the environment. Amongst all states, Hg^{2+} and its derivatives are particularly non-biodegradable and persistent, leading to the contamination of water, soil, and food products (Raicopol et al., 2020). In addition, Hg^{2+} can easily penetrate the skin or enter through the respiratory tract, leading to the irreversible disruption of immune, endocrine, and central nervous systems, thereby causing various health problems (Kim, Kabir, & Jahan, 2016).

Pesticide contamination in soil, water, and atmosphere can occur in various ways, and it impacts the food industry and environmental safety (Jia et al., 2020). TM is a highly effective broad-spectrum benzimidazole fungicide with low toxicity. TM residues can be detected in the soil and agricultural products, such as vegetables and fruits. TM and carbendazim (methyl benzimidazol-2-ylcarbamate) can be interconverted and both contaminants persist in crops for long durations, resulting in excessive pesticide residues in agricultural products. This poses a serious threat to human health as TM and carbendazim contamination can cause endocrine disruption, embryotoxic, and teratogenic effects (Jiang et al., 2017). Therefore, the development of a rapid, sensitive and selective

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Rapid and highly sensitive colorimetric biosensor for the detection of glucose and hydrogen peroxide based on nanoporphyrin combined with bromine as a peroxidase-like catalyst

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ABSTRACT

Peroxidase is a popular amplifier of biosensor signals, but its application is limited by chemical instability and expensive purification. We developed a sensitive, novel colorimetric biosensor to detect glucose and hydrogen peroxide (H_2O_2) using Zinc tetrakis (4-pyridinyl) porphyrin (ZnTPyP)-dodecyl trimethyl ammonium bromide (DTAB) nanoparticles (NPs) as peroxidase-like catalysts. ZnTPyP-DTAB NPs can oxidize colorless 3, 3', 5, 5'-tetramethylbenzidine to a blue product (652 nm) in the presence of H_2O_2 *via* electron transport between porphyrin and bromine. This peroxidation mechanism was further verified using quantum chemical calculations. The detection limits of the colorimetric ZnTPyP-DTAB NP sensor were 0.15 and 0.5 μmol L^{-1} for glucose and H_2O_2, respectively, and the linear range was 3–70 and 8–50 μmol L^{-1}, respectively. Recovery ratios of the biosensor in spiked human serum and saliva samples were 100 % ± 10 %. This simple method is robust, color stable, and reliable, thus providing an effective colorimetric biosensing platform for biomedical diagnosis.

1. Introduction

Peroxidases are a class of oxidoreductases that catalyze many chemical reactions through the H_2O_2-dependent single-electron oxidation of multiple substrates [1]. Peroxidases are components of many clinical diagnostic kits and commercial immunoassays [2]. Among them, horseradish peroxidase (HRP) is widely included in immunoassays to amplify biosensor signals [3]. However, the inherent instability, high cost of purification, and source restriction of natural enzymes limit their practical applications. Therefore, artificial enzymes are urgently required to function as natural enzyme mimics. During our investigation of the peroxidase properties of ferrosoferric oxide magnetic nano particles (NPs) [4,5], we became aware of a series of metal oxide or metal nanomaterials such as CuO NPs [6,7], CeO_2 NPs [8], PEG-MoS_2 nanoflowers [9], and Au/Ag/Pt NPs [10–13]. These nanomaterials have better flexibility, efficiency, substrate specificity, and stability under mild reaction conditions, compared with natural enzymes. Furthermore, heme and its assembly fluids also have similar properties [14]. These metal oxide or metal nanomaterials with peroxidase activity mimic the binding sites of natural enzymes and can improve catalytic activity and stability.

Porphyrin compounds are found in polymers and electroluminescent materials and are also applied as biomimetic enzymes in chemical catalysis and catalytic oxidation. Metal porphyrins can mimic many biological enzyme analogs such as cytochrome P450, myoglobin, and hemoglobin, thus catalytically activating molecular oxygen under relatively mild conditions. Moreover, metal porphyrins serve as substitutes instead of reducing agents for simulating mimic enzyme catalysts. However, few studies of metal-porphyrin NPs including (NiO-H_2TCPP) [15], CNPs-porphyrin [16], H_2TCPP-ZnS nanocomposites [17],

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Rapid and low-temperature synthesis of N, P co-doped yellow emitting carbon dots and their applications as antibacterial agent and detection probe to Sudan Red I

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ARTICLE INFO

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Yellow-emitting carbon dots
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ABSTRACT

The preparation of long-wavelength emitting carbon dots (CDs) with good antibacterial function and biosensing ability through element doping method is the hotspot of present researches. This paper reports the rapid synthesis of nitrogen and phosphorus co-doped long wavelength-emitting CDs (N, P-CDs, λ_{em} = 530 nm) under low reaction temperature (30 min, 60 °C). This method used glucose, polyethyleneimine and phosphoric acid as raw materials, and each raw material worked multi-functionally during the synthesis process. The impacts of raw materials and reaction parameters upon optical properties of prepared N, P-CDs have been studied, and the synthesis mechanism has been discussed. Meanwhile, N, P-CDs were used as antibacterial material with minimum inhibitory concentrations against *Staphylococcus aureus* and *Escherichia coli* at 7.5 $\mu g \cdot mL^{-1}$ and 0.5 $mg \cdot mL^{-1}$ respectively. The prepared CDs were also used to realize fluorescence imaging of *S. aureus*, and work as fluorescence probe to detect Sudan Red I with limit of detection at 43 nM.

1. Introduction

Due to their excellent optical properties, chemical stability and biological compatibility, carbon dots (CDs) have been widely applied in the fields like biochemical detection [1], optical device [2], biological imaging [3], drug delivery [4], and disease treatment [5]. The element doping in CDs [6–14] is the new-rising area of nanomaterial science and has attracted increasing interests from scientists because the doping of elements like nitrogen, sulfur, phosphorus and boron could effectively adjust the electronic energy level structures and some local chemical properties of prepared CDs [6], changing CDs into functional nanomaterials. Among these elements, the nitrogen could strongly combine with carbon atom because of its five valence electrons [7]. Phosphorus can works as n-type donor to change the electrons and the optical properties of CDs [8]. Therefore, the doping of N and P onto CDs would make more active sites and better optical properties for prepared CDs [9,12–15].

At present, researchers have chosen lots of materials as N and P sources for N, P co-doping CDs, including natural plant extracts [9], small biological molecules [6,10], aniline compounds [11–13], ammonia ($NH_3 \cdot H_2O$) [14], ethylenediamine (EDA) [15–17] and polyethyleneimine (PEI) [18] as nitrogen sources, and ammonium phosphate [19,20], phosphate [10], adenosine phosphate [10,21], and phosphoric acid (H_3PO_4) [9,11–13,15,17,18] as phosphorus sources. Wide range of options in raw materials make prepared N, P-CDs vary greatly in their properties. For instance, with sodium citrate as a carbon source, diammonium phosphate as both nitrogen and phosphorus source, Xu et al. [19] prepared blue-emitting N, P-CDs (170 °C, 6 h) with a quantum yield (QY) at 53%. Liu and his team acquired green-emitting N, P-CDs (QY at 9.6%) with glucose (Glc) as a carbon source, EDA as a nitrogen source and H_3PO_4 as a phosphorus source [15]. Zhao et al. prepared red-emitting N, P-CDs with *o*-phenylenediamine as both carbon and nitrogen source, and concentrated H_3PO_4 as phosphorus source (5 h, 160 °C, QY of CDs at 15%) [13]. Although the selection of raw materials and the optimization of synthesis conditions both determine the acquisition of high-quality N, P-CDs [17,19,22,23], most of studies focused on the optimization of synthesis conditions, including reaction time, temperature and raw material ratio [19,23]. The synthesis mechanism, especially the impacts of raw materials upon the properties of product [17,22], needs to be further explored, to reduce the randomness in raw material selection.

Bacterial infection, especially those caused by drug-resistant bacteria, has always been a severe problem in clinical treatment. Because of excellent biocompatibility, CDs have been regarded as ideal “candidate” for antibacterial materials [24–29]. Doped CDs, such as S-CDs [27], N-CDs [25,28], and Ga-CDs [29] have been discovered to have

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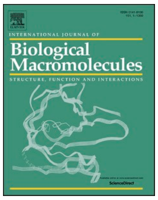

Five distinct fucan sulfates from sea cucumber *Pattalus mollis*: Purification, structural characterization and anticoagulant activities

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Sea cucumber
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ABSTRACT

Fucan sulfates from echinoderm possess characteristic structures and various biological activities. Herein, comprehensive methods including enzymolysis, ion-exchange chromatography and size exclusion chromatography lead to the purification of five fucan sulfates (FSI, FSII, FSIII, FSIV, FSV) from the sea cucumber *Pattalus mollis*. Chemical composition analysis showed that they were all composed of L-fucose. Their sulfate content was determined by a conductimetric method. The molecular weight (Mw) of FSI, FSII, FSIII, FSIV and FSV were measured as 238.3 kDa, 81.0 kDa, 82.0 kDa, 23.2 kDa and 6.12 kDa, respectively. Detailed NMR spectroscopic analysis revealed that the structural sequence of FSI and FSII was $\rightarrow$3)-L-Fuc_{S}-α(1$\rightarrow$, where Fuc_{S} were Fuc_{2S4S} (10%), Fuc_{2S} (44%), Fuc_{0S} (10%), Fuc_{4S} (36%), that of FSIII was $\rightarrow$4)-L-Fuc_{2S}-(α1 $\rightarrow$ 4)-L-Fuc_{2S}-(α1 $\rightarrow$ 4)-L-$\mathrm{Fuc}_{0S/3S}$-(α1$\rightarrow$, where Fuc_{0S} and Fuc_{3S} were in equal molar, and that FSIV was $\rightarrow$4)-L-Fuc_{2S3S}-(α1 $\rightarrow$ 4)-L-Fuc_{2S3S}-(α1 $\rightarrow$ 4)-L-Fuc_{2S}-(α1$\rightarrow$4)-L-Fuc_{2S}-(α1 $\rightarrow$ 4)-L-Fuc_{2S}-(α1 $\rightarrow$ 4)-L-Fuc_{2S}-(α1 $\rightarrow$. This is the first report that such a diversity of fucan sulfates were obtained from the same sea cucumber species. Biological activity showed that FSI, FSII, FSIII and FSIV exhibited potent anticoagulant by prolonging the APTT. Among them, FSII, FSIII and FSIV showed the similar potency, while FSI owned the strongest. Structure-activity relationships analysis showed that molecular weight and sulfation degree should be the crucial factors for the activity.

1. Introduction

Sea cucumbers (Echinodermata, Holothuroidea) are important human food sources for their nutrition and medicinal benefits. The processed body wall is mainly exported from producing countries to Asia, especially Chinese seafood markets, where it is popular and of high value [1]. Studies have shown sea cucumber contains protein, collagen fibers, amino acids, and bioactive components such as glycosides and sulfated polysaccharides. Sulfated polysaccharides such as fucan sulfate are endowed with various biological activities, including anti-coagulation and anti-thrombosis [2], hematopoietic stimulation [3], anti-cancer [4], hepatic inflammatory response and insulin resistance modulation [5].

Fucan sulfate is mainly composed of fucose and sulfate groups that is mostly found in brown algae and invertebrates. The fucan sulfates isolated from brown algae was also called as fucoidan. In contrast with the apparently complex and heterogeneous algal fucoidans, the fucan sulfate from invertebrates (FS) such as sea cucumber usually possesses more regular structures. Most of FSs are linear polysaccharides linked by α(1 → 3), α(1 → 4) or α(1 → 2) glycosidic bonds in repeating units, and the α-L-fucose residues sulfated at O-2, O-3 and/or O-4 positions. For example, FSs from *Holothuria fuscopunctata* [6], *Stichopus herrmanni* [7], *Stichopus horrens* [8] are highly regular fucan sulfates with monosaccharide repeating units. FSs from *Acaudina molpadioides* [9], *Holothuria polii* [3], *Holothuria tubulosa* [10], *Isostichopus badionotus* [2], *Thelenota ananas* [11] are all linear polysaccharides consisting of α(1 → 3) linked tetrafucose repeating units, but with different sulfation patterns. FS from *Holothuria albiventer* is composed of regular α(1 → 3) linked hexasaccharide repeating units [12]. Additionally, some FSs were discovered to bear the mono-fucose and di-fucose side chain that linked to the central core. FSs from *Holothuria coluber* [12], *Apostichopus japonicas* [13], *Pattalus mollis* [14] are branched polysaccharides, in which the repeating structural unit of AjFS has a disaccharide side chain, and the repeating structural unit of HcFS and PmFS are branched by a mono-

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An Integrated Approach to Determine the Boundaries of the Azaphilone Pigment Biosynthetic Gene Cluster of *Monascus ruber* M7 Grown on Potato Dextrose Agar

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Monascus-type azaphilone pigments (MonAzPs) are produced in multi-thousand ton quantities each year and used as food colorants and nutraceuticals in East Asia. Several groups, including ours, described MonAzPs biosynthesis as a highly complex pathway with many branch points, affording more than 110 MonAzP congeners in a small group of fungi in the Eurotiales order. MonAzPs biosynthetic gene clusters (BGCs) are also very complex and mosaic-like, with some genes involved in more than one pathway, while other genes playing no apparent role in MonAzPs production. Due to this complexity, MonAzPs BGCs have been delimited differently in various fungi. Since most of these predictions rely primarily on bioinformatic analyses, it is possible that genes immediately outside the currently predicted BGC borders are also involved, especially those whose function cannot be predicted from sequence similarities alone. Conversely, some peripheral genes presumed to be part of the BGC may in fact lay outside the boundaries. This study uses a combination of computational and transcriptional analyses to predict the extent of the MonAzPs BGC in *Monascus ruber* M7. Gene knockouts and analysis of MonAzPs production of the mutants are then used to validate the prediction, revealing that the BGC consists of 16 genes, extending from *mrpigA* to *mrpigP*. We further predict that two strains of *Talaromyces marneffei*, ATCC 18224 and PM1, encode an orthologous but non-syntenic MonAzPs BGC with 14 genes. This work highlights the need to use comprehensive, integrated approaches for the more precise determination of secondary metabolite BGC boundaries.

Keywords: *Monascus* azaphilone pigment, gene cluster boundary, comparative genomics, transcription analysis, gene knockout

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Article

Structural Characterization and Heparanase Inhibitory Activity of Fucosylated Glycosaminoglycan from *Holothuria floridana*

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Abstract: Unique fucosylated glycosaminoglycans (FG) have attracted increasing attention for various bioactivities. However, the precise structures of FGs usually vary in a species-specific manner. In this study, HfFG was isolated from *Holothuria floridana* and purified by anion exchange chromatography with the yield of ~0.9%. HfFG was composed of GlcA, GalNAc and Fuc, its molecular weight was 47.3 kDa, and the -OSO_3^-/-COO^- molar ratio was 3.756. HfFG was depolymerized by a partial deacetylation–deaminative cleavage method to obtain the low-molecular-weight HfFG (dHfFG). Three oligosaccharide fragments (Fr-1, Fr-2, Fr-3) with different molecular weights were isolated from the dHfFG, and their structures were revealed by 1D and 2D NMR spectroscopy. HfFG should be composed of repeating trisaccharide units -{(L-FucS-α1,3-)D-GlcA-β1,3-D-GalNAc$_{4S6S}$-β1,4-}-, in which sulfated fucose (FucS) includes Fuc$_{2S4S}$, Fuc$_{3S4S}$ and Fuc$_{4S}$ residues linked to O-3 of GlcA in a ratio of 45:35:20. Furthermore, the heparanase inhibitory activities of native HfFG and oligosaccharide fragments (Fr-1, Fr-2, Fr-3) were evaluated. The native HfFG and its oligosaccharides exhibited heparanase inhibitory activities, and the activities increased with the increase of molecular weight. Additionally, structural characteristics such as sulfation patterns, the terminal structure of oligosaccharides and the presence of fucosyl branches may be important factors affecting heparanase inhibiting activity.

Keywords: *Holothuria floridana*; fucosylated glycosaminoglycans; oligosaccharide; chemical structure; heparanase

1. Introduction

Sea cucumber has long been used as food and folk medicine, particularly in some parts of Asia [1]. It is rich in bioactive components such as proteins, collagen, saponins and sulfated polysaccharides [2]. Various studies have shown that these components possess multiple biological and pharmacological activities, such as anti-thrombotic, anticancer, antioxidant, anti-inflammatory, anti-bacterial, anti-diabetic, anti-obesity and anti-angiogenic activities [3–5].

Fucosylated glycosaminoglycan (FG), a distinct glycosaminoglycan derivative found up to now exclusively in sea cucumbers, generally possesses a chondroitin sulfate-like backbone, fucose side chains and a high degree of sulfate substitution [6]. FG has numerous functions, such as anticoagulant, antiviral, anti-tumor, anti-inflammatory and anti-human

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A double-layer hydrogel based on alginate-carboxymethyl cellulose and synthetic polymer as sustained drug delivery system

Yan Hu[1,2]✉, Sheng Hu[1,2], Shangwen Zhang[1,2], Siyi Dong[1,2], Jie Hu[1,2], Li Kang[1,2]✉ & Xinzhou Yang[1,2]

A new double-layer, pH-sensitive, composite hydrogel sustained-release system based on polysaccharides and synthetic polymers with combined functions of different inner/outer hydrogels was prepared. The polysaccharides inner core based on sodium alginate (SA) and carboxymethyl cellulose (CMC), was formed by physical crosslinking with pH-sensitive property. The synthetic polymer out-layer with enhanced stability was introduced by chemical crosslinking to eliminate the expansion of inner core and the diffusion of inner content. The physicochemical structure of the double-layer hydrogels was characterized. The drug-release results demonstrated that the sustained-release effect of the hydrogels for different model drugs could be regulated by changing the composition or thickness of the hydrogel layer. The significant sustained-release effect for BSA and indomethacin indicated that the bilayer hydrogel can be developed into a novel sustained delivery system for bioactive substance or drugs with potential applications in drugs and functional foods.

A hydrogel is a three-dimensional network based on polymers. It has been applied in various fields, such as drug delivery[1], tissue engineering[2], cell engineering[3], shape memory[4], sensors[5], and soft robots[6]. Stimuli-responsive hydrogels can control drug release owing to their chemical modification and adjustable network pore size[7,8]. Therefore, it is the most promising drug delivery platform. Oral administration remains the most tolerable route of drug administration for patients, but many drugs are unstable owing to the effects of pH and enzyme in the gastrointestinal tract[9]. As an oral drug delivery system, intelligent hydrogels can be used to protect drug activity and improve its bioavailability[10,11]. These intelligent materials can also become a trend in drug delivery in the future.

Compared with the traditional monolayer hydrogels, multilayer hydrogels have many advantages, such as multilayer structure, relatively independent layers, and controllable layers. It can better highlight its advantages to be developed as a drug carrier system[12,13]. In many studies, various materials have been used to prepare multilayer hydrogels, but these studies focused on the preparation methods[14–16], physicochemical properties[17], and formation mechanism of the materials[18,19], and most of them used the same materials to prepare multilayer hydrogels[19–21]. Hydrogels with different gel layers from different materials are rare in constructing a drug delivery system.

Usually, hydrogels can be fabricated by either natural polymers or fully synthetic polymers[22]. The natural polymers such as sodium alginate (SA) and carboxymethyl cellulose (CMC) are well known for their excellent non-toxicity, biocompatibility and biodegradability[23,24], which are usually prepared by physical or chemical crosslinking with crosslinkers[1,25]. Both SA and CMC are polyanionic polysaccharides containing abundant carboxyl group in the polymer chain, and easily form the hydrogel by Ca^{2+} crosslinking[26]. However, these physical hydrogels such as SA-Ca^{2+} system always possessed the notable drawbacks of instability and rapid dissolution[27]. On the contrast, the hydrogels formed by synthetic polymers by polymerization crosslinking or physiochemical crosslinking possessing the advantages of excellent mechanical strength and physicochemical stability[28,29]. But the hydrogels fabricated either by natural polymers or synthetic polymers with single network and microporous structure are always limited by the drug leakage problem that the drug concentrations can not be maintained effectively at the sustainable and desired levels for a longer period of time[30,31]. Therefore, in order to solve the

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$Ti_3C_2T_x$ MXene Liquid Crystal: Access to Create Background-Free and Easy-Made Alignment Medium

You Zhao,[‖] Qinghua Yu,[‖] Wei-Wei Cheng, Jia-Qian Li, Ai-Qing Zhang, Xinxiang Lei,* Yingkui Yang, and Si-Yong Qin*

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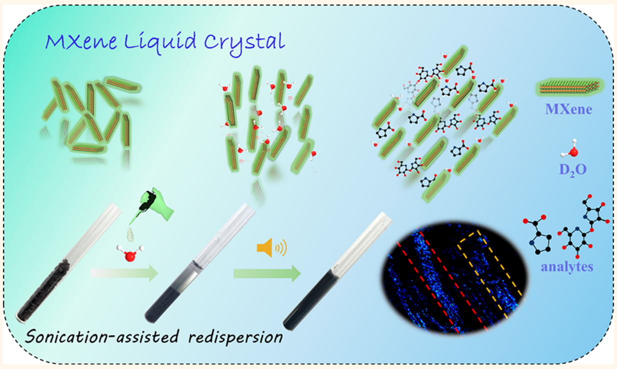

ABSTRACT: **The formation of lyotropic liquid crystals (LCs) in two-dimensional (2D) colloidal dispersions enables the production of mesoscopic/macroscopic ordered materials from nanoscale building blocks. In contrast to graphene oxide (GO) LCs, the practical applications of MXene LCs are less exploited. This study bridges the gap by utilizing a simple and versatile fabrication method to prepare $Ti_3C_2T_x$ MXene LC that can be applied as a background-free alignment medium for the residual dipolar coupling (RDC) measurement of organic molecules. $Ti_3C_2T_x$ LC displays the size- and concentration-dependent alignment degree. $Ti_3C_2T_x$ nanoflakes with an average size of around 600 nm can provide the quadrupolar ^2H splitting of 71 Hz at a concentration of 50 mg/mL and show excellent fluidity at such a high concentration. Compared with other alignment media, $Ti_3C_2T_x$ LC exhibits the features of no-background and narrow line broadening, which actualizes the acquirement of clean and high-quality NMR spectra for the accurate RDC extraction. Notably, the alignment of LCs is determined to be maintainable in the redispersed solution after freeze-drying, providing the great convenience for the preparation of alignment $Ti_3C_2T_x$ media, long-term sample preservation, and quantitative evaluation of alignment degree. Meanwhile, the alignment LC media for RDC measurement can be established in other MXenes such as Ti_2CT_x and Ti_3CNT_x. Collectively, our findings demonstrate the potential of creating various alignment media from the fascinating MXene family.**

KEYWORDS: *$Ti_3C_2T_x$, MXene, liquid crystal, alignment media, residual dipolar couplings (RDCs)*

Since the discovery of graphene in 2004, two-dimensional (2D) materials have become a major research interest in the field of materials science.[1,2] During the past nearly two decades, various 2D species such as transition metal dichalcogenides, phosphorene, and boron nitride (BN) have rapidly spurred up. Among them, MXenes, a newly discovered family of 2D transition metal carbides and/or nitrides, have attracted tremendous attention. They have unique merits such as high metallic electrical conductivities, superior mechanical properties, controllable surface functionalities, excellent hydrophilicity, and efficient absorption of electromagnetic waves.[3,4] Specifically, $Ti_3C_2T_x$ MXene film with a thickness of 214 nm achieved an electrical conductivity as high as 15 100 S cm^{-1}, and a tensile strength of up to 570 MPa was obtained for the 940 nm film.[5] Moreover, a thermally treated Ti_3CNT_x MXene film with 40 μm thickness provided an excellent electromagnetic interference (EMI) shielding effectiveness of 116 dB, showing the strong potential for EMI shielding and related applications.[6]

Until now, more than 30 different MXenes have been reported and synthesized. They have been successfully exploited in the fields of energy storage,[7,8] EMI shielding,[9,10] catalysis,[11] gas-sensor,[12] environment,[13,14] and biomedical fields.[15−17] Despite the rapid development of MXene materials, more than half of the studies focused on $Ti_3C_2T_x$ because of the established synthesis technique, the enhanced structural stability compared to N-containing MXenes, and the higher electrical conductivity compared to $TiNbCT_x$, $Ta_4C_3T_x$, $Ti_3CN_zT_x$, *etc.*[18] The ability to scale up the fabrication process further advanced

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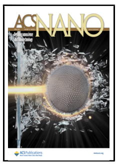

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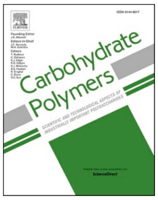

Re-understanding of structure and anticoagulation: Fucosylated chondroitin sulfate from sea cucumber *Ludwigothurea grisea*

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ARTICLE INFO

Keywords:
Fucosylated chondroitin sulfate
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Structure
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Disaccharide branch

ABSTRACT

Fucosylated chondroitin sulfate (FCS) from sea cucumber *Ludwigothurea grisea* (FCS_{Lg}) is the first one that reported to bear the di-fucosyl branches. Here we deciphered it by analyzing the physicochemical properties and its derivatives. Oligosaccharides prepared by selective cleavage of glycosidic linkages presented the mono-fucose and heterodisaccharide branches in FCS_{Lg}. The disaccharide branch was determined as D-$GalNAc_{R1}$-(α1,2)-L-Fuc_{R2} rather than the di-fucosyl branch, where R1 was 4-mono-O- or 4,6-di-O-sulfation, and R2 was 3-mono-O- or 3,4-di-O-sulfation, respectively. The diversity of sulfation patterns in branches complicated the structure. These results give us a new understanding of FCS_{Lg} and provided a reliable method to decipher the FCS with complex branches. Bioanalysis of chemically modified derivatives showed that modulating the molecular mass could enhance the Xase target selectivity. Side chains conferred the Xase complex inhibition by binding to FIXa with a high affinity. Whether monosaccharide and disaccharide branches have differential effects needs to be further explored.

