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白玉兰花的代谢物成分及药用价值解析

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摘要: 以白玉兰花(*Magnolia denudata*)为实验材料, 基于液相色谱-质谱联用(LC-MS)代谢组学技术对花蕾和花朵中代谢产物进行分析。共鉴定出492种代谢物, 其中确定药用价值及对应化学结构的化合物共计4类22种: 苯丙素类化合物最多, 其次是萜类化合物、有机酸化合物和生物碱类化合物。本研究解析了白玉兰花蕾和花朵中含有的特殊药用成分及相应药用价值, 并对花蕾与花朵的药用化合物差异进行了比较分析, 发现共有9种化合物在花朵中显著上调, 13种化合物在花蕾中显著上调。白玉兰花朵在抗癌与抗肿瘤、抗流感与抗菌中以及花蕾在抗氧化及抗炎和糖尿病治疗中具有重要的潜在药用价值。

关键词: 白玉兰; 花蕾; 盛花; LC-MS; 代谢产物; 药用价值

Analysis of metabolomic composition and medicinal value of *Magnolia denudata*

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Abstract: The metabolites in flower buds and blooming flowers of *Magnolia denudata* were identified by using liquid chromatography-mass spectrometry (LC-MS) metabolomics. A total of 492 metabolites were analyzed, and 22 compounds of four categories were identified with medicinal value and their corresponding chemical structure: phenylspropanoids were the most, followed by terpenoids, organic acids compounds and alkaloid compounds. In this study, the special medicinal components and their corresponding medicinal values of the flower buds and blooming flowers of *M. denudata* were analyzed, and the differences in medicinal compounds between flower buds and blooming flowers were analyzed. A total of 9 compounds were found to be up-regulated in blooming flowers and 13 compounds were found to be up-regulated in flower buds. The blooming flowers of *M. denudata* have important potential medicinal value in anti-cancer and anti-tumor, anti-influenza and anti-bacterial, as well as the flower buds in antioxidant, anti-inflammatory and diabetes treatment.

Key words: *Magnolia denudata*; flower bud; blooming flower; LC-MS; metabolite; medicinal value

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白玉兰(*Magnolia denudata*)属原始基部被子植物类群木兰科玉兰属高大乔木(Liu等2015), 其树干高大通直, 北方早春时花开满树, 兼具美化环境、药用与观赏价值(徐晨等2021), 深受国内外研究者关注。

白玉兰潜在的药用价值早在我国《神农本草经》中即有记载: 玉兰"皮, 气味苦, 寒, 无毒。恶风癫疾, 明耳目"; 在李时珍的《本草纲目》中也记录到"治酒疸, 利小便, 疗重舌; 花主治鱼哽骨哽, 化铁丹用之"。近年来, 研究者不仅从玉兰树枝中发现厚木酚和香草酸具有抗炎作用(Chung等2015); 还从玉兰果实中发现2种新酚类化合物(denudalide和denudaquinol)可用于药理学研究(Noshita等2009); 此外, 玉兰种子中的厚朴酚和厚朴醇用于研制杀蚊剂(Wang等2019); 特别是玉兰挥发油在我国传统医学中常被用于治疗鼻塞、急慢性鼻窦炎等(尹原森2015; Hu等2018; 程嘉莉等2020), 其主要来源称之为"辛夷"的白玉兰或望春玉兰等的干花蕾。由于早期分析技术的限制, 尚缺乏针对玉兰新鲜盛开花朵的药用成分解析, 且玉兰花蕾及盛花的药用成分差异目前尚不明确。

随