1. Introduction

Fucosylated chondroitin sulfate (FCS) belongs to the family glycosaminoglycan, differing in the numerous sulfated fucoses as sidechains. Its backbone consists of the disaccharide repeating units of →3)-D-GalNAc-(β1,4)-D-GlcA-(β1→. This distinct polymer has been found ubiquitously and exclusively in Holothuroidea till now (Pomin, 2014). While the structure of FCSs varied in a species-specific manner (Ustyuzhanina et al., 2019a). Its variation allegedly embodies in the sulfation pattern and size of branches (Ustyuzhanina et al., 2019b). It first appeared in Fan's report in 1980, while internationally, the first description about the existence of the unique marine glycosaminoglycan is the work of Vieira and Mourão, from the body wall of the sea cucumber *Ludwigothurea grisea* (also named *Holothuria grisea*) (Fan et al., 1980; Mourão & Bastos, 1987; Soares et al., 2018).

Since then, the group of Prof. Mourão pioneered studies on the possible structure of *L. grisea* FCS. Its structure has been revised in the course of ongoing research (Fig. 1). It was initially hypothesized as that the β-D-GalNAc residues in the chondroitin sulfate core were sulfated including at 4,6-di-O- positions, and at 4-mono-O-/6-mono-O-position, and for β-D-GlcA residues, the O-3 positions were substituted half by sulfate groups and half by disaccharide units of α-L-Fuc_{3S4S} 2-linked to α-L-Fuc_{4S} (Vieira et al., 1991; Vieira & Mourão, 1988). The disaccharide conception was later revised: the branches of the cluster concentrated toward the non-reducing end of the polysaccharide chains as a single fucose residue (49 % Fuc_{4S}, 20 % Fuc_{2S4S} and 17 % Fuc_{3S4S}), while those at the reducing terminal may be di-fucoses (Mourão et al., 1996). The branches were further revised as that the preponderance formed by di-fucosyl units (53 %) and the residual branches were composed of Fuc_{2S4S} (27 %) and Fuc_{3S4S} (20 %) (Santos et al., 2015; Santos et al., 2017). Till now, the fine structure, especially the rare di-fucosyl branches of L. *grisea* FCS has not been proved unequivocally and thus needs further investigation.

In addition to the achievements in structural research, Prof. Mourão also pioneered studies on the therapeutic properties of FCS, especially the anticoagulation and antithrombosis (Mourão et al., 1996; Mourão et al., 1998). And, the early studies on pharmacological activity and structure-activity relationships were mainly based on the FCS from *L. grisea*. Its bioactivity, along with its structure, were considerably

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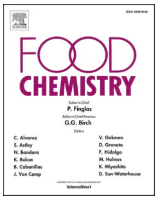

Short communication

Construction of high internal phase Pickering emulsions stabilized by bamboo fungus protein gels with the effect of pH

Minghao Zhang [a,b], Li Zhou [a,b,*], Fu Yang [a,b], Jiaxu Yao [a,b], Yue Ma [a,b], Jikai Liu [a,b,*]

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ARTICLE INFO

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ABSTRACT

This study is a contribution to explore natural protein sources as high internal phase Pickering emulsions (HIPPEs) stabilizers and to achieve full utilization of biological resources. Bamboo fungus proteins were obtained by alkaline extraction and subsequently transformed into protein gels by enzymatic cross-linking method. 1% (w/v) of bamboo protein gel particles (BGPs) were used to stabilize high HIPPEs ($\varphi = 80\%$) using a one-step homogenization method. At pH 3, 9 and 11, BGPs could produce stable, gel-like oil/water HIPPEs with excellent storage stability. In contrast, at pH 5 and 7, stable HIPPEs could not be formed, which might be attributed to the variation of contact angle and electrostatic repulsion of BGPs. Structure analysis indicated that HIPPEs with gel-like structures were mainly stabilized by physical barriers and electrostatic repulsion. The present study is expected to provide new insight on comprehensive utilization of fungi sources.

1. Introduction

High internal phase Pickering emulsions (HIPPEs) are emulsions stabilized by colloidal particles with a volume fraction (φ) of the dispersed phase exceeding 74%. HIPPEs have received a lot of attention in the last two decades because of the wide range raw material sources, simplicity preparation process, outstanding stability and the diverse functional properties (Abdullah, Weiss, Ahmad, Zhang, & Zhang, 2020). Previous studies mainly focused on the colloidal particles to stabilize HIPPEs, including inorganic particles such as diatomite or synthetic substances such as University of Oslo-66 metal organic framework (Bai et al., 2020; Zhu, Zhang, & Zhu, 2016). However, considering the concept of green and non-toxic, various natural substances have been used as particulate stabilizers (Liu, Geng, Jiang, & Liu, 2020; Qin, Gao, & Luo, 2021; Tan, Pajoumshariati, Arshadi, & Abbaspourrad, 2019).

Plant proteins including soy protein, peanut protein, zein and gliadin were frequently-used plant proteins (Jiang et al., 2021; Jiao, Shi, Wang, & Binks, 2018; Wen, Zhang, Jin, Sui, & Jiang, 2020; Zeng et al., 2017). Soy protein gel (1.75 wt%) can stabilize the HIPPEs ($\varphi = 80\%$) at pH 9, these HIPPEs can manufacture porous scaffold materials (Wen et al., 2020). Peanut protein gels (1.5 wt%) can stabilize HIPPEs ($\varphi = 88\%$) at pH 3 and 9, which can be used in tissue engineering (Jiao et al., 2018). Animal proteins such as whey protein, ovalbumin, bovine serum protein, oval transferrin, pork and fish protein can also stabilize HIPPEs (Chen & Tang, 2021; Wei, Cheng, Zhu, & Huang, 2019; Xu, Yang, Liu, & Tang, 2020). Pork protein particles (2.0 wt%) stabilized HIPPEs ($\varphi = 86\%$) exhibited excellent stability during storage (Li et al., 2020). Fish protein (5.0 wt%) stabilized HIPPEs ($\varphi = 90\%$) under alkaline conditions were successfully used for 3D printing, oil contamination adsorption and cell culture scaffolds (Wu et al., 2021).

Many factors including stabilizers concentration, oil type and volume fraction, pH and ionic strength affect the stability of HIPPEs during manufacturing. Amongst, pH is an important factor, and the impact of pH on HIPPEs varies from stabilizer. For example, HIPPEs can be well stabilized by myofibrillar dispersions at pH 6–12. As for whey protein isolate-low methoxyl pectin coacervates, HIPPEs couldn't be stabilized above pH 4 (Wu et al., 2021; Zhu, Zhang, Huang, & Xiao, 2020). Although numerous studies have reported about the feasibility and mechanism of proteins to stabilize HIPPEs, fungus as a kind of special protein source is neglected.

Dictyophora indusiata (*Vent ex. Pers.*) Fischer, known as bamboo fungus, is an edible saprophytic fungus. The fresh bamboo fungus contains protein (4.8%), fat (4.7%), crude fiber (6.03%) and Vitamin C (2.3%) (Sitinjak, 2017). The current in-depth exploitation of bamboo fungus was focused on the isolation of active polysaccharides and the investigation on their therapeutic effects, such as antioxidant,

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Digital image colorimetry in combination with chemometrics for the detection of carbaryl based on the peroxidase-like activity of nanoporphyrins and the etching process of gold nanoparticles

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ARTICLE INFO

Keywords:
Noble metal nanoparticles
Etching
Carbaryl
Digital image colorimetry
Partial least squares regression

ABSTRACT

Carbaryl is a typical carbamate pesticide that plays an essential role in agricultural production, but its residues cause serious harm to the environment and human health. Here, we developed a polychromatic colorimetric sensor based on ZnTPyP-DTAB peroxidase activity and gold nano-bipyramids (Au NBPs) etching to detect carbaryl. ZnTPyP-DTAB catalyzes the decomposition of H_2O_2 to hydroxyl radicals, and Au NBPs are etched. The coordination of zinc and nitrogen in nanometer porphyrins was affected by the steric effects of carbaryl, which resulted in decreased activity of ZnTPyP-DTAB peroxidase. The detection limit of carbaryl was 0.26 mg/kg. The recoveries of carbaryl in reaal sample ranged from 91 % to 107% (RSD $\leq$ 0.7%). The sensor platform displayed a series of high-resolution multicolor variations of rainbow colors within the above concentration range. The rich color variation facilitates the acquisition of digital images. RGB value transformation combined with partial least squares regression model can accurately and quantitatively detect carbaryl in vegetables, fruits and Chinese medicinal materials.

1. Introduction

Carbamate insecticides are highly valued in agricultural production due to their low toxicity, high efficiency, and short residual period (Yan et al., 2019, Pannek et al., 2020, Cheshari et al., 2021). As a typical carbamate pesticide, carbaryl is commonly used to control leafhoppers, rice lice, thrips, soybean heartworms, bean aphids, forestry and fruit tree pests. Insecticides have powerful contact action on pests. It has gastric toxicity and a slight inhalation effect, usually no specific odor, is stable in an acidic environment and decomposes when in contact with alkali, and most varieties are less toxic than organophosphate pesticides (Ahn et al., 2021). Compared with other carbamate pesticides such as carbofuran, carbaryl has low toxicity and wide insecticidal spectrum, so it is more favored by agricultural producers and widely used in modern agriculture (Chen et al., 2022). Although carbaryl has been banned in European Union, it is still used in many areas, especially in developing countries. The mode of action of carbaryl is the inhibition of cholinesterase, residual carbaryl can enter the human body through the food chain and inhibit acetylcholinesterase activity in the human body, disrupting the hydrolysis of the neurotransmitter acetylcholine and affecting the normal secretion of the human system (Fadic et al., 2017, Saquib et al., 2021). In addition, carbaryl has a variety of toxicity to the human beings (Chen et al., 2022), carbaryl also can damage DNA and cause chromosomal aberrations (CAs), resulting in reproductive abnormalities in the production of human sperm (Shahdost-fard et al., 2021). Thus, widespread use of carbaryl will lead to a series of public health problems, and residual carbaryl can seriously affect food safety, so it is necessary to build an effective, convenient, and fast method to detect

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Visual classification for sesame oil adulteration detection and quantification of compounds used as adulterants using flavor compounds targeted array sensor in combination with DD-SIMCA and PLS

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ARTICLE INFO

Keywords:
Sesame oil
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Visual array sensor
DD-SIMCA

ABSTRACT

Sesame oil is a kind of vegetable oil, which is loved by people all over the world due to its unique aroma, edible and medicinal value. Driven by interests, counterfeit and shoddy sesame oil products often appear on the market. This study is based on the color change caused by the competitive coordination of Zn^{2+} at the phase interface between four polyphenol dyes (Alizarin Red S, bromocatechol red, pyrogallol red and catechol violet) and volatile authenticity markers (VAM) in sesame oil. The DD-SIMCA model was constructed based on the RGB values of each sensing point after the reaction of real sesame oil and adulterated sesame oil with four polyphenol dyes. The results of the DD-SIMCA classification model show that the accuracy of sesame oil classification can reach 100%, and the result of the array sensor is much better than that of the single dye. Furthermore, the PLSR quantitative analysis model is used to verify that the RGB value obtained by the sensor is linearly related to the adulteration concentration. Therefore, this study established a visual array sensor for rapid authenticate of sesame oil adulteration based on the flavor compounds.

1. Introduction

Sesame is one of the oldest oil crops, known as the "queen" of oil crops, mainly distributed in tropical and subtropical regions such as China, India, Ethiopia and Sudan [1]. Sesame oil is rich in various nutrients such as sesamin, sesamol and n-6 and n-3 series of unsaturated fats. It has numerous medicinal values such as anti-inflammatory, antioxidant and immune enhancement [2–5], and has a pleasant smell and good taste [6,7]. Therefore, it is widely welcomed and loved by the people. Sesame, the raw material of sesame oil, is expensive, its market price is usually more than 5 times that of ordinary vegetable oil. Driven by profit, sesame oil adulteration incidents have been happening since ancient time. Some illegal traders often use cheap vegetable oil to mix sesame oil, even in cheap or inferior oils are added with pigments and essence to imitate the real appearance and flavor of sesame oil to obtain high profits. The most common adulterated oils in sesame oil are soybean oil, corn oil and rapeseed oil [8]. Adulteration not only harms the health and interests of consumers, but also affects the virtuous circle of the market [9].

At present, modern analytical techniques for the authenticity of sesame oil mainly include chromatography, spectroscopy, mass spectrometry and nuclear magnetic resonance spectroscopy [10–14]. The above-mentioned detection analytical techniques for sesame oil mainly rely on large and medium-sized instruments. Although gas chromatography-mass spectrometry, spectroscopy and electronic nose have the advantages of accurate separation performance, high precision and high sensitivity, and are effective analytical techniques for analyzing and detecting the quality and adulteration of sesame oil. However, for the common medicinal and food samples such as sesame oil, the above techniques have the limitations of expensive equipment and the need for professional operators. A simple, economic, visual, and universally applicable method for ordinary people is required to quickly and accurately verify the authenticity of sesame oil.

Visual array sensor is an instrument-free detection method that

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Synthesis of Nucleoside and Nucleotide Analogues by Cyclization of the Guanine Base with 1,1,3,3-Tetramethoxypropane

Ting-Ting Deng,[§] Yi-Bing Xie,[§] Wen-Wu Sun,* Jie Huang, Ting-Ting He, Ji-Kai Liu,* and Bin Wu*

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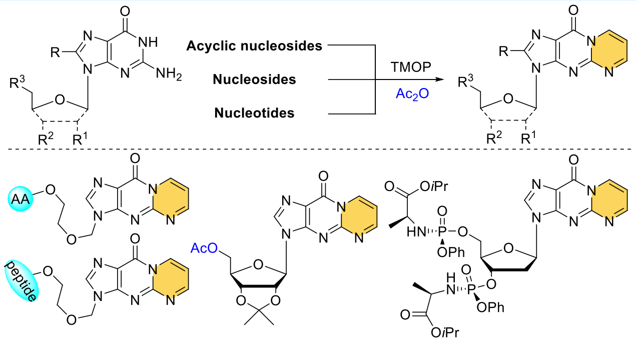
ABSTRACT: 3-(2-Deoxy-β-D-erythropentofuranosyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (M$_1$dG) is an endogenous DNA adduct in bacterial and mammalian cells that could be explored as a biomarker for oxidative stress. Nonetheless, the lack of an efficient methodology for the preparation of M$_1$dG hampers the deep investigation of its biosynthesis and biorelevant processes. In this project, we aimed to address this issue by developing a highly efficient method to synthesize M$_1$dG and its analogues. This method has wide functional group tolerance, as various guanine-based nucleosides and nucleotides are suitable for the reaction. Furthermore, large-scale and derivatization reactions were carried out to showcase the possibility for biochemists to study DNA damage and repair processes in the future.



Chemical modification of functional groups in complex biomolecular settings with a high degree of precision remains a challenge for organic chemists, biochemists, and medicinal chemists, but this ability would expand the diversity of biomolecular derivatives and increase the opportunities for drug treatment of new targets.[1] The recent approval of the antiviral drugs remdesivir[2] and molnupiravir[3] by the U.S. FDA for the treatment of COVID-19 greatly underscores the advantages and significance of nucleoside and nucleotide analogues. Guanine-based nucleosides are among the most prevalent structural units in DNA and RNA and play a key role in the maintenance of important intracellular processes, such as nucleic acid structure, energetic metabolism, and signal transduction via G proteins.[4] Guanine-based nucleosides are also noteworthy for their strong effect on HIV-1 RNA transcripts.[5] Based on the guanine structure, many guanosine-relevant antiviral and anticancer drugs have been explored and are currently used on the market (Figure 1a).[6] Therefore, to improve the drug-like and drug-forming properties of nucleoside analogues, considerable effort has been devoted to the development of efficient methods for modifying the groups at the 2, 6, and 8 positions of guanine bases.[1a,7] The inclusion of an additional cyclic moiety at the 1,2-position of the guanosine base to construct nucleosides has been limited (Figure 1b).[8] 3-(2-Deoxy-β-D-erythropentofuranosyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (M$_1$dG) is an endogenous DNA adduct in bacterial and mammalian cells that arises from the reaction of 2-deoxyguanosine with the lipid peroxidation product malondialdehyde or the DNA peroxidation product base propenal. As detected by urinary analysis, M$_1$dG is believed to be a potentially attractive biomarker for oxidative stress (Figure 1c).[9] Nonetheless, deep investigations of further metabolic studies and process balance factors for DNA damage and repair with M$_1$dG have been highly elusive due to the shortage of robust methods to efficiently prepare these endogenous substances.[10] The current synthesis of M$_1$dG suffers from low yields, multistep synthetic routes, and tedious workup procedures (Figure 1d).[11] Thus, the development of a cyclization reaction with general guanine-based nucleosides and nucleotides is highly desirable. However, this process may face considerable challenges, such as the following:

(1) There are many reaction sites for modification of the fundamental structure of guanosine, leading to chemo- and regioselectivity issues, as indicated in Figure 1b.[8]
(2) There are many basic nitrogen atoms that could be involved in coordination and reaction processes to inhibit the modification reaction.[1]
(3) The *N*-glycosidic bond in guanine-based nucleosides and nucleotides is prone to cleavage under strongly acidic conditions, resulting in low yields of the desired molecules.[11h,j]

Herein we report our efforts to address these issues and achieve a straightforward and efficient synthetic protocol for the late-stage diversification of guanine-based nucleosides and

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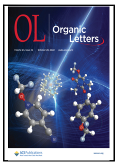

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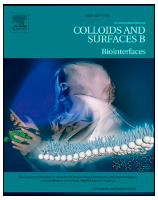

Preparation of green luminescent silicon quantum dots by synergistic method for VB_{12} detection and antimicrobial property research application

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Internal filtration effect
Antibacterial inhibition biofilm

ABSTRACT

The studies on the preparation of high-quality and long-wavelength-emitting silicon quantum dots and their application in biochemical detections have attracted increasing interests from researchers. In particular, the exploration of the effect of SiQDs and their complex in antibacterial and inhibition of biofilm areas, is of great significance to human health. This paper reports the fast synthesis of green-fluorescent SiQDs (TC-SiQDs, QYs=25%, Em=520 nm) with the synergistic effect of thiourea and catechol through microwave-assisted one-step hydrothermal route. Based on internal filtering effect, TC-SiQDs were then successfully employed as selective probes to detect vitamin B_{12}, with detection range at 0.05–30 μM and limit of detection at 50 nM. Thanks to the excellent biocompatibility and fluorescence property of TC-SiQDs, they have been applied in bacterial imaging. The prepared TC-SiQDs also exhibit certain antibacterial ability with their minimum inhibitory concentration (MIC) against *Staphylococcus aureus* (*S. aureus*) at 250 μg/mL, but their inhibitory ability is effective to the growth of *S. aureus* biofilm only when the concentration reaches 1.3 mg/mL. TC-SiQDs-lysozyme complex were prepared, based on the effects of singlet oxygen, charge effect and lysozyme hydrolysis of peptidoglycan in the cell wall, the complex exhibits high inhibiting activity with MIC against *S. aureus* at 10 μg/mL and exhibits superior inhibition activity against *S. aureus* biofilm at a concentration of only 62.5 μg/mL. This paper provides good theoretical and practical basis for the synthesis of long-wavelength emission and ultra-bright SiQDs and their applications in detection, antibacterial and biofilm growth inhibition, and other biomedical fields.

1. Introduction

Silicon quantum dots (SiQDs), as a fluorescence nanomaterial with easy availability, multiple synthesis routes, excellent optical properties, and low toxicity [1–3]. The development of a fast and simple one-step synthesis route for long-wavelength-emitting water-soluble SiQDs, and their further applications in biochemical detections and clinical fields, like imaging, drug delivery and treatment, are of great significance. The infection caused by pathogenic bacteria has seriously threatened food safety and human health, and thanks to their specific features in bacterial imaging and antibacterial abilities, SiQDs is an ideal candidate to infection treatment. For the present, the major problem in treating bacterial infections for antibiotics and nano antibacterial materials is the treatment of infection caused by bacterial biofilm, because it is complex microbial community attaching to the surface and encapsulated in extracellular matrix of microbial origin [4]. Biofilm matrix enables bacteria to tolerate harsh conditions and resist antimicrobial treatment [5]. To enhance the antibacterial ability of TC-SiQDs, we prepared TC-SiQDs-enzyme complex to study its ability in inhibiting biofilm. Recently, one-step hydrothermal route to prepare water-soluble SiQDs, under effect of reducing agents, has been widely accepted because of its simplicity and fastness without the requirement for complicated equipment [6]. However, most SiQDs prepared by one-step hydrothermal route are mostly blue-emitting [7]. Some research groups prepared green-emitting SiQDs through one-step route with proper selection of reducing agents, including catechol or glucose [8,9]. Though these methods can prepare green-emitting SiQDs, most products exhibit obvious drawbacks like low quantum yields (QYs) and weak optical stability, unbeneficial to the practical application in biomedical fields. And our team has developed a synthesis method for super-bright SiQDs based on the synergic effect [10,11]. The blue-emitting SiQDs were prepared with N-[3-(trimethoxysilyl)propyl]-ethylenediamine (DAMO) as silicon source based on the synergic effect between double reducing agents citric and sodium oxalate, and the QYs of prepared SiQDs reached

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Enhanced healing of oral chemical burn by inhibiting inflammatory factors with an oral administration of shengFu oil

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ShengFu oil is a compounded Chinese medicinal prescription, and provides antibacterial, anti-inflammatory, and analgesic effects, favoring burn wound repair. In this study, we aimed at investigating the effects of topical applications of ShengFu oil and its active ingredients in oral chemical burns and elucidating its regulatory effects on β-catenin, COX-2, and MMP-9 expression caused by exposure to acid or alkaline agents. ShengFu oil contains 16 components, such as Frankincense, Radix Scutellariae and Radix Rehmanniae, and the main active ingredients from Frankincense are α-pinene, linalool, and n-octanol. Mouse models of oral chemical burns were induced by using glacial acetic acid or sodium hydroxide. Hematoxylin and eosin staining and immunohistochemical staining were used to detect the protein expressions of β-catenin, COX-2, and MMP-9 in wound tissues. They were further quantified by multispectral imaging analysis to clarify the effective mechanism of ShengFu oil for intervening inflammatory factors and active components. Our results indicated that the application of ShengFu oil on oral chemical burns effectively stopped the oral burn bleeding and reduced the inflammatory reaction in the damaged tissues, demonstrating that ShengFu oil can promote wound tissue repair in burns caused by heat, acids, and alkalis. The immunohistochemical staining results illustrated that ShengFu oil and its active ingredients significantly reversed the abnormal changes in inflammation-related proteins in mouse tongue tissues that were caused by chemical burns. Regarding long-term toxic effects of ShengFu oil on the gastrointestinal tract, liver, and kidney system, the results of hematoxylin and eosin staining experiments depicted that ShengFu oil was safe and effective for liver, kidney, intestine, esophagus, and tongue. All of these demonstrated that ShengFu oil and its active ingredients are effective and safe in preventing and treating oral chemical burns by interfering with the inflammatory microenvironment.

KEYWORDS

Shengfu oil, Frankincense, oral chemical burn, subacute toxicity, inflammatory microenvironment

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ORIGINAL RESEARCH
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Immunosuppressive Isopimarane Diterpenes From Cultures of the Endophytic Fungus *Ilyonectria robusta*

Ke Ye [1], ***Xiao Lv*** [1], ***Xian Zhang*** [1], ***Pan-Pan Wei*** [1], ***Zheng-Hui Li*** [1], ***Hong-Lian Ai*** [1]*, ***Da-Ke Zhao*** [2]* **and** ***Ji-Kai Liu*** [1]*

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Five new isopimarane diterpenes, robustaditerpene A-E (**1**–**5**), which include 19-nor-isopimarane skeleton and isopimarane skeleton, were isolated from the liquid fermentation of the endophytic fungus *Ilyonectria robusta* collected from *Bletilla striata.* The structure elucidation and relative configuration assignments of all compounds were accomplished by interpretation of NMR and HRESIMS spectrometric analyses and ^{13}C NMR calculation. And the absolute configuration of **1**-**5** were identified by single-crystal X-ray diffraction and ECD calculation. Compound **3** inhibited lipopolysaccharide-induced B lymphocytes cell proliferation with an IC_{50} value at 17.42 ± 1.57 μM while compound **5** inhibited concanavalin A-induced T lymphocytes cell proliferation with an IC_{50} value at 75.22 ± 6.10 μM. These data suggested that compounds **3** and **5** may possess potential immunosuppressive prospect.

Keywords: immunosuppressive activity, endophytic fungus, natural products, isopimarane diterpenes, ECD calculation

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INTRODUCTION

Immunosuppressive agents are a significant class of clinical drugs for organic transplantation and treatment of autoimmune diseases, such as rheumatoid arthritis, systemic lupus, multiple sclerosis, myasthenia gravis, and pemphigus (Dangroo et al., 2016). Although excellent advantages were taken, these immunosuppressive agents have some inevitable and serious side effects including the renal and liver toxicity, infection, malignancy, and others (Smith et al., 2003). Therefore, it is a significant requirement to develop new, efficient, and safe immunosuppressive agents.

Natural products play a highly important role in the drug discovery and development process. Many clinically applied drugs derived from or were natural products (Newman and Cragg, 2016). Several immunosuppressive agents, such as mycophenolic acid, cyclosporin A, tacrolimus, sirolimus, corticosteroids and so on, were also generated from natural products (Kahan, 2003; Wang et al., 2019).

Endophytic fungi are a rich source of natural products (Ye et al., 2021). The number of natural products from endophytic fungi are more than any other endophytic microorganism class, and they have various structures and a broad spectrum of bioactivities. Furthermore, natural products from endophytic fungi have various, even novel structures, which can be grouped into several types including alkaloids, steroids, terpenoids, quinones and so on (Tan and Zou, 2001; Zhang et al., 2006). One of the largest groups of bioactive natural products that have been identified is the terpenoids. Diterpenoids derived from C20 precursor (*E*, *E*, *E*)-geranylgeranyl diphosphate with more than 12,000 described compounds (Quin et al., 2014; Zi et al., 2014). Some isopimarane diterpenes with immunosuppressive activity have been reported (Chen et al., 2020).

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ORIGINAL PAPER

Colorimetric assay based on peroxidase-like activity of dodecyl trimethylammonium bromide-tetramethyl zinc (4-pyridinyl) porphyrin for detection of organophosphorus pesticides

Gaoqiong Deng[1] · Hengye Chen[1] · Qiong Shi[1] · Lixue Ren[1] · Ke Liang[1] · Wanjun Long[1] · Wei Lan[1] · Xiaole Han[2] · Yuanbin She[3] · Haiyan Fu[1]

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Abstract

A simple and sensitive colorimetric assay for detecting organophosphorus pesticides (OPs) was developed based on *3,3′,5,5′*-tetramethylbenzidine (TMB)/hydrogen peroxide (H_2O_2)/dodecyl trimethylammonium bromide (DTAB)-tetramethyl zinc (4-pyridinyl) porphyrin (ZnTPyP). In this system, based on the peroxidase-like activity of DTAB-ZnTPyP, H_2O_2 decomposes to produce hydroxyl radicals, which oxidize TMB, resulting in blue oxidation products. The OPs (trichlorfon, dichlorvos, and thimet) were first combined with DTAB-ZnTPyP through electrostatic interactions. The OPs caused a decrease in the peroxidase-like activity of DTAB-ZnTPyP due to spatial site blocking. At the same time, π-interactions occurred between them, and these interactions also inhibited the oxidation of TMB (652 nm), thus making the detection of OPs possible. The limits of detection for trichlorfon, dichlorvos, and thimet were 0.25, 1.02, and 0.66 μg/L, respectively, and the corresponding linear ranges were 1–35, 5–45, and 1–40 μg/L, respectively. Moreover, the assay was successfully used to determine OPs in cabbage, apple, soil, and traditional Chinese medicine samples (the recovery ratios were 91.8–109.8%), showing a great promising potential for detecting OPs also in other complex samples.

Highlights

- A novel assay based on the peroxidase-like DTAB-ZnTPyP was developed to detect OPs.
- DTAB-ZnTPyP interacts more strongly with OPs than other nanoporphyrins.
- This colorimetric assay exhibits a low detection limit of 0.25 μg/L for OPs.
- The assay was applied to a real sample with good results.

Keywords Nanoporphyrin · Organophosphorus pesticides · Colorimetric assay · Food safety

Introduction

Pesticides are used widely to suppress pests in agricultural production and human premises. However, their widespread use has resulted in increasingly serious environmental problems and food safety issues [1]. Of the various types of pesticides available, organophosphorus pesticides (OPs) are among those used most widely in the production of food, crops, and herbs owing to their high efficiency [2]. As systemic pesticides, OPs work by moving into a plant through root uptake. They are then conducted in vivo and spread throughout the plant cells. Hence, they are difficult to remove by simple washing and pose a greater risk to consumers [3].

Gaoqiong Deng and Hengye Chen equally contributed to this work.

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Journal of *Fungi*

Article

Immunosuppressive Sesquiterpenoids from the Edible Mushroom *Craterellus odoratus*

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Abstract: The aim of this work was to comprehensively understand the chemical constituents of the edible mushroom *Craterellus ordoratus* and their bioactivity. A chemical investigation on this mushroom led to the isolation of 23 sesquiterpenoids including eighteen previously undescribed bergamotane sesquiterpenes, craterodoratins A–R (**1**–**18**), and one new victoxinine derivative, craterodoratin S (**19**). The new structures were elucidated by detailed interpretation of spectrometric data, theoretical nuclear magnetic resonance (NMR) and electronic circular dichroism (ECD) calculations, and single-crystal X-ray crystallographic analysis. Compounds **1** and **2** possess a ring-rearranged carbon skeleton. Compounds **3**, **10**, **12**–**15**, **19**, **20** and **23** exhibit potent inhibitory activity against the lipopolysaccharide (LPS)-induced proliferation of B lymphocyte cells with the IC_{50} values ranging from 0.67 to 22.68 μM. Compounds **17** and **20** inhibit the concanavalin A (ConA)-induced proliferation of T lymphocyte cell with IC_{50} values of 31.50 and 0.98 μM, respectively. It is suggested that *C. ordoratus* is a good source for bergamotane sesquiterpenoids, and their immunosuppressive activity was reported for the first time. This research is conducive to the further development and utilization of *C. ordoratus*.

Keywords: *Craterellus ordoratus*; sesquiterpenoids; isolation and structural elucidation; immunosuppressive activity

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1. Introduction

Edible mushrooms are a large and fascinating group of fungi. Many species of wild edible mushrooms are valued ingredients due to their unique taste and short growth cycle. Yunnan Province is located in southwest China. Its unique climate and geological diversity make this area very favorable for the growth of wild mushrooms. It is estimated that more than 40% of the world's and 90% of Chinese edible mushrooms (about 900 species) grow in Yunnan [1,2]. Many wild edible mushrooms are regarded as local delicacies such as *Tricholoma matsutake*, *Collybia albuminosa*, *Cantharellus cibarius*, and several species of the genus *Boletus*. Studying the chemical constituents of these edible mushrooms, therefore, has become our long-term research project [2–4]. The systematic mining of chemical components and evaluation of their biological activity will be beneficial to the scientific development and utilization of these edible fungi.

Species of the genus *Craterellus* (Cantharellaceae) include well-known edible mushrooms. At present, 142 records of *Craterellus* have been found and about 74 species are currently recognized as members of the genus. Ten species are originally described from Asia and four of these species have been reported in China [5]. Of them, *C. odoratus* is an edible mushroom in the family widespread in mainland China and characterized by possessing a bright orange or yellow cap [5–8]. In China, this wild edible mushroom is especially popular in Yunnan Province, where it is a delicacy on the dinner table from

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Rapid identification of the geographical origin of *Eucommia ulmoides* by using excitation-emission matrix fluorescence combined with chemometric methods

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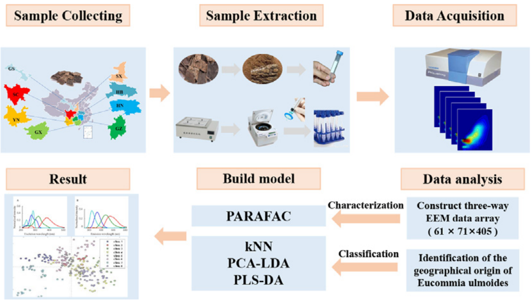
HIGHLIGHTS

- EEM fluorescence combined with chemometrics was proposed for rapid identification the origin of *Eucommia ulmoides* for the first time.
- PARAFAC were used for spectral characterization.
- Classification model for the identification the geographical origin was established by kNN, PCA-LDA and PLS-DA.
- Compared to other models, kNN model achieved satisfactory results.

GRAPHICAL ABSTRACT



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ABSTRACT

Eucommia ulmoides is an important and valuable traditional Chinese medicine with various medical functions, and has been widely used as health food in China, Japan, South Korea and other Asian countries for many years. The efficacy and quality of *E. ulmoides* are closely associated with the geographical origin. In this work, the potential of excitation-emission matrix (EEMs) fluorescence coupled with chemometric methods was investigated for simple, rapid and accurate for identification *E. ulmoides* from different geographical origins. Parallel factor analysis (PARAFAC) was applied for characterizing the fluorescence fingerprints of *E. ulmoides* samples. Moreover, k-nearest neighbor (kNN), principal component analysis-linear discriminant analysis (PCA-LDA) and partial least squares discriminant analysis (PLS-DA) models were used for the classification of *E. ulmoides* samples according to their geographical origins. The results showed that kNN model was more suitable for identification of *E. ulmoides* samples from different provinces. The kNN model could identify *E. ulmoides* samples from eight different geographical origins with 100% accuracy on the training and test sets. Therefore, the proposed method was available for conveniently and accurately determining the geographical origin of *E. ulmoides*, which can expect to be an attractive alternative method for identifying the geographic origin of other traditional Chinese medicines.

1. Introduction

E. ulmoides is a deciduous tree, which generally grows in warm and humid climate and sunny environment, and is mainly found in

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Cu(I)-Catalyzed Cross-Coupling Rearrangements of Terminal Alkynes with Tropylium Tetrafluoroborate: Facile Access to Barbaralyl-Substituted Allenyl Acid Esters and 7-Alkynyl Cycloheptatrienes

Zhe Fan,[⊥] Shao-Fei Ni,[⊥] Jin-Yu Pang, Li-Ting Guo, Hao Yang, Ke Li, Cheng Ma, Ji-Kai Liu,[*] Bin Wu,[*] and Jin-Ming Yang[*]

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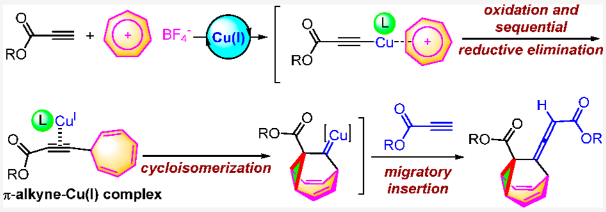
ABSTRACT: Herein, we report a novel strategy for the formation of copper carbene via the cycloisomerization of the π-alkyne−Cu(I) complex from terminal alkynes and tropylium tetrafluoroborate. Mechanistic studies and DFT calculations indicate that the reaction undergoes the intramolecular cycloisomerization process from the π-alkyne−Cu(I) complex to afford the copper carbene intermediate, followed by migratory insertion with the second terminal alkyne to afford the barbaralyl-substituted allenyl acid esters. In addition, we develop a mild and highly efficient Cu(I)-catalyzed cross-coupling protocol to synthesize 7-alkynyl cycloheptatrienes that has a broad functional group tolerance and is applicable to the late-stage functionalization of natural products.



■ INTRODUCTION

Transition-metal carbenes are versatile organometallic intermediates with metal═carbon double bonds, and studies of their structure−activity relationships and applications in organic synthesis have attracted significant interest.[1] Over past decades, considerable attention has been focused on the generation of metal carbenes through the activation of C≡C bonds, mostly by late transition metals such as Au,[2] Ag,[3] Pt,[4] Hg,[5] Ir,[6] Rh,[7] and Pd.[8] These transition metals further undergo a variety of transformations, including cyclopropanations, cycloadditions, rearrangements, C−H or X−H insertions, and carbene metathesis.[1−8] These reactions always occur in cascade transformations as inter- or intramolecular nucleophilic addition−elimination processes that deliver an α-oxo or α-imino metal carbene species (Scheme 1a). However, there are few reports of the activation of alkynes by first-row metals to form the corresponding metal carbene species. Two significant examples to date were reported by the research groups of Barluenga[9a] and Wang,[9b] namely the production of copper carbene intermediates without external oxidants from ene-yne ketones that subsequently underwent Si−H insertion and migratory insertion reactions (Scheme 1b). Very recently, the groups of Ye[10a] and Shen[10b] reported the generation of α-imino and α-oxo copper carbenes, respectively, from the activation of alkynes. As part of our ongoing study of alkyne chemistry,[11] herein we report a new strategy to generate copper carbene intermediates via the cycloisomerization of the π-alkyne−Cu(I) complex from terminal alkynes and tropylium tetrafluoroborates. The corresponding π-alkyne−Cu(I) complex undergoes intramolecular cycloisomerization and subsequent migratory insertion with the second terminal alkyne to afford a barbaralyl-substituted allenyl acid ester (Scheme 1c, this work).

■ RESULTS AND DISCUSSION

The key issue in the study of the transformation of fluxional molecules like 1,3,5-heptatrienes is the effective control of the selective transformation of the heptatriene moiety. To address this issue, suitable transition metals and optimized reaction conditions are required to guide the reactivity of heptatriene in the right direction. To this end, the research groups of Echavarren,[12] Bour with Gandon,[13a−c] and others[13d] have reported elegant examples. Considering these requirements, we commenced our study with methyl propiolate (**1a**) and tropylium tetrafluoroborate (**2**) in the presence of 10 mol % copper(I) thiophene-2-carboxylate (CuTC) and 0.5 equiv of Na_2SO_3 in THF under N_2 at 50 °C for 16 h. As shown in Table 1, a cage-like compound, namely the barbaralyl-substituted allenyl acid ester **3a**, was obtained in a 57% yield along with 7-alkynyl cycloheptatriene **4a** in a 20% yield (entry 1). Control experiments showed that both CuTC and Na_2SO_3

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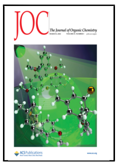

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food & nutrition research

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ORIGINAL ARTICLE

Nutmeg oil alleviates chronic inflammatory pain through inhibition of COX-2 expression and substance P release *in vivo*

Wei Kevin Zhang[1#], Shan-Shan Tao[1#], Ting-Ting Li[1], Yu-Sang Li[1], Xiao-Jun Li[1], He-Bin Tang[1*], Ren-Huai Cong[2], Fang-Li Ma[2*] and Chu-Jun Wan[3]

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Abstract

Background: Chronic pain, or sometimes referred to as persistent pain, reduces the life quality of patients who are suffering from chronic diseases such as inflammatory diseases, cancer and diabetes. Hence, herbal medicines draw many attentions and have been shown effective in the treatment or relief of pain.
Methods and Results: Here in this study, we used the CFA-injected rats as a sustainable pain model to test the anti-inflammatory and analgesic effect of nutmeg oil, a spice flavor additive to beverages and baked goods produced from the seed of *Myristica fragrans* tree.
Conclusions: We have demonstrated that nutmeg oil could potentially alleviate the CFA-injection induced joint swelling, mechanical allodynia and heat hyperanalgesia of rats through inhibition of COX-2 expression and blood substance P level, which made it possible for nutmeg oil to be a potential chronic pain reliever.

Keywords: *nutmeg oil*; *chronic pain*; *allodynia*; *COX-2*; *substance P*

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It is always unfortunate to be suffering from different chronic diseases such as inflammatory diseases, cancer, and diabetes. However, persistent pain (or chronic pain) makes conditions of those patients even worse and significantly reduces their quality of life. Hence, in clinical investigation, a great challenge is to discover safer, more effective and better-tolerated analgesics (1, 2). However, side effects such as nausea, sedation, itching, liking, and disliking of the drug and respiratory depression usually come with commercially available analgesics (3, 4). Thus, extensive research and development efforts have been directed toward the discovery of novel analgesics in both academia and industry.

Recently, many researchers have demonstrated that the herbal medicines (phytomedicine) are effective in the treatment or relief of pain, such as *Aleurites moluccana* (L.) Willd leaves extract (5), flower extract of *Tanacetum parthenium* (6), and extract of 25 more plant species traditionally used for pain relieving (7).

Nutmeg is commonly served in powder form or essential oil in the food industry worldwide. It has been reported that nutmeg oil, commercially obtained by steam distillation from kernels of nutmeg, usually contains more than 50 chemical components such as linalool, terpineol, eugenol, myristicin, camphene, dipentene, and pinene (8). Although some concerns about the toxicity of its components have been published (9, 10), lots of research still focused on its excellent activities in radical removal, lipid oxidation inhibition (11, 12), and most importantly its anti-inflammatory and antimicrobial activities (8, 13–15). Externally, nutmeg oil can also be used for rheumatic pain and, like clove oil, can be applied as an emergency treatment to dull toothache.

So far, no study has been carried out to evaluate the combined effects of nutmeg oil on inflammation and pain. Therefore, an inflammatory pain model of rat has been used in this study and three different evaluation methods have been introduced to test the anti-inflammatory and analgesic effects of nutmeg oil. Moreover, the expression levels of cyclooxygenase-2 (COX-2), a key molecule induced as an early response to pro-inflammatory mediators and stimuli such as endotoxins and cytokines (16), and blood level of substance P, a key neurotransmitter and neuromodulator in pain perception (17, 18), have also been investigated in skin samples of the model rats.

[#]These authors have contributed equally to the work.

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Salidroside suppressing LPS-induced myocardial injury by inhibiting ROS-mediated PI3K/Akt/mTOR pathway *in vitro* and *in vivo*

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Abstract

The purpose of the present study was to investigate the effect of salidroside (Sal) on myocardial injury in lipopolysaccharide (LPS)-induced endotoxemic *in vitro* and *in vivo*. SD rats were randomly divided into five groups: control group, LPS group (15 mg/kg), LPS plus dexamethasone (2 mg/kg), LPS plus Sal groups with different Sal doses (20, 40 mg/kg). Hemodynamic measurement and haematoxylin and eosin staining were performed. Serum levels of creatine kinase (CK), lactate dehydrogenase, the activities of the antioxidant enzymes catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-px), glutathione, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) were measured after the rats were killed. iNOS, COX-2, NF-κB and PI3K/Akt/mTOR pathway proteins were detected by Western blot. *In vitro*, we evaluated the protective effect of Sal on rat embryonic heart-derived myogenic cell line H9c2 induced by LPS. Reactive oxygen species (ROS) in H9c2 cells was measured by flow cytometry, and the activities of the antioxidant enzymes CAT, SOD, GSH-px, glutathione-S-transferase, TNF-α, IL-6 and IL-1β in cellular supernatant were measured. PI3K/Akt/mTOR signalling was examined by Western blot. As a result, Sal significantly attenuated the above indices. In addition, Sal exerts pronounced cardioprotective effect in rats subjected to LPS possibly through inhibiting the iNOS, COX-2, NF-κB and PI3K/Akt/mTOR pathway *in vivo*. Furthermore, the pharmacological effect of Sal associated with the ROS-mediated PI3K/Akt/mTOR pathway was proved by the use of ROS scavenger, *N*-acetyl-L-cysteine, in LPS-stimulated H9C2 cells. Our results indicated that Sal could be a potential therapeutic agent for the treatment of cardiovascular disease.

Keywords: salidroside • LPS • myocardial injury • ROS • H9C2 • PI3K/Akt/mTOR

Introduction

Sepsis is a complex syndrome with multi-organ dysfunction especially cardiovascular disease. Myocardial dysfunction and cardiac diastolic commonly occur in patients with severe sepsis. It should be noted that cardiovascular diseases remain a leading cause of morbidity and mortality around the world [1]. As the most common source of cardiac injuries, myocardial infarction (MI) is characterized by pathological myocardial hypertrophy, heart failure, excessive generations of inflammatory cytokines and overproduction of reactive oxygen species (ROS) [2]. ROS, the well-known by-products of normal cellular oxidative processes, can be produced under different stimuli including lipopolysaccharide (LPS). LPS is a main component of the outer membrane of Gram negative bacteria and has been used to induce cardiomyocytes lesion [3, 4].

The phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin mTOR (PI3K/Akt/mTOR) pathway is a critical cellular cascade in the cellular response to extracellular stimuli. Accumulating evidence indicated that PI3K/Akt/mTOR pathway participated in the cellular proliferation, differentiation, metabolism, cytoskeletal reorganization and apoptosis [5, 6]. Additionally, previous investigator demonstrated that PI3K/Akt/mTOR cascade was driven by ROS [7].

Traditional Chinese medicine, widely used for centuries around the world, is still acknowledged as a main source of medicine [8, 9]. *Rhodiola rosea* is a long-standing herbal used to relieve high altitude sickness and protect erythrocytes against oxidative stress [10]. As its important active ingredient, salidroside (Sal) (*p*-hydroxyphenylethyl-O-β-D-glucopyranoside) has been reported to have various pharmaco-

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Polysaccharides/mesoporous silica nanoparticles hybrid composite hydrogel beads for sustained drug delivery

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ABSTRACT

A simple and effective route was established to regulate the drug release kinetics of hydrogels through a combination method of the polysaccharides matrix which delivers the drug and the mesoporous silica nanoparticles (MSN) as a reservoir, making the system release the payload in a controlled manner. The composite MSN beads can construct one kind of novel sustained drug administration device maintaining 24 h activity. With the increase of the MSN ratio in the beads, the sustained-release profile can be increased. The drug release kinetics provide clear evidence that the composite MSN beads delivery systems can protect the model drug of bovine serum albumin from external denaturants and release them slowly in a predictable model. These composite MSN beads with higher drug-loading capacity and better retention ability may facilitate sustained/controlled drug delivery systems for pharmaceutical and biomedical applications.

Introduction

Sustained/controlled delivery of various drugs/biomolecules has been a target of medical biotechnology application [1]. In the past decades, various innovative approaches have been tried for sustained/controlled drug administration [2, 3]. Particularly, due to the unique water absorption and retention properties, hydrogel systems are one kind of excellent matrix for biomedical applications, especially for sensitive drugs that are unstable in harsh environments like stomach [4, 5]. The recent research shows that, the sustained drug delivery has been greatly improved—not only in typical polymeric hydrogel systems but also in novel inorganic material-based composite hydrogel systems [6, 7].

Mesoporous silica nanoparticles (MSN) [8, 9] with large surface areas, stable mesostructures [10], tuneable pore sizes [11], and good biocompatibility [12] are a promising platform for diagnosis, biosensors, biological analysis, tissue engineering, bone repair, and drug delivery [13]. Recently, delivering systems based on mesoporous silica have been widely reported [14]. For example, Zink et al. fabricated mesoporous silica nanoparticles encapsulating therapeutic compounds coated with molecular valves for

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molecules

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Article

Enzyme-Assisted Extraction Optimization, Characterization and Antioxidant Activity of Polysaccharides from Sea Cucumber *Phyllophorus proteus*

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Abstract: Enzyme-assisted extraction optimization, characterization and in vitro antioxidant activity of polysaccharides from sea cucumber *Phyllophorus proteus* (PPP) were investigated in the present study. The optimal extraction conditions with a yield of 6.44 ± 0.06% for PPP were determined as follows: Extraction time of 2.89 h, ratio of extraction solvent to raw material of 16.26 mL/g, extraction pH of 6.83, exraction temperature of 50 °C and papain concentration of 0.15%. Three purified fractions, PPP-1a, PPP-1b and PPP-2 with molecular weights of 369.60, 41.73 and 57.76 kDa, respectively, were obtained from PPP by chromatography of FPA98Cl and Sepharose CL-6B columns. Analysis of monosaccharide compositions showed that PPP-1a consisted of *N*-acetyl-galactosamine (GalNAc), galactose (Gal) and fucose (Fuc), PPP-1b of Fuc as the only monosaccharide and PPP-2 of glucuronic acid, GalNAc and Fuc. Sulfate contents of PPP, PPP-1a, PPP-1b and PPP-2 were determined to be 21.9%, 20.6%, 25.2% and 28.0% (*w*/*w*), respectively. PPP and PPP-1a had higher molecular weight and intrinsic viscosity than those of the PPP-1b and PPP-2. PPP, PPP-1a, PPP-1b and PPP-2 exhibited obvious activities of scavenging 1,1-diphenyl-2-picrylhydrazyl radical, hydroxyl radical, superoxide radical and ABTS radical in different extent, which suggested that the polysaccharides from *Phyllophorus proteus* may be novel agents having potential value for antioxidation.

Keywords: sea cucumber; polysaccharide; enzyme-assisted extraction; characterization; antioxidant activity

1. Introduction

Sea cucumbers belong to Echinodermata, Holothuroidea, and are important marine invertebrates found in most benthic marine habitats and deep seas across the world [1]. These animals have been a traditional tonic food and folk medicine in many countries for centuries and have gained increasing interest among researchers in recent years for their health benefits and diverse biological activities including anticancer, anti-diabetes, anti-inflammation, anti-obesity, immunomodulatory activity and anti-atherosclerosis [2–5]. These biofunctions of sea cucumbers can be attributed to

molecules

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Article

Isolation, Structural Elucidation of Three New Triterpenoids from the Stems and Leaves of *Schisandra chinensis* (Turcz) Baill.

Feng Qiu, Han Liu, Huan Duan, Pian Chen, Shao-Juan Lu, Guang-Zhong Yang * and Xin-Xiang Lei *

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Abstract: *Schisandra chinensis* (Turcz) Baill. is sufficiently well known as a medicinal plant worldwide, which modern research shows has many pharmacological activities such as hepatoprotective, anti-inflammatory effect, potent anti-HIV-1 activity, anti-tumor effect, and activity on the central nervous system. With considerable chemical investigation, three new triterpenoids (**1**–**3**), together with four known triterpenoids were isolated from the *S. chinensis* (Turcz) Baill. Their structures were elucidated by 1D- and 2D-NMR spectroscopic analyses, single-crystal X-ray diffraction and high-resolution mass spectroscopy, which were identified as Schisanlactone I (**1**), Schinalactone D, (**2**), Schisanlactone J, (**3**) Kadsuphilactone B (**4**), Schisanlactone C (**5**), Schisphendilactone B (**6**), and Schinchinenlactone A (**7**). The cytotoxicity of those compounds (**1**–**7**) was tested against Hep-G2 cell lines, but no apparent antitumor activity was observed at 50 µg/mL using MTT method.

Keywords: *Schisandra chinensis* (Turcz) Baill.; triterpenoids; cytotoxicity

1. Introduction

Schisandra chinensis (Turcz) Baill., Chinese magnolia vine, is widely distributed in China, the most eastern parts of Russia, Japan, Korea, USA, Europe, and all over the world [1]. The plant of *S. chinensis* (Turcz) Baill. can be found in the Chinese Pharmacopoeia, Russian Pharmacopoeia, Japanese Pharmacopoeia, Korean Pharmacopoeia, American Pharmacopoeia, and the International Pharmacopoeia [2]. According to various authors, the genus Schisandra includes from 20 to 30 species, and the major chemical composition of *S. chinensis* (Turcz) Baill. is lignans and triterpenes [2,3]. The seeds and fruits have been used to treat various diseases such as cough insomnia and arthritis [4]. Modern research shows it has many pharmacological activities such as hepatoprotective, anti-inflammatory effect, potent anti-HIV-1 activity, anti-tumor effect and activity on the central nervous system [5–9]. Most of phytochemical studies have concentrated on the analysis of fruits, and a great majority of them investigated lignans, but our studies of vegetative parts of stems and leaves are scarce. As a part of our effort to search for novel triterpene from *S. chinensis* (Turcz) Baill., we report here the isolation and structure determination of the new triterpenoids: Schisanlactone I (**1**), Schinalactone D (**2**), and Schisanlactone J (**3**), in addition to four known triterpenoids: Kadsuphilactone B (**4**), Schisanlactone C (**5**), Schisphendilactone B (**6**) and Schinchinenlactone A (**7**) (Figure 1).

frontiers in Chemistry

ORIGINAL RESEARCH
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Efficient Enantiodifferentiation of Carboxylic Acids Using BINOL-Based Amino Alcohol as a Chiral NMR Solvating Agent

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A new optically active BINOL-amino alcohol has been designed and synthesized in a good yield and applied as chiral nuclear magnetic resonance (NMR) solvating agent for enantioselective recognition. Analysis by ^{1}H NMR spectroscopy demonstrated that it has excellent enantiodifferentiation properties toward carboxylic acids and non-steroidal anti-inflammatory drugs (14 examples). The non-equivalent chemical shifts (up to 0.641 ppm) of various mandelic acids were evaluated by the reliable peak of well-resolved ^{1}H NMR signals. In addition, enantiomeric excesses of the ortho-chloro-mandelic acid with different enantiomeric ratio were calculated based on integration of proton well-separated splitting signals.

Keywords: BINOL-amino alcohol, chiral-solvating agents, ^{1}H NMR analysis, chiral discrimination, carboxylic acids

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INTRODUCTION

Chirality plays an important role in chemical, physical, pharmaceutical, and many biological events. The rapid and facial methods to detect and discriminate chiral compounds are highly desirable and urgent to accelerate advance in modern asymmetric synthesis and chiral drug screening (Izake, 2007; Wenzel and Chisholm, 2011a). In this context, the exponentially growing detection demand in this intensive area of research drives the development of chiral analysis (Pu, 2004, 2012; Liu et al., 2010; Nieto et al., 2010; Leung et al., 2012; Cheng et al., 2013; Wolf and Bentley, 2013; Jo et al., 2014; Akdeniz et al., 2016; Yu and Yao, 2017). Among these direct and non-invasive spectroscopic methods of analysis, nuclear magnetic resonance (NMR) spectroscopy plays a leading role and enjoys a special status because it is a reliable, routine technique for monitoring the optical purity and analyzing the absolute configuration of chiral molecules, offering several advantages such as cost-effectiveness, operative convenience, small sample size, and also sensor responsiveness (Parker, 1991; Zalesskiy et al., 2014; Pérez-Trujillo et al., 2015; Silva, 2017; Xu et al., 2019). The general methods to NMR spectroscopic discrimination of enantiomers through chemical shift measurement and spectral splitting observed have been developed: first is to utilize an enantiomerically pure chiral derivatization agent taking advantage of a reactive moiety of the substrate to produce two diastereomers. However, the chiral derivatization agents require cumbersome and time-consuming synthetic procedures and may cause concerns of kinetic resolution and racemization (Seco and Riguera, 2015). The second, chiral-solvating agents (i.e., CSAs) or chiral lanthanide shift reagents (i.e., CLSRs) can form two NMR-observable diastereomeric complexes/mixtures with guests via non-covalent interaction (Wenzel and Wilcox, 2003; Seco et al., 2004; Pérez-Trujillo et al., 2013). In recent years, chiral liquid crystals are also employed for spectral enantiotopic discrimination due to the effect of magnetically induced anisotropic interactions

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Article

Illudane Sesquiterpenoids from Edible Mushroom *Agrocybe salicacola* and Their Bioactivities

Quan Dai, Fa-Lei Zhang, Jiao-Xian Du, Zheng-Hui Li, Tao Feng,* and Ji-Kai Liu*

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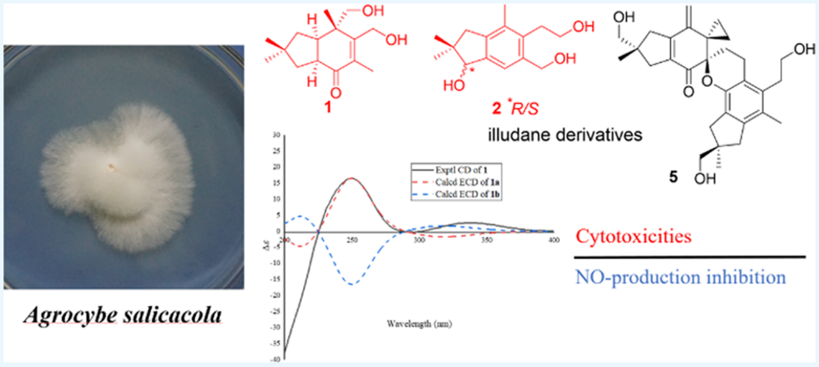

ABSTRACT: To comprehensively understand the chemical constituents of the edible mushroom *Agrocybe salicacola* and their biological functions, a phytochemical separation of the cultural broth of *A. salicacola* led to the isolation of four new illudane sesquiterpenoids, agrocybins H−K (**1**−**4**), along with 10 known analogues (**5**−**14**). Compounds **2**−**4** were racemates of which **2** and **3** were further separated into single enantiomers as **2a**/**2b** and **3a**/**3b**. All new structures with absolute configurations were elucidated on the basis of an extensive spectroscopic analysis and quantum chemistry calculations. Compound **1** possesses a new carbon skeleton that might be derived from the protoilludane backbone. Compounds **1**, **5**, **8**, and **9** show a certain degree of cytotoxicity to five human cancer cell lines. Compound **1** shows a mild inhibitory effect on nitric oxide production with an IC_{50} value of 31.4 μM. It is concluded that *A. salicacola* is rich in illudin derivatives with potential bioactivity prospects, which would make *A. salicacola* a good material of medicine and food homology.

■ INTRODUCTION

Agrocybe is a genus of mushrooms in the family Strophariaceae. Approximately 100 species in the *Agrocybe* are widely distributed all over the world.[1] *Agrocybe salicacola* is an edible mushroom similar to *Agrocybe cylindrica*. It is endemic to Yunnan Province, People's Republic of China, and is usually found at the trunks of willows and poplars from September to October.[2,3] Our previous chemical investigations on this fungus have revealed a number of illudin derivatives including agrocybone,[3] agrocybins A−G,[4] and illudin T.[5] Among them, agrocybone was a novel illudane−illudane dimer with a highly combined six-ring system,[3] while agrocybin A was also a illudin derivative having seven chiral carbons highly cyclized in a six-ring system.[4] It is understood that illudins are a group of sesquiterpene metabolites available from fruiting bodies of many wood decay fungi.[6] Previous pharmacological investigations have demonstrated that illudins have extensive cytotoxicity activities and antibacterial activities.[6−8] For instance, hydroxymethylacylfulvene (HMAF), a semisynthetic antitumor agent based on the naturally occurring illudin S from mushroom *Omphalotus olearius*,[8] has been advanced into human clinical trials for the treatment of cancers.[6,9] In addition, there are many other kinds of sesquiterpenoids such as aromadendrane-type and fomannosane-type.[10,11] Inspired by the novel structures and their significant biological activities, a comprehensive chemical investigation on the liquid fermentation of *A. salicacola* was accomplished, which resulted in the isolation of four new illudane derivatives, agrocybins H−K (**1**−**4**), together with 10 known analogues (**5**−**14**) (Chart 1). Structurally, compound **1** possesses an undescribed carbon backbone that might be derived from the protoilludane skeleton via a carbon−carbon bond cleavage, while compounds **2**−**4** are aromatized illudane racemates, of which compounds **2** and **3** are further separated into single enantiomers as **2a**/**2b** and **3a**/**3b**, respectively. All compounds were evaluated for their cytotoxicities to five human cancer cell lines and their

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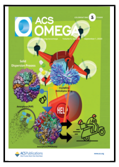

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Formal [2+2+2] Cycloaddition Reaction of 1,3,5-Triazinanes with diethyl acetylene dicarboxylate: Approach to Tetrahydropyrimidines

Ruijie Shi,[a] Limei Gao,[a] Weiji Chen,[a] Yangqing Shi,[a] Zhixing Cao,[b] Yongsheng Zheng,*[a] and Jikai Liu*[a]

An unprecedented [2+2+2] cycloaddition reaction of 1,3,5-triazinanes with diethyl acetylene dicarboxylate is disclosed. This catalyst free reaction provided an efficient and mild approach to synthesize a variety of functionalized tetrahydropyrimidines in moderate to excellent yields (up to 99% yield). Preliminary mechanistic investigation has been conducted to elucidate the reaction process.

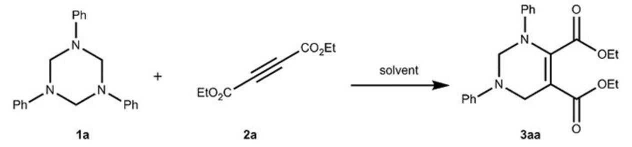
Nitrogen-containing heterocycles are of great interest in synthetic and medicinal chemists because of the diverse biological activities in pharmaceuticals and agrochemicals.[1] Among them, tetrahydropyrimidines, a six membered heterocyle containing two nitrogen atoms, represents an important structural motif, which is widely founded in natural products, functional materials and pharmaceutically active compounds. For example, the manzacidins, A, B, and C, are bioactive constituents isolated from Okinawan sponge, *Hymeniacidon* sp (Figure 1).[2] Polymers with functionalized tetrahedronpyrimidines in the backbone have unique fluorescence.[3] Tetrahydropyrimidin-2-ones were reported to be efficient HIV protease inhibitors.[4] In addition, tetrahydropyrimidines containing an amino acid unit have gained much attention due to their various properties such as muscarinic agonist activity,[5] antiviral[6] and inflammatory activity.[7]

Despite the importance of the tetrahydropyrimidine, limited approaches for the synthesis of tetrahydropyrimidine have been developed. The traditional methods are somewhat limited due to multistep reaction, tedious operation and low yields.[8] In fact, multicomponent cycloaddition reactions of electron-deficient alkynes with various nucleophilic nitrogen resources are one of the most effective and economic approaches for the synthesis of tetrahydropyrimidines. For example, Das reported a multicomponent reaction for the synthesis of tetrahydropyrimidine staring from nitro compounds and alkynes.[9] Jiang developed a one-pot quaternary components reaction to synthesize multisubstituted pyrimidine analogues containing α- and β-amino acid blocks (Scheme 1a).[10] [4+2] Cycloaddition reaction of azetidines with nitriles was also reported to be an efficient access to the tetrahydropyrimidines (Scheme 2a).[11] In addition, Sun[12] and Hashmi[13] reported the [2+2+2] cycloaddition reaction of 1,3,5-triazinanes with allenes and ynamides for the synthesis of tetrahydropyrimidines in the presence of gold species, respectively.

On the other hand, cycloaddition reaction via Huisgen's 1,4-dipoles generated from nucleophilic addition of nitrogen atoms such as imine, pyridine, quinoline and isoquinoline to electron-deficient alkynes has been demonstrated to be successful methods to access nitrogen-containing heterocycles.[14] In this context, on the basis of our interests in the triazinanes chemistry[15] and biologically active nitrogen-containing heterocycles synthesis, [16] we envisioned that nucleophilic 1,3,5-triazinanes should react with electron-deficient alkynes to form Huisgen's 1,4-dipoles, which further finish the cyclization to synthesize highly functionalized tetrahydropyrimidine in the presence of in situ generated *N*-phenylformaldimine. Herein, we wish to report our success in this [2+2+2] cycloaddition reaction for the synthesis of biologically promising tetrahydropyrimidines under transition metal free conditions.

We initiated our investigation with the reaction of 1,3,5-triphenyl-1,3,5-triazinane **1a** and diethyl but-2-ynedioate **2a** in $CHCl_3$ at 30 °C. As shown in Table 1, the reaction was performed smoothly and the corresponding cycloadduct **3aa** was obtained

Table 1. Optimization of reaction conditions.[a,b]



Entry	Solvent	T [°C]	*t* [h]	Yield
1	$CHCl_3$	30	80	85
2	DCE	30	80	34
3	DCM	30	80	37
4	Chlorobenzene	30	75	65
5	MeCN	30	80	80
6	EtOH	30	96	74
7	$CHCl_3$	50	60	88
8[c]	$CHCl_3$	50	72	48

[a] The reactions were performed with **1a** (0.2 mmol), **2a** (0.2 mmol) in solvent (2.0 mL). [b] Isolated yields. [c] 0.14 mmol **1a** was used.

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Pd(II)-catalyzed Carbonylative Cyclization of *N*-aryl-2-aminopyrimidines with Mo(CO)$_6$ as Carbon Monoxide Source

Ting-Ting Deng[+], Jie Huang[+], Guo Lian, Wen-Wu Sun,* and Bin Wu*[a]

Abstract: A convenient and efficient synthetic protocol for the preparation of pyrimidoquinazolinone through Pd(II)-catalyzed carbonylative cyclization of *N*-aryl-2-aminopyrimidines with Mo(CO)$_6$ as carbon monoxide source is established. A series of 6*H*-pyrimido[2,1-*b*]quinazolin-6-one derivatives were obtained in good yields. The scale-up synthesis was investigated.

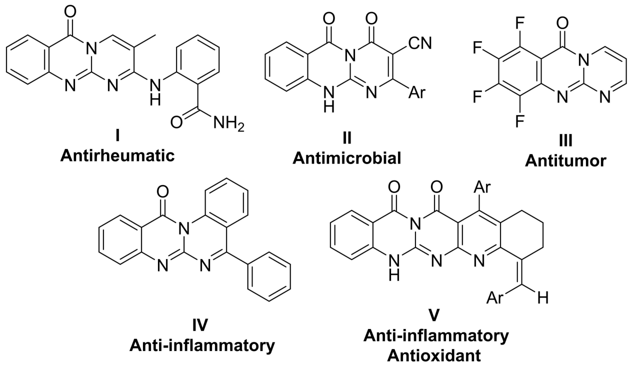
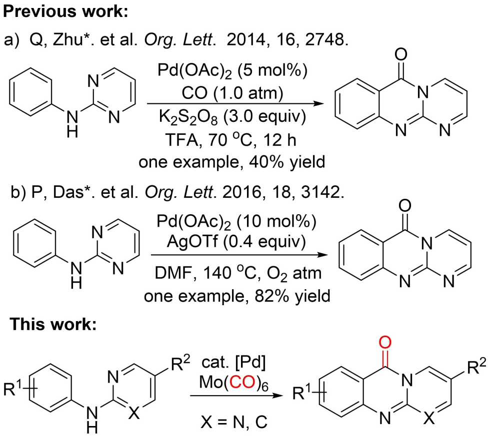


Figure 1. Biologically active compounds with pyrimido-fused quinazolinones skeletons.



Scheme 1. Strategies for the synthesis of pyrimidoquinazolinone from *N*-aryl-2-aminopyrimidines.

Pyrimido-fused quinazolinone is an important nitrogen-containing heterocyclic compound, which has a wide range of biological activities in antirheumatic,[1] antimicrobial,[2] antitumor,[3] antiinflammatory,[4] and antioxidant (Figure 1).[5] Given the potential bioactivities of these compounds, developing new strategies to construct polycycle-fused quinazolinones has been a research hotspot in organic synthesis. However, most of the published achievements were focused on the construction of pyridoquinazolinone,[6] and only a few pieces of literatures reported the synthesis of pyrimidoquinazolinone. In 2001, Smith's group reported the intermolecular cyclization of 2-fluorobenzoyl chloride and 2-aminopyrimidine to prepare pyrimidoquinazolinone in one-step.[3a] Jiang tried to use 2-(pyrimidine-2-yl amino) benzoic acid to react with POCl$_3$. However, no desired pyrimidoquinazolinone was detected.[7] Zhu developed palladium-catalyzed carbonylation of *N*-aryl-2-aminopyridine to make pyrimidoquinazolinone by using CO gas as the carbon source (Scheme 1a).[8] Das reported palladium/silver synergistic catalytic carbonylative reactions in CO gas-free situation, using DMF as both solvent and carbon monoxide source (Scheme 1b).[9] Despite the great progress has been made in this field, there are still some problems unsolved, such as using highly toxic carbon sources (CO), limited products, low yields and cumbersome operation. Therefore, the development of simple and convenient carbonylative cyclization of *N*-aryl-2-aminopyrimidines with a surrogate of CO gas is highly desirable.

Molybdenum hexacarbonyl [Mo(CO)$_6$], as a commercially available reagent, has been widely used in organic synthesis.[10] It has been used to mediate or catalyze the formation of carbon-carbon bonds,[11] the ring-opening of isoxazole,[12] the reduction of carboxylic acids,[13] and the oxidation of olefins.[14] It even more attracts much attention of organic chemists as a stable and easily handle carbonylation reagent.[15] However, there is no report on the synthesis of pyrimido-fused quinazolinone by using molybdenum hexacarbonyl as a carbon source. Based on our continuous interest in the development of transition metal-catalyzed C–H bond activation for the construction of nitrogen-containing heterocyclic compounds,[16] we herein report a Pd(II)-catalyzed carbonylative cyclization of *N*-aryl-2-aminopyrimidines with Mo(CO)$_6$ as carbon monoxide source to prepare pyrimidoquinazolinones.

Initially, we explored the carbonylative cyclization of *N*-phenyl-2-aminopyrimidine **1 a** with Mo(CO)$_6$ and K$_2$S$_2$O$_8$ in the presence of 10 mol% of Pd(OAc)$_2$. To our delight, the reaction proceeded smoothly at 70 °C within 48 h, affording 6*H*-pyrimido[2,1-*b*]quinazolin-6-one **2 a** in 57% yield (Table 1, entry 1). Other

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Communication

Chemo- and Site-Selective Fischer Esterification Catalyzed by $B(C_6F_5)_3$

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Abstract: A direct and catalytic dehydrative esterification of carboxylic acids with alcohols is described. $B(C_6F_5)_3$ is shown to be a highly effective catalyst for the Fischer esterification, providing esters in high to excellent yields. This esterification shows excellent chemo- and site-selective monoesterification of various polyols without any protection step, including bio-derived molecule glycerol.

Fischer esterification, conversion of a carboxylic acid and alcohol to an ester in the presence of acid, is a fundamental organic reaction, and plays an important role in organic chemistry.[1] However, acid-catalyzed esterification is reversible. Azeotropic distillation and Dean-Stark apparatus are always required to drive the equilibration to the ester product. To circumvent the problem of equilibration, elaborate efforts have been made involving the use of a variety of catalytic Lewis acids, such as Ti(IV),[2] Sc(III),[3] Hf(IV),[4] Fe salt[5] and graphene oxide,[6] to replace traditional reagents of hydrochloride acid and sulfuric acid. Nevertheless, few methods[7] were used to selectively synthesize the monoesterified glycerols, which are a class of bio-derived molecules of particular importance as food additives, components of cosmetic products and pharmaceutical formulations, plasticizers.[8] A classic strategy to prepare monoesters of glycerol undergoes multistep process, including protection and deprotection of adjacent diol group with acetone (Figure 1a).[9] Recently, Taylor group developed a boronic acid-promoted site-selective Fischer esterification of glycerol, in which stoichiometric phenylboronic acid was used to protect diol group (Figure 1b).[7b] Therefore, from a step and economic point of view, the development of a straight, efficient and site-selective monoesterification of glycerol is still highly desirable.

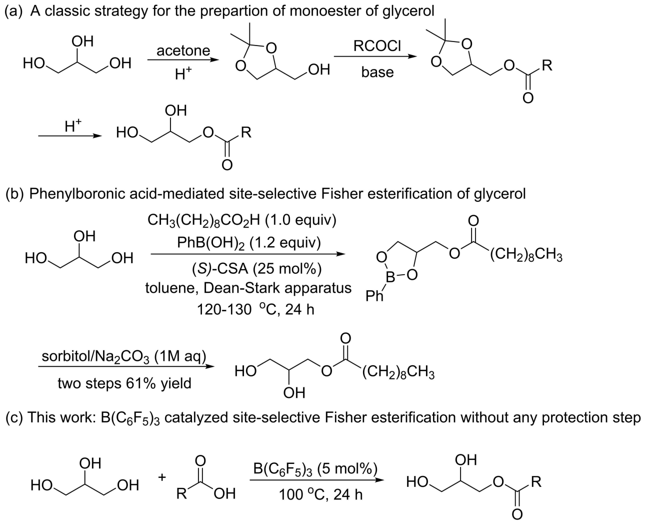

Figure 1. Strategies for preparation of monoesters of glycerol.

Over the past decades, tris(pentafluorophenyl)borane $B(C_6F_5)_3$ has witnessed its robust and sustainable development in a range of powerful transformations,[10] especially in Frustrated Lewis Pairs chemistry.[11] Its unique reactivity and thermal stability in a variety of reaction conditions has attracted great interest from organic chemists. $B(C_6F_5)_3$ was used as a catalyst to activate a number of small molecules.[12] Furthermore, $B(C_6F_5)_3$ was found to be tolerant of water in some reaction conditions.[13] Nonetheless, this advantageous ability of $B(C_6F_5)_3$ has not been used in Fischer esterification reaction. Herein, we report an efficient method to synthesize various esters through $B(C_6F_5)_3$-catalyzed Fischer esterification of carboxylic acids and alcohols. Various amino acids and polyols are amenable to this reaction to illustrate its practicability. Furthermore, monoesterification of glycerol is achieved with high yields in one step in the presence of catalytic $B(C_6F_5)_3$.

Initially, we explored the direct dehydrative esterification of 1-methyl-3-indoleacetic acid (**1a**) with methanol in the presence of 5 mol% of $BF_3 \cdot Et_2O$. To our delight, the reaction proceeded smoothly at 100 °C within 24 h affording methyl 2-(1-methyl-1H-indol-3-yl)acetate **2a** in 86% yield (Table 1, entry 1). Next, the Lewis acid catalysts $B(C_6F_5)_3$ and $CeCl_3 \cdot 7H_2O$, Brønsted acids CF_3SO_3H and *p*-TsOH were screened, giving rise to 100% yield of **2a** when $B(C_6F_5)_3$ (5 mol%) was used (Table 1, entries 2–5). In the absence of catalyst, the yield of the desired product **2a** decreased to 43% (Table 1, entry 6). Then, we studied the effect of solvents on the reaction. When 10.0 equivalents of methanol were used, the reaction in toluene produced **2a** in good yield, while other solvents (MeCN, DCE, DMSO, DMF, HFIP and 1,4-dioxane) gave less yields (Table 1, entries 7–13). Decreasing the loading of $B(C_6F_5)_3$ led to a slightly lower yield, and even 1 mol% of $B(C_6F_5)_3$ was used to give **2a** in 82% yield (Table 1, entries 14–16). Decreasing the reaction temperature reduced the product yield (Table 1, entries 17–18).

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Mechanisms Underlying the Inhibition of KV1.3 Channel by Scorpion Toxin ImKTX58Ⓢ

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ABSTRACT

Voltage-gated $K_V1.3$ channel has been reported to be a drug target for the treatment of autoimmune diseases, and specific inhibitors of Kv1.3 are potential therapeutic drugs for multiple diseases. The scorpions could produce various bioactive peptides that could inhibit $K_V1.3$ channel. Here, we identified a new scorpion toxin polypeptide gene *ImKTX58* from the venom gland cDNA library of the Chinese scorpion *Isometrus maculatus*. Sequence alignment revealed high similarities between *ImKTX58* mature peptide and previously reported $K_V1.3$ channel blockers—LmKTX10 and ImKTX88—suggesting that ImKTX58 peptide might also be a $K_V1.3$ channel blocker. By using electrophysiological recordings, we showed that recombinant ImKTX58 prepared by genetic engineering technologies had a highly selective inhibiting effect on $K_V1.3$ channel. Further alanine scanning mutagenesis and computer simulation identified four amino acid residues in ImKTX58 peptide as key binding sites to $K_V1.3$ channel by forming hydrogen bonds, salt bonds, and hydrophobic interactions. Among these four residues, 28th lysine of the ImKTX58 mature peptide was found to be the most critical amino acid residue for blocking $K_V1.3$ channel.

SIGNIFICANCE STATEMENT

In this study, we discovered a scorpion toxin gene *ImKTX58* that has not been reported before in Hainan *Isometrus maculatus* and successfully used the prokaryotic expression system to express and purify the polypeptides encoded by this gene. Electrophysiological experiments on ImKTX58 showed that ImKTX58 has a highly selective blocking effect on $K_V1.3$ channel over Kv1.1, Kv1.2, Kv1.5, SK2, SK3, and BK channels. These findings provide a theoretical basis for designing highly effective $K_V1.3$ blockers to treat autoimmune and other diseases.

Introduction

Autoimmune diseases are caused by excessive immune responses resulting from immune dysfunction. Epidemiologic studies showed that a large number of people in America suffer from autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes (Miller et al., 2012; Wang et al., 2015). Although traditional autoimmune drugs such as steroids and cyclophosphamide can inhibit autoimmune responses and alleviate the symptoms caused by these responses (Teles et al., 2017; Matsubayashi et al., 2019), they lack selectivity and compromise normal protective immune responses, thereby increasing the chance of secondary infection, and severe side effects including nephrotoxicity, liver injury, and malignant tumors (Chandy et al., 2004; Wulff et al., 2019). Therefore, it is urgent to identify specific and therapeutic targets to selectively and effectively cure autoimmune diseases but maintain normal protective immune responses with minimal side effects.

Numerous studies indicate that the pathogenesis of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and type 1 diabetes is mainly related to abnormal activation and proliferation of effector memory T (T_{EM}) cells (Spanier et al., 2017; Falcao et al., 2018;Chemin et al., 2019).

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All authors declare no conflicts of interest.

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ABBREVIATIONS: ADWX-1, autoimmune drug from Wenxin group; APC, anterior piriform cortex; BK, large conductance voltage and Ca^{2+}-activated potassium; ChTX, Charybdotoxin; DRG, dorsal root ganglion; GSH, glutathione; GST, glutathione *S*-transferase; HPLC, high performance liquid chromatography; ImKTX58, number 58 potassium channel toxin peptide identified from the venom gland cDNA library of *Isometrus maculatus*; ImKTX88, number 88 potassium channel toxin peptide identified from the venom gland cDNA library of *Isometrus maculatus*; α-KTX, alpha-potassium channel toxin peptides; Kv, voltage-gated potassium; LmKTX10, number 10 potassium channel toxin peptide identified from the venom gland cDNA of *Lychas mucronatus*; MALDI-TOF-MS, matrix assisted-laser-desorption/ionization time-of-flight mass spectrometry; MD, molecular dynamic; SK2 channel, small conductance calcium-activated potassium channel 2; SK3 channel, small conductance calcium-activated potassium channel 3; T_{EM} cell, effector memory T cell; WT, wild-type.

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Article

Thiazolo[5,4-*b*]pyridine Alkaloid and Seven *ar*-Bisabol Sesquiterpenes Produced by the Endophytic Fungus *Penicillium janthinellum*

Wen-Jing Wang,[†] Liang-Xiu Liao,[†] Ze-Diao Huang, Fu-Ting Wei, and Xiao-Long Yang*

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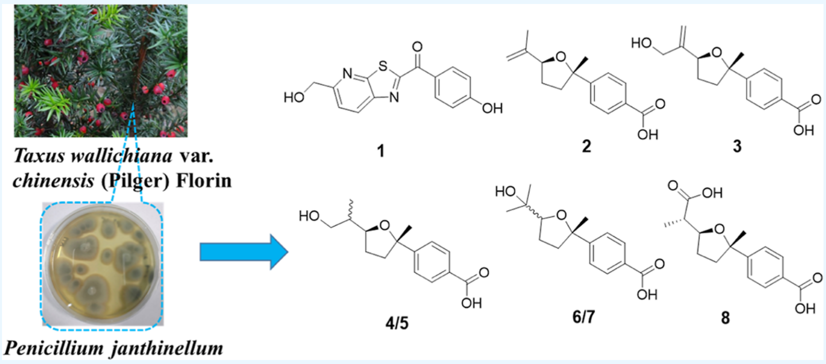

ABSTRACT: We investigated the secondary metabolites present in *Penicillium janthinellum* MPT-25, an endophytic fungus isolated from *Taxus wallichiana* var. *chinensis* (Pilger) Florin. Chemical characterization of the solid cultured extract resulted in the isolation of 11 compounds, including eight previously undescribed metabolites: a thiazolo[5,4-*b*]pyridine alkaloid, janthinedine A (**1**), and seven *ar*-bisabol sesquiterpenes, janthinepenes A−G (**2**−**8**). Their structures were elucidated by a combination of extensive spectroscopic methods, including single-crystal X-ray diffraction and ECD spectra. The antimicrobial activities of these compounds were evaluated against seven agricultural pathogenic fungi and eight clinically drug-resistant bacteria.

■ INTRODUCTION

Plant endophytic fungi can inhabit various types of healthy tissues in host plants without causing disease symptoms.[1] The mutually beneficial symbiotic relationship between host plants and their endophytic fungi has been established due to a long period of co-evolution and, consequently, endowed with the ability of fungi to encode biologically active metabolites with distinctive scaffolds.[2−6] Since Strobel discovered the "gold" bioactive compound taxol from an endophytic fungus acquired from the phloem of *Taxus brevifolia*, endophytic fungi have received increasing attention as potential producers of peculiar and bioactive metabolites.[7] Furthermore, the endophytic fungus *Fusarium proliferatum* (MTCC 9690), isolated from *Dysoxylum binectariferum*, can produce the same chromane alkaloid, rohitukine, as the host plant, which suggests that the metabolites generated by endophytic fungi are potential candidates for natural medicines that can be directly isolated from plant tissues.[8] Additionally, chemical investigations on endophytic fungi have provided new methods to solve the problem of shortage of some natural plants.[9]

Owing to our interest in antimicrobial compounds extracted from endophytic fungi, the strain MPT-25, which was obtained from the stems of *Taxus wallichiana* var. *chinensis* (Pilger) Florin and identified as *Penicillium janthinellum*, has attracted our attention. *P. janthinellum* produces diverse metabolites, including brefeldin A (BFA) derivatives,[10−12] alkaloids,[13−20] azaphilones,[21,22] terpenoids,[23,24] meroterpenoids,[25] restricticin derivatives,[26] and heterocyclic dipeptides,[27,28] and exhibits extensive antitumoral,[10,12,19] antibacterial,[15,16,18,21] and cytoprotective activities.[27,28] A phytochemical investigation on the EtOAc extract of this fungus led to the isolation of 11 metabolites: janthinedine A (**1**), janthinepenes A−G (**2**−**8**), and three known compounds (**9**−**11**). Janthinedine A possesses a thiazolo[5,4-*b*]pyridine skeleton[29] and janthinepenes A−G belong to a medicinally interesting class of sesquiterpenes—*ar*-bisabol sesquiterpenes.[30,31] Herein, the detailed isolation and structural elucidation, in addition to the antimicrobial activities, are described.

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Peptide probes with high affinity to target protein selection by phage display and characterization using biophysical approaches†

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Polypeptides provide unique possibilities for the development of efficient and selective fluorescent probes for different biomarkers because of their highly modular nature, the feasibility of chemical synthesis and fluorescence modification, and biomolecular recognition potential. Herein, a bacteriophage (phage) display was utilized to screen affinity peptides against dihydrofolate reductase. On this basis, positive peptide DHFR-Y1(NH_2-WSLGYTG-COOH) was obtained utilizing solid-phase peptide synthesis. Furthermore, fluorescein FAM was used to chemically modify the N-terminus and C-terminus of the peptide, respectively, to generate N-terminal fluorescent peptide DHFR-Yn (Flu-βA-WSLGYTG-COOH) and C-terminal fluorescent peptide DHFR-Yc (NH_2-WSLGYTL(Flu)-COOH). In the subsequent experiment, multiple *in vitro* detection methods (including DSF, STD-NMR, BLI) indicated that the binding ability of affinity peptide DHFR-Y1 (K_D = 3.57 μM) is significant to DHFR, in contrast to the stronger noncovalent binding ability of C-terminal fluorescent peptide (K_D = 0.56 μM) and weak affinity of N-terminal fluorescent peptide (K_D = 14.70 μM). The evidence that DHFR-Y1 and DHFR-Yc bind to folic acid binding pocket of DHFR was coming up by the *in silico* study. The peptide DHFR-Yc is adequate as a fluorescent probe targeting dihydrofolate reductase.

1. Introduction

Molecular probes, as biosensors, have been becoming crucial biological tools in medical diagnostics, food safety, and drug discovery.[1] A general molecular probe contains a molecular recognition element, and a direct signal element is designed for converting biological interaction information to observable signals, such as optical and magnetic signals, because it's not easy to directly visualize biological interaction in the process of relevant research being carried out by the reality that molecules generally don't exhibit strong signal.[2–4] Given the power of functions, considerable efforts have been directed toward the improvement of molecular probes, especially fluorescent probes, containing a direct fluorescent signal element for the requirement of understanding essential recognition events in chemistry and biology.[5,6] Over the past few decades, fluorescent signal elements have made vast strides and revolutionized the realm of both analytical sensing and optical imaging on account of their high sensitivity, selectivity, fast response time, flexibility, and experimental simplicity.[7–13] Moreover, the analysis of biomolecular systems is increasingly related to our ability to visualize and quantify them with high spatial and temporal resolution within the cellular context, something for which fluorescent techniques are particularly well suited.[14] Unfortunately, it is still hard to design novel fluorescent probes using theoretical calculations against entirely new receptors due to the poor understanding of the mechanism of regulating the interaction between fluorescent probes and their targets, which limits the utility of this type of molecule.[15] Given this matter, we employ a combinatorial strategy (Fig. 1) based on phage display technology and site-specific modification of peptide ligands to rationally design peptide-based fluorescent probes for rapid recognition of proteins of interest. This strategy relies on phage display technology to efficiently screen peptide ligands by creating large volumes of combinatorial libraries for encoding peptides to find ideal ligands. Subsequently, directional chemical modifications can result in the integration of fluorophores.[16,17] The new peptide probes composed of varying amounts of amino acids with precisely carried functional side chains, will be an excellent substitute

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Research Article

Water-Soluble *N*-Acetyl-L-cysteine-Capped CdTe Quantum Dots Application for Hg(II) Detection

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A simple, rapid, and specific method for Hg(II) detection has been proposed based on the fluorescence change of *N*-acetyl-L-cysteine-capped CdTe quantum dots (QDs). The presence of Hg(II) ions could quench the fluorescence of QDs at 565 nm and meanwhile produce new peak in 700–860 nm wavelength range. The linear response range is 20–430 nM with the detection limit at 8.0 nM Hg(II). It was found that the position of the new peak was irrelevant to the size of QDs. Furthermore, the mechanism of the quenching of QDs fluorescence by Hg(II) and the appearance of new peak in near-infrared area were also discussed and deduced through ultraviolet absorption spectrum, fluorescence spectrum, and X-ray photoelectron spectrum.

1. Introduction

As a new class of potential fluorescence probes, quantum dots (QDs) have attracted great interests of the researchers because of their unique and excellent properties over traditional fluorescent dyes and fluorescent proteins [1–3]. Compared to conventional organic fluorescent dyes, QDs possess higher photoluminescence (PL), excellent quantum yield (QY), size-dependent tunable luminescence wavelength, wide continuous absorption, narrow fluorescence band, and better photostability. Over the past two decades, great efforts have been focused on the development of sensors [4–8] based on QDs, and the detection of metal ions is the active field. Some researchers have realized the specific detection of metal ions through modification of QDs with different surface-attached ligands [9–13], such as the detection of Cu^{2+} ions through thioglycerol-capped CdS QDs [9] and mercaptopropionic acid-coated core/shell CdTe/CdSe QDs [10], the detection of Zn^{2+} ions through L-cysteine-capped CdS QDs [9], the detection of Ag^{+} ions through thioglycolic acid-coated CdSe QDs [11], the detection of Cu^{2+} and Ag^{+} ions through peptide-coated CdS QDs [12], and the detection of Pb^{2+} ions through glutathione-capped ZnCdSe and CdTe QDs [13].

As one of the most toxic heavy metals and persistent contaminants which cannot be biodegraded in ecosystem [14, 15], mercuric ion (Hg^{2+}) requires new and efficient detection methods. The major challenges in developing QDs-based Hg probe are the preparation of water-soluble QDs with high luminescence quantum yield and the selectivity of the system [16–19]. Herein, through hydrothermal route, a series of high-quality *N*-acetyl-L-cysteine- (NAC-) capped QDs with excellent water solubility, stability, and high QY (the average QY is 50%) have been synthesized [20–22]. Based on the prepared NAC-capped CdTe QDs as the fluorescence probe, a rapid, cost-efficient, sensitive, and selective detection method for Hg(II) ions has been developed in which Hg(II) efficiently quenches the fluorescence of QDs and produces a new peak in near-infrared area. Since size effect is a basic characteristic of semiconductor nanocrystals, the impact of particle diameter of QDs upon the system was also studied. The proposed Hg(II) detection mechanism was also deduced through fluorescence spectrum, ultraviolet absorption spectrum, and X-ray photoelectron spectrum (XPS).

2. Experimental

2.1. Chemicals. Tellurium (reagent powder, 99.8%) and NAC were purchased from Sigma. $CdCl_2{\cdot}H_2O$, Hg $(ClO_4)_2$, Rhodamine 6G, and sodium borohydride ($NaBH_4$) were obtained from Aldrich. Deionised distilled (DI) water prepared from

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Research Article

Electroacupuncture Treatment Alleviates Central Poststroke Pain by Inhibiting Brain Neuronal Apoptosis and Aberrant Astrocyte Activation

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Electroacupuncture (EA) is reported to effectively relieve the central poststroke pain (CPSP). However, the underlying mechanism remains unclear. The present study investigated the detailed mechanisms of action of EA treatment at different frequencies for CPSP. A CPSP model was established with a single collagenase injection to the left ventral posterolateral nucleus of the thalamus. The EA-treated groups then received EA treatment at frequency of 2, 2/15, or 15 Hz for 30 min daily for five days. The pain-related behavioral responses, neuronal apoptosis, glial activation, and the expression of pain signal transmission-related factors (β-catenin, COX-2, and NK-1R) were assessed using behavioral tests, Nissl staining, TUNEL staining, and immunohistochemical staining, respectively. The low-frequency EA treatment significantly (1) reduced brain tissue damage and hematoma sizes and (2) inhibited neuronal apoptosis, thereby exerting abirritative effects. Meanwhile, the high-frequency EA treatment induced a greater inhibition of the aberrant astrocyte activation, accompanied by the downregulation of the expressions of COX-2, β-catenin, and subsequently NK-1R, thereby alleviating inflammation and producing strong analgesic effects. Together, these findings suggest that CPSP is closely related to pathological changes of the neocortex and hippocampus. EA treatments at different frequencies may exert abirritative effects by inhibiting brain neuronal apoptosis and aberrant astrocyte activation in the brain.

1. Introduction

As a type of the neuropathic pain, central poststroke pain (CPSP) is one of the most troublesome sequelae of stroke, which can be caused by a primary lesion that affects the central somatosensory system following intracerebral hemorrhagic stroke [1]. In the clinic, patients exhibit thermal and mechanical hyperalgesia, which produces a low quality of life. A demographic census shows that the incidence of CPSP in stroke patients was approximately 7.3%–10.5% [2]. However, recent studies on neuropathic pain mainly focus on the peripheral nervous system instead of the injury to the central nervous system, particularly the CPSP [3].

In Western medicine, CPSP is mainly treated with drugs, including analgesics, antidepressants, and anticonvulsants, which may produce resistance and addiction [4]. As an important part of Chinese traditional medicine, acupuncture treatment obtains consistent international affirmation for its reliable analgesic effect. Electroacupuncture (EA) is a form of acupuncture in which a small electric current is passed

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Accessing substituted pyrrolidines via formal [3+2] cycloaddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes

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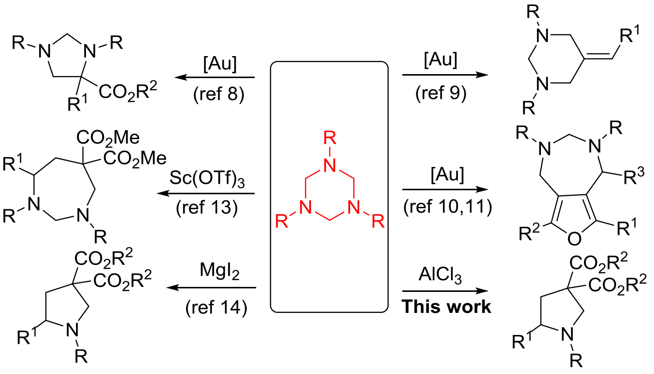
ABSTRACT

The formal [3+2] cycloaddition of 1,3,5-triaryl-1,3,5-triazinanes with donor-acceptor cyclopropanes has been found to provide pyrrolidines in good to excellent yields under mild reaction conditions. Preliminary mechanistic investigation indicates that this formal [3+2] cycloaddition reaction proceeds through competing S_N1 and S_N2 pathways.

Pyrrolidines are one of the most ubiquitous building blocks for a large number of natural products, pharmaceuticals and biologically active compounds.[1] They are also widely used as the core structure of synthetic catalysts.[2] Consequently, highly efficient strategies have been developed to construct pyrrolidine motifs.[3] Among the myriad of developed frameworks, the [3+2] cycloaddition of donor-acceptor cyclopropanes with various nitrogen-containing dipoles offers the most straightforward method and has received considerable attention with respect to atom economy and efficiency.[4] For example, Moshkin and co-workers employed spiroanthraceneoxazolidine as a synthetic equivalent of methanimine in the reaction with donor-acceptor cyclopropanes to afford pyrrolidines.[5]

1,3,5-Triaryl-1,3,5-triazinanes, which are readily available from the condensation of paraformaldehyde and various arylamines, are well-known as precursors of corresponding *N*-aryl formaldimines in the aminomethylation reactions with various nucleophiles in the presence of Lewis acids.[6] During the past few years, 1,3,5-triazinanes have attracted increasing attention in the synthesis of *N*-containing compounds due to their combination of nucleophilicity of the nitrogen atom and electrophilicity of the imine carbon. For example, Krische described the Ruthenium-catalyzed hydroaminomethylation of allenes/dienes by using 1,3,5-triazinanes as the surrogate of formaldimines.[7] Feng and co-workers reported the asymmetric Mannich-type reaction between *β*-keto-esters/amides and 1,3,5-triazinanes, in which 1,3,5-triazinanes were involved as bench stable Mannich reagents.[8]

Different from these aminomethylation protocols, triazinanes were also employed as dipolar adducts in cycloadditions to synthesize heterocycles (Scheme 1). For example, Sun and co-workers described gold-catalyzed [4+1]/[4+3] cycloaddition reactions of triazinanes with diazo esters to construct five- and seven-membered heterocycles.[9] Soon after, the same group reported [2+2+2] annulations of 1,3,5-triazinanes with functionalized allenes to provide the six-membered heterocycles.[10] In addition, Xu[11] and Sun[12] et al. developed the gold catalyzed [3+2+2] tandem dual heterocyclization reaction of enynones with 1,3,5-triazinanes to prepare



Scheme 1. Cycloadditions of 1,3,5-triazinanes.

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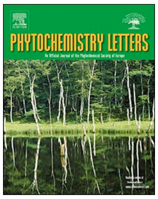

Cadinane-type sesquiterpenoids and an indolizine alkaloid from the rice fermentation of the fungus *Rigidoporus microporus*

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ABSTRACT

Two previously undescribed cadinane-type sesquiterpenoids, rigidoporones A and B (**1** and **2**), along with an undescribed racemic indolizine alkaloid, (±)-rigidoporine A (**3**), were isolated from the rice fermentation of the wood-decay fungus *Rigidoporus microporus*. The structures of the compounds were established by extensive spectroscopic methods, including 1D & 2D NMR and HRMS spectroscopic analysis. Compounds **1** and **3** were evaluated for their inhibitory activity on NO production in murine monocytic RAW264.7 macrophages ($IC_{50} > 25\ \mu M$).

1. Introduction

The wood-decay fungus *Rigidoporus microporus* (Sw.) Overeem belongs to the family of Meripilaceae. This fungus is known to cause white rot disease on many tropical trees that have threatened the rubber plantation across the rubber growing countries across Asia to Africa (Goh et al., 2018). As our program to explore structurally intriguing and biologically promising natural products from various species of higher fungi (Liu et al., 2013; Wang et al., 2018; Yang et al., 2012; Yin et al., 2013, 2014; Zhao et al., 2017), a rice fermentation of *R. microporus* was selected for investigation, which led to the isolation of two previously undescribed cadinane sesquiterpenoids, rigidoporones A (**1**) and B (**2**), along with a previously unreported racemic indolizine alkaloid (±)-rigidoporine A (**3**) (Fig. 1). The inhibitory activity of compounds **1** and **3** against the human palace cancer cell line and the NO production in murine monocytic RAW264.7 macrophages were evaluated.

2. Results and discussion

Compound **1** was isolated as a colorless oil. The molecular formula was determined as $C_{15}H_{22}O_3$ by the HR-ESI-MS at *m/z* 251.16400 $[M+H]^+$ (calcd for $C_{15}H_{23}O_3^+$, 251.16417, Δ 0.67 ppm), corresponding to five degrees of unsaturation. The ^1H NMR spectroscopic data (Table 1) displayed signals of two methyls at δ_H 1.37 (s, Me-14), 1.67 (s, Me-15), a hydromethyl group at δ_H 4.06 (dd, J = 14.7, 5.6 Hz) and 4.00 (dd, J = 14.7, 5.6 Hz), along with two terminal double bond protons (H-13) at δ_H 5.18 and 5.02. The ^{13}C NMR and DEPT spectroscopic data (Table 2) presented fifteen carbon resonances which were ascribable for two methyls, five methylenes (one oxygenated), four methines (one olefinic), and four quaternary carbons (a carbonyl at δ_C 199.7, two olefinic ones, and one oxygenated sp^3-hybrid carbon at δ_C 70.7). The NMR data of **1** showed that it is a congener of panutorulon A, a cadinane sesquiterpenoid from the cultures of the basidiomycete *Panus conchatus* (Ding et al., 2017). The HSQC spectrum revealed the presence of two hydroxy groups at δ_H 3.57 (s, 10-OH) and 3.96 (t, J =5.6 Hz, 13-OH). As for the planar structure, the key HMBC correlations from H-13 to C-7, C-11, and C-12 suggested that C-11–C-13 was a terminal double bond (Fig. 2) while it was a methyl attached at C-12 in panutorulon A. The other part of the structure **1** was same with that of panutorulon A which was confirmed by HMBC and ^1H–^1H COSY correlations (Fig. 2). Thus, the planar structure of **1** was elucidated as a cadinane-type sesquiterpene as shown in Fig. 1.

The relative configuration of **1** was settled by analysis of the ROESY spectrum. The obvious ROESY correlations between Me-10 (δ_H 1.37) and H-1 (δ_H 2.16), H-2 (δ_H 2.64) suggested that the two six-membered rings were *cis* fused, and thus OH-10 was *β* orientation. The coupling constants of H-7 (δ_H 2.21, ddd, J = 12.1, 12.1, 3.9 Hz) reflected that H-7 was *β* orientation, which presented two axial-axial couplings with H-6 and H-8α (both 12.1 Hz), and a axial-equitorial coupling with H-8β (3.9 Hz) (Fig. 3). Thus, the relative configuration of **1** was determined as 1*R**,6*R**,7*S**,10*S**. To corroborated the above assignement, a ^{13}C NMR calculation was performed for compound **1** (Frisch et al., 2016). As shown in Fig. 4 and Table 2, the calculated and experimental data were in good aggrement with a MAE 1.76 ppm. Hence, the structure of

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Cytotoxic ergosteroids from the fungus *Stereum hirsutum*

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Stereum hirsutum
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ABSTRACT

Phytochemical investigation on the fermentation broth of the fungus *Stereum hirsutum* led to the isolation of ten steroids, including two previously unreported ones, namely steresterones A (**1**) and B (**2**). The semi-synthesis products **3a** and **3b** were prepared by reduction of the known compound **3** with $NaBH_4$. Their structures and absolute configurations were established via 1D & 2D NMR spectroscopic analysis, and TDDFT/ECD calculations as well as single crystal X-ray diffraction analysis. The structure of **3** which harbored a 5β-H was confirmed by single crystal X-ray diffraction analysis for the first time. All the compounds reported in this study were evaluated for their cytotoxicity against five human cancer cell lines. Bioassay results revealed that **3**, **4**, **6—9** displayed significant anti-proliferative effects with IC_{50} values varying from 2.3 to 34.3 μM. The structure-activity relationships of **3**, **3a**, **3b** were discussed.

1. Introduction

A series of prevalent chronic diseases such as cancer are now the major causes of morbidity and mortality (World Health Organization, 2018, https://www.who.int/news-room/fact-sheets/detail/cancer). Lots of studies have expanded the concept that many cancers arise from sites of infection, inflammation, and chronic irritation (Coussens and Werb, 2002). Natural products from plants and fungi play critical roles in the discovery of lead compounds for the development of drugs for treating human diseases. The progress in research and development of cancer therapeutic agents have witnessed the approval of many blockbuster drugs by the governments, such as taxol, vinblastine, podophyllotoxin, and omacetaxine mepesuccinate (Kinghorn et al., 2009).

Steroids play important roles in mediating biological or pharmacological properties, such as anti-NO production, cytotoxicity, acetylcholinesterase inhibitory, and neurite outgrowth-promoting activities, and have long been privileged lead compounds in drug discovery (Salvador et al., 2013). Steroids are dominate secondary metabolites with diverse structural features which have aroused much attentions both in the isolation and synthetic studies in recent years (Duecker et al., 2018; Zhao et al., 2017).

Stereum hirsutum, a wood-decaying fungus belonging to the family Stereaceae (basidiomycetes), usually lives on dead limbs and trunks of both hardwoods and conifers. Previous phytochemical investigations on this fungus have led to the isolation of plenty of bioactive compounds, such as benzoate derivatives and hirsutane-type sesquiterpenoids (Ma et al., 2014; Qi et al., 2015; Wang et al., 2014). As a part of our ongoing interest in exploring anti-proliferative compounds as promising lead structures from higher fungi (Chen and Liu, 2017), ten steroids, including two unreported ones, namely steresterones A (**1**) and B (**2**) (Fig. 1), were isolated from the liquid cultures of *S. hirsutum*. Herein, we report the isolation, structure elucidation, semi-synthesis, and cytotoxicity of the steroids as well as a simple discussion of the structure-activity relationships.

2. Experimental

2.1. General experimental procedures

Optical rotations were obtained on a JASCO P-1020 digital polarimeter (Horiba, Kyoto, Japan). UV spectra were recorded on a Shimadzu UV-2401PC UV–vis recording spectrophotometer (Shimadzu, Kyoto, Japan). 1D and 2D NMR spectra were obtained on Bruker Avance III 600 or Ascend 800 MHz spectrometers (Bruker Corporation, Karlsruhe, Germany). HRESIMS was recorded on an Agilent 6200 Q-TOF MS system (Agilent Technologies, Santa Clara, CA, USA). HREIMS was recorded on a Waters AutoSpec Premier P776 MS system. The crystal data were detected on an APEX II DUO spectrophotometer (Bruker AXS

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Iron-Catalyzed Tandem Radical Addition/Cyclization: Highly Efficient Access to Methylated Quinoline-2,4-diones

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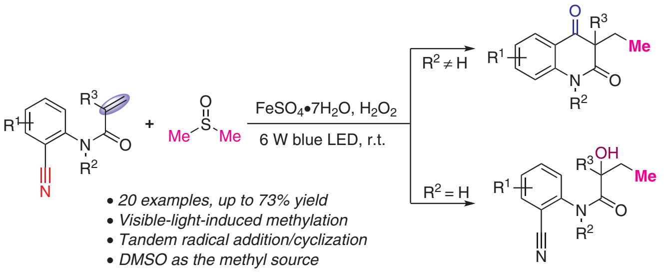

- 20 examples, up to 73% yield
- Visible-light-induced methylation
- Tandem radical addition/cyclization
- DMSO as the methyl source

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Abstract A visible-light-induced and iron-catalyzed oxidative radical addition/cyclization cascade reaction of *N*-(*o*-cyanoaryl)acrylamides with dimethyl sulfoxide has been developed. The method exhibits a wide substrate scope and an excellent functional-group tolerance, thus providing an efficient and convenient access to a variety of methylated quinoline-2,4-diones.

Key words photochemical reaction, iron catalysis, methylation, quinolinediones, cascade reaction

Quinoline-2,4-diones, which show good antiplatelet, antibacterial, and herbicidal activities, belong to a highly valuable class of heterocycles widely found in natural products and pharmaceuticals (for examples, see Figure 1).[1]

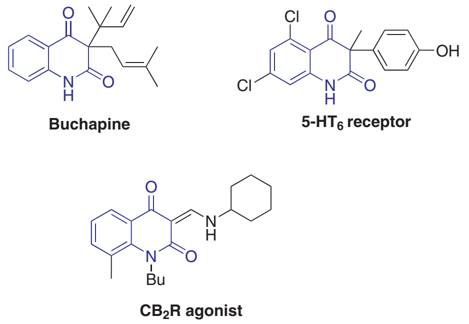

Figure 1 Selected molecules containing quinoline-2,4-dione scaffolds

The importance of quinoline-2,4-dione derivatives has promoted the development of numerous synthetic methodologies.[2] However, classical strategies such as the oxidation of 4-hydroxyquinoline-2-ones[3] or the intramolecular cyclization of *N*-acylanthranilates[4] are limited by the need for complex substrates and/or multiple synthetic steps. Therefore, the development of efficient and straightforward methods for synthesizing quinoline-2,4-diones is of great significance. The direct radical addition/cyclization cascade reaction of *N*-(*o*-cyanoaryl)acrylamides has been demonstrated to be one of the most efficient routes to quinoline-2,4-diones;[5] this process is triggered by radical addition to the C=C double bond, followed by an intramolecular radical cyclization onto the nitrile group and a subsequent imine hydrolysis reaction. A variety of functional groups, such as carbonyl,[6] phosphoryl,[7] sulfonyl,[5d] fluoro-containing groups,[8] or nitro groups,[9] among others, have been successfully incorporated into the quinoline-2,4-dione skeletons through radical oxidation difunctionalization of *N*-(*o*-cyanoaryl)acrylamides. We recently reported a method for introducing a difluoromethyl group into quinoline-2,4-diones under visible-light irradiation.[10]

The methyl group is one of the most prevalent functional groups in biologically active molecules.[11] The so-called magic methyl effect in medicinal chemistry[12] provides constant motivation for the development of simpler but nevertheless efficient strategies and novel but practical sources of methyl groups for the methylation of organic molecules. Apart from conventional methylated metal reagents and organic halides [such as $SnMe_4$, $MeB(OH)_2$, $MeBF_3K$, MeMgCl, MeI, or Me_2CuLi], acetic acid, dicumyl peroxide (DCP),[13] phenyliodine(III) diacetate (DIB),[14] and di-*tert*-butyl peroxide (DTBP)[15] have been reported to act as novel precursors of methyl groups. Furthermore, dimethyl sulfoxide (DMSO), a well-known organic solvent and oxidant, also displays potential as a good source of methyl groups. Recently, a methylation of *N*-arylacrylamides with DMSO to give 3-ethyl-3-methyl-1,3-dihydro-2*H*-indol-2-ones has been reported (Scheme 1).[16] Because of our interest in visible-light-induced difunctionalization of arylacrylamides[10] and the biological and synthetic importance of the methyl group and

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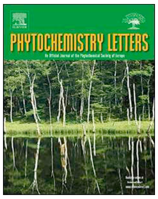

Bisabolane sesquiterpenes and α-pyrone derivative from endophytic fungus *Zopfiella* sp

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ABSTRACT

Three undescribed bisabolane sesquiterpenoids, zopfiellins A–C (**1**–**3**), and one new α-pyrone derivative, zofiellone (**4**), have been isolated from cultures of the endophytic fungus *Zopfiella* sp. Compound **2** is a rare trinor-bisabolane sesquiterpenoid and **3** has an unusual aromatic core. Compounds **3** and **4** possess mild cytotoxicities against three human cancer cell lines with a range of IC_{50} values from 12.3–27.3 μM.

1. Introduction

Natural products have been proved to be good candidates as leading compounds for drug discovery (Newman and Cragg, 2016), while the fungal natural products played an important role (Schueffler and Anke, 2014). As our long-term research interest on fungal secondary metabolites, a large number of bioactive compounds have been reported. For instance, vibralactone from fungus *Boreostereum vibrans* has been identified as a pancreatic lipase inhibitor (Liu et al., 2006), its biosynthesis and total synthesis studies make it a promising leading compound for obesity medicines (Cohen et al., 2013; List et al., 2014; Nistanaki et al., 2019; Yang et al., 2016). Endophytic fungi, due to the process of co-evolution with the host plants, produced a series of secondary metabolites, which have the functions of anti-tumor (Stierle et al., 1993), anti-bacteria (Li et al., 2014), and promoting the stress resistance of the host plant (Ferus et al., 2019; Waller, 2005), *etc.* Our recent studies on endophytic fungi also reported kinds of novel and bioactive secondary metabolites (He et al., 2019; Li et al., 2018; Liu et al., 2006; Wang et al., 2019a, b; Wang et al., 2019c, Wang et al., 2019; Wang et al., 2018). The current chemical investigation on an endophytic fungus *Zopfiella* sp. resulted in the isolation of three bisabolane sesquiterpenoids, zopfiellins A–C (**1**–**3**), and one new α-pyrone derivative, zofiellone (**4**) (Fig. 1). Their structures were identified by extensive spectroscopic methods. All of them were evaluated for their cytotoxicities against three human cancer cell lines. Herein, the isolation, structural elucidation, and cytotoxicites of the compounds are going to be reported.

2. Results and discussion

Compound **1** was isolated as a colorless oil. The molecular formula was determined to be $C_{15}H_{26}O_4$ based on a pseudo-molecular ion peak at m/z 293.17211 $[M + Na]^+$ in its positive mode HR-ESI-MS (calcd for $C_{15}H_{26}O_6Na^+$, 293.17233), implying three degrees of unsaturation in the molecule. The UV spectrum of **1** displayed absorption bands at 235 and 325 nm, showing the typical characteristic of α,β-unsaturated ketone. The IR spectrum suggested the presence of hydroxyl (3412 cm^{-1}), and confirmed the existence of an α,β-unsaturated ketone (1670, 1622 cm^{-1}). The ^1H NMR spectrum (Table 1) of **1** recorded in methanol-d_4 displayed signals for three tertiary methyl groups as singlets at δ_H 1.10 (s), 1.06 (s), 1.24 (s), one secondary methyl group as a doublet at δ_H 1.08 (d, J = 6.9 Hz), one olefinic methine at δ_H 5.78 (s), and one oxygenated methine at δ_H 3.17 (d, J = 9.9 Hz). The ^{13}C NMR data (Table 1) revealed the presence of 15 carbons attributed to three methyls, four methylenes, three methines (including one olefinic carbon) and four quaternary carbons (including one carbonyl carbon, one olefinic carbon) as edited by the DEPT and HSQC spectra.

Based on spectroscopic data analyses and comparison with literature values, it was found that the NMR spectroscopic data of **1** were quite similar to those of trichodone A (Ding et al., 2012), a bisabolane sesquiterpenoid, except for the changes happened in the six-membered ring. According to 2D NMR data (Fig. 2), an α,β-unsaturated

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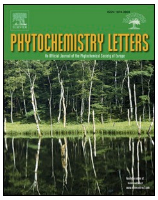

Secondary metabolites from cultures of the kiwi-associated fungus *Diaporthe phragmitis* and their antibacterial activity assessment

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Pseudomonas syringae pv. *actinidae*

ABSTRACT

Three previously undescribed compounds including two ergosterols, diaporthins A and B (**1** and **2**), and a pyrrolidinone derivative, (±)-diaporthin C (**3**), together with three known compounds **4**–**6**, were isolated from cultures of kiwi-associated fungus *Diaporthe phragmitis*. The racemic **3** was further separated into pure enantiomers. Their structures with absolute configurations were elucidated by means of spectroscopic analysis, as well as single crystal X-ray diffraction analysis and electronic circular dichroism (ECD) calculations. Compounds **5** and **6** showed antibacterial activity against *Pseudomonas syringae* pv. *actinidae* with MIC values of 25 and 6.25 μg/mL, respectively.

1. Introduction

Kiwi is a famous fruit that enjoys good reputation all over the world. The kiwi plant has, therefore, become an important economic crop (Richardson et al., 2018). However, the kiwi plant is seriously damaged by the canker disease, which is caused by the bacterium *Pseudomonas syringae* pv. *actinidiae* (Psa) (Gardan et al., 1999; Scortichini et al., 2012; Takikawa et al., 1989). In addition to chemical bactericides such as lime sulfur mixture, streptomycins, and copper preparations, there is still a lack of green and effective Psa inhibitors (Di Lallo et al., 2014; Goto, 1993; Vanneste and Voyle, 2003; Vanneste et al., 2008). Plant endophytic fungi reside in the internal tissues of living plants without causing any apparent disease, which produce a wide variety of secondary metabolites, recognized as a rich source of biomolecules with potential medicinal applications (Gunatilaka, 2006; Shiono and Kimura, 2011; Strobel, 2008; Strobel et al., 2004). In order to find natural antibiotics, this project tried to excavate anti-Psa agents among the secondary metabolites of the endophytes from kiwi plant itself. In our previous work, 3-decalinoyltetramic acids (Yi et al., 2021) and cytochalasins (Zhang et al., 2021) were characterized as anti-Psa agents from the endophytic fungus *Zopfiella* sp. Currently, a selected kiwi endophytic fungus *Diaporthe phragmitis* was studied for its secondary metabolites, which resulted in the isolation of two ergosterols, namely diaporthins A and B (**1** and **2**), a pyrrolidinone derivative, namely (±)-diaporthin C (**3**), together with three known compounds **4**–**6** (Fig. 1). Their structures were established by extensive spectroscopic methods, while structures of compounds **1** and **4** were confirmed by single crystal X-ray diffractions. Compound **3** was a racemate which was further isolated into pure enantiomers, whose absolute configurations were determined by the ECD calculations. All compounds were evaluated for their inhibitory activities against Psa. Herein, the isolation, structure elucidation, and biological evaluation of these compounds are described.

2. Results and discussion

Compound **1** was obtained as colorless crystals. It has a molecular formula $C_{21}H_{32}O_4$ as deduced from the HRESIMS data (measured at *m/z* 371.21848 $[M + Na]^+$, calcd for $C_{21}H_{32}O_4Na^+$ 371.21928), corresponding to six degrees of unsaturation. The IR absorption bands at 3433 and 1722 cm^{-1} revealed the existence of hydroxy and carbonyl groups. The ^{13}C NMR and DEPT data showed 21 carbons, which were assigned as five methyls, five methylenes, three methines, two quaternary carbons, two nonprotonated olefinic carbons, two protonated olefinic carbons, one carboxyl carbon, and one ketone carbon (Table 1). Primary analysis of HMBC and ^1H–^1H COSY data (Fig. 2), as well as the literature investigation, suggested that **1** should be a degraded ergosterol derivative related to fusosteride A (Chen et al., 2018). The major difference was the replacement of a methylene carbon at δ_C 34.4 (d, C-18) in

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New chromone analog and pyrrole alkaloid produced by *Penicillium sclerotiorum* and their antibacterial activity

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ABSTRACT

A new chromone analog (**1**) and a new pyrrole alkaloid (**2**), together with four known compounds, were isolated from the endophytic fungus *Penicillium sclerotiorum* MPT-250 obtained from the stems of *Taxus wallichiana* var. *chinensis* (Pilger) Florin. The structural elucidation of these metabolites was performed by high-resolution mass spectrometry and NMR spectroscopy. Compounds **1** and **5** exhibited significant antibacterial activity against carbapenems-resistant *Pseudomonas aeruginosa* and multidrug-resistant *Enterococcus faecium* with an minimum inhibitory concentration (MIC) value of 3.13 μg/ml respectively.

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KEYWORDS
Penicillium sclerotiorum; chromone analog; pyrrole alkaloid; antibacterial activity

1. Introduction

Bacterial resistance, a terrible hazard to human health, can directly lead to patient treatment failure, increased medical costs, rising mortality, etc. More seriously, development of drug-resistant bacteria even may re-expose humans to the threat of infectious diseases [1–3]. Therefore, the investigation for novel antibiotics against resistant bacteria is urgent and necessary. Discovery of antibacterial drugs such as penicillin, tetracycline, streptomycin, and vancomycin has proved that it is an efficient way to exploit lead compounds from microbial metabolites depending on their structural diversities and extensive bioactivities [4–8]. However, the development and application of microbial active substances make it increasingly difficult to search for novel active structures from conventional microorganisms, and then, the special habitat microorganisms have attracted more attention. Due to their special living environment and long-term mutually beneficial symbiotic relationship with host plants,

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MITOGENOME ANNOUNCEMENT

The complete chloroplast genome sequence of a traditional Chinese medicine: *Achyranthes bidentata* (Amaranthaceae)

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ABSTRACT
Achyranthes bidentata (Amarathaceae) has been commonly used as a traditional Chinese medicine in the treatment of osteoporosis and bone nonunion. Here, the complete chloroplast genome of *A. bidentata* was assembled and characterized. The cp genome is 151,451 bp in length, composed of a pair of 25,150 bp inverted repeat (IR) regions separated by a large single-copy (LSC) region of 83,899 bp and a small single-copy (SSC) region of 17,252 bp. The whole cp genome of *A. bidentata* contains 130 genes(85 protein-coding genes, 37 tRNAs and eight rRNAs) and the overall GC content is 36.5%. Phylogenetic analysis based on the cp genome data showed that *A. bidentata* was close to *Cyathula capitata*.

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KEYWORDS
Achyranthes bidentata; chloroplast genome; medicinal plant; phylogenetic analysis

Achyranthes bidentata Blume (Amarathaceae), has been used for thousands of years as a blood-activating and stasis-resolving medicine for the treatment of osteoporosis in China and India (He et al. 2017). Moreover, its major component, *A. bidentata* alcohol, has anti-asthmatic, anti-inflammatory, anti-pyretic, anti-rheumatic, and diuretic activities (Hua and Zhang 2019), and *A. bidentata* polypeptides (ABPP) possess neuroprotective activity (Shen et al. 2008; Peng et al. 2018). In this study, we aim to establish and characterize the complete chloroplast (cp) genome of *A. bidentata*, and assess its phylogenetic position within Amaranthaceae.

Fresh and clean leaves of *A. bidentata* were sampled from Longping town of Jianshi county, Hubei, China (N30°48′24″, E110°1′47″, 1,750 m). The voucher specimen (HSN12316) was deposited in the herbarium of South-Central University for Nationalities (HSN). The total genomic DNA was extracted and used for sequencing on Illumina HiSeq 4000 Platform at the Beijing Novogene Bioinformatics Technology Co., Ltd. (Nanjing, China). About 2 GB raw data were used to *de novo* assemble the complete cp genome using SPAdes (Bankevich et al. 2012). The complete genome sequence was annotated using PGA (Qu et al. 2019) with manual adjustments. The sequence of cp genome was deposited in GenBank (accession numbers MN652923).

The circular cp genome of *A. bidentata* is 151,451 bp in size, and exhibits a typical quadripartite structure found in most land plants which is made up of a large single-copy region (LSC) of 83,899 bp, a small single-copy region (SSC) of 17,252 bp, isolated by a pair of identical inverted repeat (IR) regions of 25,150 bp. The total GC content of the whole sequence is 36.5%. The complete cp genome encodes 130 genes, including 85 protein-coding genes, 37 tRNA genes, and eight rRNA genes. Most of the genes occurred in a single copy, while four rRNA genes (i.e. *4.5S*, *5S*, *16S*, and *23S rRNA*), seven tRNA genes (i.e. *trnA-UGC*, *trnI-CAU*, *trnI-GAU*, *trnL-CAA*, *trnN-GUU*, *trnR-ACG*, and *trnV-GAC*), and six protein-coding genes (i.e. *ndhB*, *rpl2*, *rpl23*, *rps7*, *rps12*, and *ycf2*) occurred in double. Among the 113 unique genes, 14 had one intron, and three had two introns (*clpP*, *rps12*, and *ycf3*).

The phylogenetic position of *A. bidentata* was analyzed based on the complete cp genomes of this species and other seventeen species belonging to Achatocarpaceae, Amaranthaceae and Caryophyllaceae. The sequences were aligned with MAFFT (Katoh and Standley 2013). The maximum-likelihood (ML) and Bayesian inference (BI) phylogenetic trees were reconstructed using RAxML (Stamatakis 2014) and MrBayes (Ronquist et al. 2012). The ML and BI analyses generated the same tree topology (Figure 1). As shown in the phylogenetic tree (Figure 1), *A. bidentata* was closely related to *Cyathula capitata* with 100% bootstrap and 1.0 posterior probability support, respectively. Our findings will provide a foundation for further investigation of cp genome evolution and phylogenetic studies of *Achyranthes*.

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MITOGENOME ANNOUNCEMENT

Characterization of the complete chloroplast genome of a well-known Chinese medicinal herb, *Scrophularia ningpoensis*

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ABSTRACT
Scrophularia ningpoensis has been used as a famous traditional medicinal herb in Asian countries to treat jaundice, dysentery, and the pain of rheumatism. In this paper, the complete chloroplast (cp) genome sequence of *S. ningpoensis* was reported and characterized. The cp genome is 153,175 bp in length, composed of a pair of 25,490 bp inverted repeat (IR) regions separated by a large single copy (LSC) region of 84,257 bp and a small single copy (SSC) region of 17,938 bp. There were 130 predicted genes (85 protein-coding genes, 37 tRNA genes, and 8 rRNA genes) in the genome, and the overall GC content of the genome is 38%. Phylogenetic analysis based on the cp genome data showed that *S. ningpoensis* was sister to *S. buergeriana*.

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KEYWORDS
Chloroplast genome; medicinal herb; *Scrophularia ningpoensis*; phylogenetic analysis

Scrophularia ningpoensis Hemsl. (Scrophulariaceae), a well-known traditional Chinese medicine herb, has been used for centuries in many Asian countries for the promotion of health and longevity (Yu et al. 2017). In clinical practice, it is commonly used to treat pharyngalgia, arthritis, rheumatism, constipation, tussis, conjunctival congestion and various inflammation diseases, and it is especially effective for the treatment of throat and vocal cord (Zhu et al. 2013; Ma et al. 2019; Su et al. 2019). Here, we reported the complete chloroplast (cp) genome sepuence of *S. ningpoensis*, and revealed its phylogenetic relationships with other species in the *Scrophularia*.

Fresh leave materials of *S. ningpoensis* were collected from Longping town of Jianshi county, Hubei, China (N30°48′24″, E110°1′47″, 1,750 m). Meanwhile, the voucher specimen (HSN12443) were deposited in the Herbarium of South-Central University for Nationalities (HSN). The total genomic DNA of *S. ningpoensis* was extracted and sequenced on Illumina HiSeq 4000 Platform at the Beijing Novogene Bioinformatics Technology Co., Ltd (Nanjing, China). About 2 Gb raw data were used to *de novo* assemble the complete cp genome using SPAdes (Bankevich et al. 2012). The complete genome sequence was annotated using Dual Organellar Genome Annotator (DOGMA) (Wyman et al. 2004) with manual adjustments. The sequence of cp genome was deposited in GenBank (accession numbers MN734369).

The complete cp genome of *S. ningpoensis* represents a typical quadripartite circular molecule with 153,175 bp in size. This genome is composed by a small single copy (SSC) region of 17,938 bp, a large single copy (LSC) region of 84,257 bp and a pair of inverted repeat (IR) regions of 25,490 bp. The GC content of this genome is 38%. There were a total of 130 genes including 85 protein-coding genes, 37 tRNA genes, and 8 rRNA genes in the genome. Most of the genes occurred in a single copy, while four rRNA genes (i.e. 4.5S, 5S, 16S, and 23S rRNA), seven tRNA genes (i.e. *trnA-UGC*, *trnI-CAU*, *trnI-GAU*, *trnL-CAA*, *trnN-GUU*, *trnR-ACG*, and *trnV-GAC*) and six protein-coding genes (i.e. *rpl2*, *rpl23*, *ycf2*, *ndhB*, *rps7*, and *rps12*) occurred in double. Among the 130 genes, twenty of them had one intron, and three had two introns (*clpP*, *rps12* and *ycf3*).

To identify the phylogenetic position of *S. ningpoensis*, phylogenetic analysis was conducted based on the complete cp genome of this species and other six species belonging to Scrophulariaceae. The sequences were aligned with MAFFT (Katoh and Standley 2013). The maximum-likelihood (ML) and Bayesian inference (BI) phylogenetic trees were reconstructed using RAxML (Stamatakis 2014) and MrBayes (Ronquist et al. 2012). The ML and BI analyses generated the same tree topology (Figure 1). As shown in the phylogenetic tree (Figure 1), *S. ningpoensis* was closely related to *S. buergeriana* with 100% bootstrap and 1.0 posterior probability support, respectively. Our findings will provide a foundation for further investigation of cp genome evolution in *Scrophularia*, and also could be further applied for evolutionary and phylogenetic studies of *Scrophularia*.

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附：中文核心首页

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近红外光谱指纹图谱的灵芝品种快速鉴别方法

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摘要:目的　文章利用近红外漫反射光谱法(NIDRS)结合主成分分析(PCA)方法及聚类分析对不同品种的灵芝品种快速判别。方法　对九种540个灵芝样品进行近红外漫反射光谱指纹图谱采集,经多元散射校正(MSC)光谱预处理后,运用主成分分析方法和基于明氏距离度量的聚类分析进行判别分析。结果　通过PCA降维后,前两个主成分贡献率达到82.32%,并通过聚类分析获得了不同灵芝品种间相似性和差异性的分类界限特征。结论　近红外光谱法结合基于多元散射校正指纹图谱的主成分分析方法及聚类分析方法,能快速对灵芝品种判别和确定其分类界限,为灵芝品种快速识别和谱性相似度评价提供一种快速、简便的有效途径。

关键词:灵芝;　近红外漫反射光谱;　多元散射校正;　主成分分析;　聚类分析

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Rapid identification of different kinds of *Ganoderma lucidum* based on near infrared spectroscopy fingerprint information

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Abstract: **Objective** Near infrared diffuse reflection spectroscopy (NIDRS) combined with principal components analysis (PCA) method was employed to identify different kinds of *Ganoderma lucidum*. **Methods** Near-infrared spectra of nine kinds of 540 *Ganoderma lucidum* samples was firstly collected and pretreated by multiple scattering correction (MSC), then the discriminant analysis was performed by PCA and Minkowski distance - cluster analysis. **Results** Contribution rate of the two principle component reached 82.32%, and accurately discriminated obtained by PCA and classification boundary of similarities and differences among different varieties can be also obtained by the cluster analysis. **Conclusion** NIDRS fingerprint information with MSC combined with PCA and cluster analysis as the identification models can effectively to identify varieties of *Ganoderma lucidum* and acquire the classification boundary. The proposed method can as a rapid and effective alternative for identification of *Ganoderma lucidum* species and evaluation of spectral similarity.

Key words: *Ganoderma lucidum*;　NIDRS;　MSC;　PCA;　Cluster analysis

灵芝是我国传统中药中的瑰宝,别名“石耳”,属于真菌门多孔菌科,具有抗肿瘤、抗衰老、降血糖、调节免疫及护肝等药理作用。灵芝作为药食两用的真菌,在医药和食品行业具有广泛的应用[1]。灵芝品种繁多,而不同品种灵芝、野生和人工栽培灵芝功效差异较大,因此,发展一种快速、简便、有效的灵芝品种鉴别方法具有重要的现实意义。目前,灵芝品种鉴别方法主要为感官识别和色谱与质谱联用等方法[2,3]。感官识别方法受人为因素影响大,且存在个体差异,难以客观评价灵芝品种;色谱或与质谱联用能取得理想的结果,但前处理复杂,耗材耗时,难以实现实时在线的快速检测。近红外光谱检测方法由于其简单、快速、分析成本低等优点,近年来被众多学者运用于中药和食品质量控制的在

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·论 著·

石见穿多糖对脂多糖和D-氨基半乳糖胺联合诱导小鼠急性肝衰竭的保护作用

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摘要:目的 研究石见穿多糖(PSSC)对脂多糖(LPS)/D-氨基半乳糖胺(GalN)诱导小鼠急性肝衰竭(ALF)的保护作用及可能机制。**方法** 将昆明小鼠随机分为正常组、模型组、PSSC 30和100 mg·kg^{-1}给药组。给药组每日1次,连续给药1周。给药结束后,除正常组外,其余各组ip给予LPS 10 μg·kg^{-1}和GalN 700 mg·kg^{-1},制备小鼠ALF模型。HE染色法检测肝组织病理变化;用试剂盒法检测血清谷草转氨酶(GOT)和谷丙转氨酶(GPT)及肝过氧化氢酶(CAT)、超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GSH-Px)、丙二醛(MDA)和谷胱甘肽(GSH)水平;DCFH-DA荧光探针法检测肝组织活性氧(ROS)的相对含量;ELISA法测定血清及肝组织中肿瘤坏死因子α(TNF-α)、白细胞介素1β(IL-1β)和IL-6的含量;胱天蛋白酶3活性测试试剂盒检测小鼠肝组织匀浆中胱天蛋白酶3的活性。**结果** 与正常对照组相比,模型组小鼠肝细胞排列杂乱,胞质皱缩,细胞边界模糊,可见较大量的炎症细胞浸润和明显的肝组织内出血,病理评分明显升高($P<0.01$); MDA和ROS含量分别升高至正常对照组的2.2倍和4.3倍($P<0.01$),GSH含量下降至51%($P<0.01$),抗氧化酶SOD,CAT和GSH-Px的活性分别降低至74%,36%和42%($P<0.01$),TNF-α,IL-1β和IL-6的水平有明显提高($P<0.01$),胱天蛋白酶3活性升高至正常对照组的5.3倍($P<0.01$)。与模型组相比,PSSC组小鼠存活比例明显升高($P<0.01$);小鼠肝组织病理评分降低($P<0.01$);MDA和ROS含量升高($P<0.01$),GSH含量下降($P<0.01$);TNF-α,IL-1β和IL-6的含量降低($P<0.01$);胱天蛋白酶3活性降低($P<0.01$)。**结论** PSSC对LPS和GalN联合诱导的小鼠ALF具有良好的缓解作用,该作用可能与降低肝氧化应激、抑制肝炎症反应和细胞凋亡相关。

关键词: 多糖,石见穿;急性肝衰竭;脂多糖;氨基半乳糖

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急性肝衰竭(acute liver failure,ALF)是一种由短时间内肝细胞大量死亡而导致的一种严重临床综合征,死亡率极高。目前临床上特异性地针对ALF的有效治疗手段仍然十分缺乏[1]。石见穿(*Salvia chinensis* Benth.)是唇形科植物华鼠尾草的干燥地上部分,主产于苏、皖、赣、湘、鄂、粤和桂等省区。传统中医认为,石见穿活血化瘀、清热利湿和散结消肿,可用于治疗湿热黄疸、热毒血痢、风湿骨痛、带状疱疹、麻风和跌打伤肿等病症[2-3]。临床上常将该药材用于炎症及肿瘤相关疾病的治疗。多糖是石见穿药材的主要化学成分之一。植物来源的多糖具有广泛的生物学活性[4-6]。石见穿多糖(polysaccharides from *S.chinensis*, PSSC)具有显著的免疫调节活性[7-8]。免疫细胞和免疫因子在ALF发生发展过程中扮演了重要角色。然而,目前关于PSSC对ALF药效作用的理论研究尚不完善。脂多糖(lipopolysaccharide,LPS)和D-氨基半乳糖胺(D-galactosamine,GalN)联合诱导小鼠ALF是实验室常用的ALF动物模型。本研究用该模型评价了PSSC对ALF的缓解作用,并对可能的机制进行了初步探索。

1 材料与方法

1.1 动物、药物、试剂和仪器

昆明种雄性小鼠,8周龄,购自湖北省疾病预防控制中心,SPF级动物许可证书编号:SCXK(鄂)2015-0018。实验小鼠饲养于中南民族大学药学院

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近红外光谱模式识别三聚氰胺掺假牛奶

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摘　要:运用近红外光谱技术结合模式识别方法对液态奶中违法添加三聚氰胺进行快速检测。采集纯牛奶以及9种不同质量浓度掺假三聚氰胺牛奶的近红外光谱图,运用主成分分析方法、线性判别分析方法以及基于虚拟矢量编码的偏最小二乘判别分析方法对纯牛奶和不同质量浓度掺假三聚氰胺的牛奶近红外光谱数据进行判别分析。结果表明,相比主成分分析模型和线性判别分析模型,基于虚拟矢量编码的偏最小二乘判别分析模型的训练和预测性能均最好,识别训练集和预测集正确率能分别达到100%和90.32%。该法简单、快速、准确,为客观评价食品质量等提供了一种新的可选的方法。

关键词:液态奶;三聚氰胺;近红外光谱分析;偏最小二乘判别分析方法
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NIR fiber technology combined with pattern recognition forrapid identification of melamine adulteration in milk

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Abstract: In this paper, near-infrared (NIR) spectroscopy fiber technology combined with pattern recognition was used for rapid identification of melamine adulteration in milk.The fingerprint information of the pure milk and different melamine-adulterated milk were obtained by NIR fiber technology, subsequently, pattern recognition models including principal component analysis (PCA), linear discriminant analysis (LDA) and partial least squares discriminant analysis(PLSDA) based on dummy code of vector were employed to identify the pure milk and different melamine-adulterated level in milk. The obtained results indicated that PLSDA model can achieve a best satisfactory recognition performance compared with PCA and LDA models. Recognition rates of PLSDA model for train set and prediction are 100% and 90.32%, respectively.Therefore, the proposed method holds great potential to be extended as a promising alternative for more applications in food quality control field.

Key words: Liquid milk; Melamine; Near-infrared spectroscopy; pattern recognition

0　引　言

牛奶是一种营养丰富的乳制品,主要通过测定氮含量来判断牛奶品质[1-4]。因此一些不法商贩在牛奶中掺杂三聚氰胺等提高蛋白质含量[5],引发了严重的乳制品安全问题,导致结石、癌症等疾病[6-7]。目前常用的检测方法有高效液相色谱法和液质联用法[8-10],这些方法样品前处理步骤非常复杂。而近红外光纤技术具有成本低,实时在线分析、速度快等优点而被应用于食品品质的快速检测[11-15]。但因近红外光谱难以直接从其吸收峰解析,因此关联合适的化学计量学方法对实现牛奶品质快速判别至关重要[12-15]。

本文针对掺假牛奶的判别问题,运用主成分分析[16-17](principal component analysis, PCA),线性判别分析[17](linear discriminant analysis, LDA),基于矢量编码的偏最小二乘判别分析[18](partial least squaresdiscriminant analysis, PLSDA)三种模式识别方法对光谱数据进行分类判别,所构建的PLSDA模型获得了最佳的判别效果。

1　实　验

1.1　材料与仪器

高钙低脂调制牛奶(部分脱脂调制乳),产地为内蒙古呼和浩特市,其脂肪质量分数为1.3%,蛋白质质量分数为3.0%。

三聚氰胺,化学纯(CP),化学名$C_3H_6N_6$,白色粉末结晶,分子量126.12 g/mol,灼烧残渣(以硫酸盐计)≤0.05%,酸度(以H^+计)≤0.05 mmol/g,乙酸溶液含量合格,含量($C_3H_6N_6$)≥99.0%。

Antaris Ⅱ型傅立叶变换近红外光谱仪;配有光纤工作流的采样系统、InGaAs检测器和石英样品杯;Result软件用于采集光谱;所有算法的编写和数据处理均在MATLAB环境下运行。

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恩施建始县土家族、苗族常见药用植物资源调查

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摘　要：目的：调查湖北省恩施自治州建始县土家族、苗族常见药用植物资源种类，为发展当地传统品牌优势药材提供科学参考，促进资源优势向产业优势转换。**方法：**通过野外标本采集、鉴定与文献查阅等方法，对建始县药用植物资源进行统计分析，采用排除筛选法探明建始县道地药材和鲜药资源品种。**结果：**调查共发现药用植物90科226属376种，其中被子植物77科208属312种，蕨类植物8科8属14种，裸子植物5科10属11种，含道地药材28种，鲜植物药22种。**结论：**建始县药用植物资源丰富，品种繁多，道地药材品质优良，鲜药资源应用历史悠久，具有进一步开发利用价值。

关键词：民族医药；建始县；药用植物；资源调查

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象依然存在，对民间中医药传统知识的传承和发展有一定阻碍。

（4）传承范围较狭窄。本次调查结果表明，中医药传统知识项目的主要来源以祖传为主，自学、民间收集、医院、师承占比较少，项目传承人的学历偏低，传承意识淡漠。尽管一些项目传承人在民间也收了徒弟，但由于传承人本身经济比较拮据，因而学徒对自己以后的发展十分担忧，加之学徒质量不高，导致很多半途而废。此外，即便传承人有意愿招收徒弟，但对于是否要将自己的看家本领全盘教给徒弟，一些人还有顾虑，他们认为这要看学徒的表现。因此，民间特色技术的传承时间紧迫，尤其是对于一些年龄较大的民间中医的传承，更是迫在眉睫。

（5）传承人的知识结构和医学素养较低。本次调查发现，普遍存在中医药传统知识项目传承人的文化素质和传承意识较弱，导致项目的传承和保护均不佳。同时，大部分项目传承人都有对自身医学素养进一步提升的强烈意愿，在临床实践的过程中也发现自身的局限，有的愿意购书自学，大部分则更愿意参加相关培训班学习提高。

近年来，中医药传统知识项目保护工作取得了飞速发展，比如《中医药法》的颁布实施，以及《中医医术确有专长人员医师资格考核注册管理暂行办法》（国家卫生计生委令第15号）和《河南省中医医术确有专长人员医师资格考核注册管理实施细则（暂行）》（豫卫发［2018］6号）等文件的出台，但中医药传统知识项目的保护和推广依然任重道远，需要不断摸索和总结经验，以制定更加符合中医药传统知识项目自身特点的保护措施和制度，更好地为广大患者服务。

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黎族医药的特色与发展现状调查

——以昌江黎族自治县为例

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摘　要：为调查海南省昌江黎族自治县黎医药的特色与传承现状，以黎族聚居的昌江县王下乡为主要调研点，通过问卷调查了当地百姓对黎族医药的了解程度，走访了民间黎族医生、村卫生室、乡卫生院、村镇领导等。调研结果表明，民间黎医难以取得合法身份，黎族医药的发展面临着后继无人的窘迫境地。但民间医药物美价廉，有着深厚的群众基础和丰富的行医经验，是当地百姓健康的重要保障，对现代医疗体系有着良好的补充作用。因此，保护黎族医药健康发展势在必行。

关键词：海南省；昌江县；黎医药；特色；传承与发展

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Study on the Characteristics and Development Status of Li Medicine

——A Case of Changjiang Li Autonomous Country

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Abstract：To investigate the characteristics and development status of li medicine of Changjiang Li autonomous country in Hainan province，the survey was carried out on the basis of fieldwork in Wangxia village of Changjiang country，through analyzing questionnaire，interviewing local residents，visiting folk doctors，village clinics，township hospitals and township leaders.The results of the survey showed that li-medicine is lack of legal protection，which hinders its further marketization and industrialization，and fails to satisfy the socioeconomic requirement.However，folk medicine is simple，convenient，inexpensive and effective，which has a deep folk foundation，as a good supplement to the modern medical system，it is an important means of local residents to prevent and treat diseases.It is necessary to strengthen the protection and inheritance of folk medicine culture through guidance by policies.

Keywords：Hainan Province；Changjiang Country；Li Medicine；Characteristics；Inheritance and Development

黎族医药文化迄今已有三千余年的历史，是黎族人民在漫长的历史进程中同大自然与疾病作斗争所积累和创造的智慧结晶，既是黎族宝贵的文化遗产，也是我国医学宝库中的重要组成部分。卫生部原常务副部长何界生在出席海南首届黎医药论坛暨海南省民族医药学会成立大会时指出“黎族医药是黎族的文化瑰宝，是海南的绿色财富”[1]。

1　黎族医药的特色

经过数千年的医疗用药实践，黎族医药不断汲取融合中医药学、苗医药等传统医药学理论和经验的精华，逐渐形成了独具民族特色的医药理论体系，有着本民族医药特有的基础理论、诊断方法、疾病理论、治疗方法和药物理论[2]。黎医药治疗许多常见病、多发病效果突出，在治疗肝脏疾病、乳腺增生、关节炎、甲状腺结节、胃出血、坐骨神经痛、骨髓炎、股骨头坏死及毒蛇咬等常见病及肿瘤等疑难杂症方面有着独特的疗效，治疗方法形式多样，如药物疗法、骨伤疗法、刮痧疗法、火针疗法、灯草疗法、藤灸疗法和饮食疗法。时至今日，黎医药还在海南中南部黎族村寨发挥着独特作用[3]。

海南植被资源极其丰富，素有“天然药库”之称。黎苗少数民族聚居地五指山地区集中分布了绝大多数药用植

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实验研究

土家药千足虫草抗胃溃疡作用的实验研究

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【摘　要】　**目的**：探究土家药千足虫草多糖提取物对无水乙醇致小鼠胃黏膜急性损伤的保护作用。**方法**：将检疫合格的小鼠随机分为正常对照组、模型组、阳性对照组、低剂量组、中剂量组、高剂量组，以无水乙醇制作小鼠急性胃溃疡损伤模型，测量黏膜出血条带的长度、宽度，计算出血点数目。**结果**：千足虫草多糖提取物中剂量（350 mg/kg）能较为有效地预防无水乙醇引起的小鼠急性胃黏膜出血损伤。**结论**：千足虫草多糖提取物中剂量（350 mg/kg）对小鼠胃黏膜损伤具有一定保护作用。

【关键词】　胃黏膜损伤；千足虫草；多糖；溃疡指数；损伤抑制率

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Study on the Anti－gastric Ulcer Effect of *Arrhenatherum Elatius var. Bulbosum* ‘Variegatum’, a Tujia Nationality Medicine

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Abstract: **Objective** To investigate the protective effect of polysaccharide extract of *Arrhenatherum elatius var. bulbosum* ‘Variegatum’ on acute injury of gastric mucosa caused by anhydrous ethanol in mice. **Methods** The mice were randomly divided into control group, model group, positive control group, low dose group, medium dose group and high dose group. **Result** The medium dose (350mg/kg) of *Arrhenatherum elatius var. bulbosum* ‘Variegatum’ sinensis polysaccharide extract could effectively prevent acute gastric mucosal bleeding injury caused by anhydrous ethanol in mice. **Conclusion** The medium dose (350mg/kg) of *Arrhenatherum elatius var. bulbosum* ‘Variegatum’ sinensis polysaccharide extract had a protective effect on gastric mucosa injury in mice.

Key words: Acute Gastric Mucosal Injury; *Arrhenatherum Elatius var. Bulbosum* ‘Variegatum’; Polysaccharide; Ulcer Index; Rate of Damage Inhibition

胃溃疡是临床多发疾病，调查研究[1]显示大约有 10% 的人曾患胃溃疡。胃黏膜作为胃组织的最表层结构，具有维持胃正常功能的作用，当其受到酒精等因素刺激时，会首先受到损害，长时间将导致胃黏膜产生病理变化[2]。

千足虫草，学名为“球茎燕麦”，又名“银边草”[3]，拉丁名为 *Arrhenatherum elatius var. bulbosum* ‘Variegatum’，为禾本科燕麦草属燕麦草的变种，与原变种区别为杆基部膨大呈念珠状，具有明显的肉质球茎，叶片较长，带状，具黄白色边缘，中间绿。粉末显微特征（如图 1 所示）可见根含复粒淀粉粒、草酸钙簇晶，导管为螺纹导管和梯纹导管；叶含单粒淀粉粒、草酸钙方晶，导管为螺纹导管和梯纹导管。民间主要以其叶子入药，也可以其根入药，但使用叶子居多。割取叶子后用酒浸泡，以药酒涂抹于外伤，对伤口愈合有较为明显的作用。

现代中药研究[4－7]显示中药材中的多糖成分是

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2-苯基吡啶钴配合物的合成、表征与晶体结构

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摘　要　报道了钴参与的2-苯基吡啶（ppy）sp^{2}碳氢键活化反应，通过钴催化的2-苯基吡啶氧化生成2-甲酸吡啶（pcl），以此为配体，合成了一个结构新颖的钴配合物. 通过核磁共振氢谱和X射线单晶衍射对其结构进行了表征. 单晶X-衍射分析表明：该配合物属单斜晶系，C2/c空间群，晶胞参数$a=23.6645(19)$ nm，$b=9.1479(7)$ nm，$c=15.5736(12)$ nm，$\alpha=90.00°$，$\beta=127.2720(10)°$，$\gamma=90.00°$，$V=2682.8(4)$ nm^3.

关键词　2-苯基吡啶；钴配合物；碳氢键活化；氧化；晶体结构

中图分类号　O621.3　**文献标识码**　A　**文章编号**　1672-4321(2018)03-0019-04

Synthetic Characterization and Crystal Structure of 2-Phenylpyridine Cobalt Complex

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Abstract　A novel cobalt complex was synthesized by cobalt-mediated C(sp^2)-H bond activation of 2-phenylpyridine (ppy) and 2-formate pyridine (pcl) as the ligands，in which 2-formate pyridine was formed via oxidation reaction of 2-phenylpyridine by cobalt catalysis. The complex was characterized by ^{1}H NMR and single crystal X-ray diffraction. Single crystal X-ray diffraction analysis shows that the compound belongs to the monoclinic crystal system and is crystallized in space group C2/c，$a=23.6645(19)$ nm，$b=9.1479(7)$ nm，$c=15.5736(12)$ nm，$\alpha=90.00°$，$\beta=127.2720(10)°$，$\gamma=90.00°$，$V=2682.8(4)$ nm^3.

Keywords　2-phenylpyridine；cobalt complex；C-H activation；oxidation；crystal structure

金属参与的有机反应广泛应用于药物分子、天然产物和材料分子的合成. 由于碳氢键是有机化合物中最为广泛的基团，C-H键直接转化为其他官能团的方法引起了科研工作者的极大兴趣[1-3]，利用过渡金属催化的碳氢键活化反应在有机合成上具有非常深远的意义. C-H键直接转化成目标基团能够最大限度地缩短反应路线，减少反应试剂和溶剂的使用，提高反应的效率，是具有原子经济性和步骤经济性的理性合成方法之一[4-6].

利用钯、铑、钌和铱等贵金属催化的碳氢键活化及其反应机理研究已经取得了令人瞩目的成果. 最近，丰富且廉价的第一排过渡金属在构建新的碳碳键和碳杂键方面也展示了独特的催化性能[7]. 尽管如此，钴催化的碳氢键官能团化研究仍然处于初步阶段. 相比铑催化体系，在催化反应过程中钴的活性物种是以什么样的形式存在仍然不清楚. 可能由于碳氢键活化形成的钴络合物具有可逆性，或者环金属中间体活性很高，导致分离和表征存在困难. 合成钴金属络合物，有助于研究钴催化的反应机理，阐明反应的本质，并提供一种设计新反应的研究方案.

吡啶基团是金属有机催化中一类重要的导向基团，通过吡啶基团的导向作用利用过渡金属活化2-苯基吡啶化合物中苯基的sp^2 C-H键，能构筑多种新的碳碳键和碳杂键[8-10]. 在前期工作钴催化的2-苯基吡啶（ppy）sp^{2}碳氢键活化合成二聚体的研究

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油脂营养

石榴籽油在 *D* - 半乳糖诱导的衰老小鼠体内的抗氧化作用

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摘要：研究了石榴籽油（PGSO）在 *D* - 半乳糖诱导的衰老小鼠体内的抗氧化作用。将 60 只昆明小鼠随机分为 6 组：健康组、模型组、维生素 E（V_E）阳性对照组以及 PGSO 低、中、高剂量组，持续给药 45 d 后，测定各组小鼠的体重，分析 PGSO 对小鼠肝、肾、脑与血清中抗氧化系统的作用；检测各组小鼠肝、肾中 G6PD 的活性和 NADPH 含量。结果表明：与模型组比较，PGSO 可拮抗小鼠体重的减轻，降低肝、肾、脑及血清中 MDA 含量，增加 GSH 含量，提高 T - AOC 活性以及抗氧化酶 SOD 和 GSH - Px 的活性；且 PGSO 各剂量组小鼠肝和肾中 G6PD 的活性均增强，NADPH 含量均增加。研究表明 PGSO 对 *D* - 半乳糖诱导的衰老小鼠体内的氧化应激具有明显的拮抗作用。

关键词：石榴籽油；*D* - 半乳糖；衰老小鼠；抗氧化

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Antioxidant activity of *Punica granatum* seed oil on aging model mice induced by *D* - galactose

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Abstract：The antioxidant activity of *Punica granatum* seed oil（PGSO）on aging model mice induced by *D* - galactose was studied. Sixty Kunming mice were randomly divided into six groups：healthy group，model group，vitamin E（V_E）positive control group，and low - ，medium - ，and high - dose PGSO groups. After 45 d treatment，body weights of mice in each group were measured. The effects of PGSO on antioxidant system in liver，kidney，brain and serum of mice were analyzed. And the activity of G6PD and the content of NADPH in liver and kidney of mice were examined. The results showed that PGSO antagonized the decrease of body weight of mice compared with model group. In liver，kidney，brain and serum of mice，PGSO reduced the content of MDA and increased the content of GSH and activity of T - AOC，as well as the activities of antioxidant enzymes SOD and GSH - Px. In addition，in liver and kidney of mice，PGSO elevated the activity of G6PD and the content of NADPH. Taken together，the data indicated that PGSO had the capacity of antagonizing oxidative stress in aging model mice induced by *D* - galactose.

Key words：*Punica granatum* seed oil；*D* - galactose；aging mice；antioxidation

衰老一般是指高等动物随着时间的推移，机体各项机能不断减退的过程[1]。大量研究结果表明，活性氧类（ROS）的积累和氧化应激与衰老的发生发展密切相关。随着年龄的增长，机体内清除 ROS 的抗氧化酶的合成减少、活性降低，氧化和抗氧化平衡失调，过剩的 ROS 与细胞内蛋白质、核酸等生物大

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拍摄于圆明园的地黄林　供图 / 陈艳梅

中华本草——地黄

撰文　梁馨琳　陈艳梅

人们对地黄的认识大多源于风靡大江南北的中成药——六味地黄丸。地黄作为我国民间传统植物药，有着久远的历史记载。其栽培记录亦可追溯到明朝，《神农本草经》中记载：“生咸阳川泽，黄土地者佳，八月采根。”地黄是著名的“四大怀药”之一，其药效久负盛名，早在古代就经丝绸之路传到海外，且被当作名贵药材馈赠给欧

基因组学与应用生物学，2021 年，第 40 卷，第 7-8 期合刊，第 2565-2573 页

研究报告
Research Report

脊椎动物 *GSDM* 基因家族的生物信息学分析

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摘　要　多数脊椎动物的基因组中都存在 gasdermin (*GSDM*)基因家族成员。该家族中的 gasdermin D (GSDMD)和 gasdermin E (GSDME)与高等动物体内的细胞焦亡紧密相关。然而，目前关于 GSDM家族其它成员的研究还比较缺乏，对其系统演化的模式也知之甚少。本研究首先对人 *GSDM* 家族基因的基因结构、染色体定位、表达的组织特异性、编码蛋白的理化性质与二级结构进行了生物信息学分析。随后，对 18 个物种中的 *GSDM* 基因家族成员进行系统进化树的构建和选择压力分析。结果表明，人 *GSDM* 家族各成员的基因结构和表达的组织分布均存在较大差异。其编码蛋白多为酸性，亲水性高，二级结构则以 α- 螺旋与无规则卷曲为主。系统发育分析表明，*Pejvakin* (*PJVK*)和 *GSDME* 存在于脊椎动物的所有类群中，是 *GSDM* 基因家族中的原始成员。*GSDMB*、*GSDMC* 和 *GSDMD* 存在于哺乳动物中，可能是由鸟类 *GSDMA* 演化而来。选择压力分析表明，*GSDMB*、*GSDMC*、*GSDME* 和 *PJVK* 均受负选择作用，且以 *PJVK* 所受的负选择最强。*GSDMD* 则受到明显的正选择作用。以上结果既可为理解 *GSDM* 基因家族的功能提供新线索，又可为进一步针对该家族开展实验研究提供新的参考依据。

关键词　*GSDM* 基因家族; 脊椎动物; 生物信息学; 系统发育; 选择压力

Bioinformatics Analysis of the *GSDM* Gene Family in Vertebrates

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Abstract　The gasdermin (*GSDM*) gene family widely exists in the genome of vertebrates. Gasdermin D (GSDMD) and gasdermin E (GSDME) play important roles in the pyroptosis of cells from higher animals. However, little is known about other members of GSDM family and its system evolution mode. First of all, this study analyzed gene structure, chromosome distribution, tissue-specific expression, physical/chemical properties, and secondary structures of human *GSDM* family genes and their encoded proteins through bioinformatical methods. Then, we constructed a phylogenetic tree of *GSDM* gene family members from 18 species and analyzed the selection pressure. Our results revealed that there were significant differences in gene structure and expression tissue distribution among members of human *GSDM* family. Most of the proteins encoded by human *GSDM* family genes were acidic and highly hydrophilic. The majority of secondary structure of these proteins was α-helices and random coils. Phylogenesis analysis unveiled that *pejvakin* (*PJVK*) and *GSDME* exist in all groups of vertebrates, constituting the original members of the *GSDM* gene family. *GSDMB*, *GSDMC* and *GSDMD* existed in mammals and may be evolved from *GSDMA* in birds. Selection pressure analysis showed that *GSDMD*, *GSDMC*, *GSDME* and *PJVK* were all affected by negative selection and *PJVK* was the most affected. In contrast, *GSDMD* undergoes

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二氧化硫残留量检测新方法研究进展

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摘要:二氧化硫类化合物是国内外允许使用的一种食品/药品添加剂,可发挥防腐、抗氧化、漂白和护色等作用,主要以亚硫酸盐的形式存在。但超过最大允许残留量的二氧化硫类化合物不仅会影响食药的质量,更会损害人体健康。因此准确、高效的二氧化硫类化合物检测方法是食品/药品质量安全的重要保障之一。综述了近五年来食品/药品中二氧化硫残留量的检测新方法,分析了各种技术的优点及不足,并对其发展方向进行了展望。

关键词:二氧化硫;色谱-质谱法;荧光传感法;表面增强拉曼光谱法;电化学分析法;免仪器检测法

中图分类号:TS219;R284.1 **文献标识码**:A **文章编号**:0258-3283(2021)12-1668-09

Advances in New Methods for Detection of Sulfur Dioxide Residues *CHEN Xiao-lei, DENG Gao-qiong, WANG Shuo, WEI Liu-na, CHEN Heng-ye, FU Hai-yan, LAN Wei** (School of Pharmaceutical Science, South-Central University for Nationalities, Wuhan 430074, China), Huaxue Shiji, 2021, **43(12)**, 1668~1676

Abstract: Sulfur dioxide compounds are a class of permitted food/medicine additives, which can play anticorrosive, antioxidant, bleaching, and color protection functions. They mainly exist in the form of sulfites. However, sulfur dioxide residues more than the maximum allowable amount will not only affect the quality of food and medicine, but also harm human health. Therefore, an accurate and efficient method for detecting sulfur dioxide compounds is one of the important guarantees for the quality and safety of food/medicine. The new methods for the determination of sulfur dioxide residues in the last five years were reviewed. The advantages and disadvantages of these methods were analyzed, and the development direction of the detection methods was prospected.

Key words: sulfur dioxide; chromatography-mass spectrometry; fluorescence sensing method; surface enhanced raman spectroscopy; electrochemical analysis; instrument-free testing

二氧化硫是国内外允许使用的一种食品/药品添加剂,主要以焦亚硫酸钾、焦亚硫酸钠、亚硫酸钠、亚硫酸氢钠、低亚硫酸钠等亚硫酸盐的形式添加至食品中[1,2],或采用硫磺熏蒸的方式对食品或中药材进行处理,从而起到漂白、防腐、抗氧化、抑制虫害及霉菌滋生等作用[3-5]。然而,过量添加以及无后续的去除过程等常常会造成食品、药品中的二氧化硫残留量超标,这可能引起哮喘、呼吸困难、荨麻疹、腹痛、低血压以及过敏反应等损害消费者健康的严重后果[1,6]。为维护人民群众切身利益,保障国民健康权益,我国制定了《食品安全国家标准食品添加剂使用标准》(GB 2760—2014)[7],规定了包括葡萄酒等食物在内的二氧化硫类化合物的用量标准,同时《中华人民共和国药典》也明确了各种中药材中其最大允许残留量,并且规定了二氧化硫残留量检测的标准方法。这些标准的成熟方法包括:滴定法、离子色谱法和气相色谱法。然而,食品中 SO_3^{2-}/HSO_3^- 以游离态、可逆结合态和不可逆结合态形式存在,游离亚硫酸盐很容易用现有的大多数方法来定量;通过调整 pH、加热等制样步骤,将可逆性结合的亚硫酸盐释放出来并定量。而不可逆结合的亚硫酸盐非常稳定,很难量化。近年来,新技术和新材料快速发展,如多种多样的纳米材料与光谱技术相结合形成的传感器技术,表面增强拉曼光谱等,均为二氧化硫残留量的检测提供了新选择。本文对近五年来的二氧化硫残留量检测新方法进行了综述,按仪器法和免仪器法进行了分类,并对

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药物化学专业《药物评价学》课程教学内容的更新研究

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[摘 要]针对药物化学专业药物评价学课程教学内容的研究现状和未来趋势，基于创新实践型人才培养的导向，开展药物评价学科教学内容的改革探索。提出了促进教学内容革新化、现代化和实践化等措施，旨在提高学生的学习积极性和理解力、加强学生的理论结合实践的能力，全方位提升教学质量和专业竞争力，满足目前社会对药物化学专业多方面创新应用型人才的需求。

[关键词]药物化学；药物评价学；教学内容；更新；教学质量
[中图分类号]G642.1　　[文献标识码]A　　[文章编号]1007-1865(2021)24-0230-02

Research on Updating the Teaching Content of Pharmaceutical Evaluation in Pharmacochemistry Specialty

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Abstract: According to the research status and future trend of the teaching content of pharmaceutical evaluation in pharmaceutical chemistry specialty, the reform of teaching content of pharmaceutical evaluation was explored with the cultivation of innovative and practical talents as the guide. The measures to promote the innovation, modernization and practice of teaching content are put forward, aiming at improving students' learning enthusiasm and understanding ability, strengthening students' ability of integrating theory with practice, improving teaching quality and professional competitiveness in all aspects, and meeting the current social demand for innovative and applied talents in pharmaceutical chemistry.

Keywords: pharmacochemistry；pharmaceutical evaluation；teaching content；updating；teaching quality

1 引言

高等院校是贯彻国家自主创新战略以及培养创新型人才的主要力量。高校培养创新型人才最基本的要求体现在提升教学质量和完善培养方案，为了实现既定的目标，这就需要对教学内容进行与时俱进的更新，适应社会发展的基本需求[1]。药物评价学是药学类专业，尤其是药物化学和药物分析专业的一门必修课程，是一门理论与实践完美结合的综合性课程。药物评价是指药物从发现到临床应用的整个过程中，对药物从药学、药理学、毒理学、临床医学、管理学、经济学及社会学等进行多角度认识的过程。药物评价不仅贯穿药物研制与应用的全过程，而且还是保证药物研制与应用方法科学合理的重要手段。药物研制与应用水平的高低，在很大程度上取决于药物评价指标与方法的先进性与科学性[2]。

药物评价学是对药物安全性和有效性评价的综合性学科，以药物的评价指标、评价方法为核心，综合药学学科各领域的研究成果，阐述药学科研方法；以新药开发研究与新药报批资料评审内容为主，分析、评价研究方法与资料撰写过程中的常见问题。药物的评价不仅需要结合最前沿的理论知识，还需要与最新的检测手段相结合，因而内容体系种类繁多，更新迅速[3-4]。尽管已经有许多院校开设了相关课程，但是依然存在教学理念较为落后，教学内容较为陈旧的问题，同时，现有的教材只涉及对理论知识的讲解，没有与实际应用相结合，现有的考核和评价指标相对单一。为此，以创新人才培养为导向的教学内容必须进一步进行教学内容的深化改革，进一步适应学校应用型人才培养目标要求。

2 药物评价学课程内容的现状

2.1 理论教学内容较为陈旧

尽管药物评价的方法和手段日新月异，但是教材的更新相对缓慢，严重制约了学生对前沿知识的认知和学习[3]。而目前对于课程的教学改革，大多数停留在对教学手段的革新，很少有对现有教材和教学内容相关的更新，这样严重导致现有的教学内容相对滞后，体系单一，以及与实践教学相偏离。同时，大多数学生还保留着高中时期的学习模式和习惯，以一本书为教材从头到尾灌输课本知识的现象普遍存在，如不改变现有陈旧的教学内容，将会导致学生所学的知识跟不上药物评价学这门学科的前进步伐[3]。

目前药物评价学的经典教材有蒋学华教授主编的《药物评价方法概论》和《药物现代评价方法》，以及刘昌孝教授主编的《药物评价学》，这些教材都系统完整地介绍了药物评价研究的全过程[4-5]。具体包括：药物和药物评价发展概述，药物评价在药学科学中的作用，药物原料药的药学研究，药物制剂的药学评价研究，药理学评价研究，新药的毒理学评价，现代中药制剂评价方法，新药的上市后再评价等等[2]。但是这些教材距离现在有近一二十年的时间，对现有教材的内容进行更新势在必行。李晓辉教授与杜冠华教授合著的《新药研究与评价概论》针对药物评价领域的发展和教学用书的迫切需求，组织国内外著名高校、研究院所、制药企业的15位专家完成，于2013年9月出版发行。此教材的出版部分解决了药物评价领域教材更新慢的问题，但是与药学类的其它专业课的教材相比，药物评价学领域相关教材的出版还是相对滞后的。

2.2 实践性教学内容缺乏

药物评价方法的发展与新药发现方法密切相关。《神农尝百草》的故事就启示我们要敢于尝试，勇于实践。药物的分离、纯化和鉴定、药理活性和毒理活性的测试都是很严谨的实践科学。学好一门课程，尤其是实践性很强的专业课，不能只是停留在对书本上理论知识的学习，一定要理论结合实践，实践是检验真理的唯一标准。

药物评价学所涉及的理论知识非常丰富、同时评价的过程中需要借助各种实验仪器和设备。尽管对仪器使用以及检测方法的介绍较多，但是很多学生对于课本中所讲述的仪器并不熟悉，也不能运用检测方法对药物进行实践操作。而该课程目前没有配套的实验教学内容，即便给学生灌输再多的理论基础，学生也不能将知识灵活应用，无法让学生熟悉药物评价的全过程。对于培养应用型的创新人才，缺乏相应的实践教学，没有相应实验教学是不足的，学生对课程会缺乏足够的认知[7-8]。

2.3 考核与评价方式过于单一

传统的考核与评价方式过于单一，基本都是以一本教材上的理论知识为考核内容，通过期末考试评价学生掌握的程度。这样的考核方式具有很强的针对性，但是也有一定的局限性。不能充分体现出学生学习和运用知识的能力。如前所述，药物评价学是一门实践性要求很高的学科，只对课本上的理论知识点进行考核会极大地限制学生的实践动手能力和创新思维能力，而不利于学生的多元化发展。另一方面，通过每学期的期末考试进行考核与

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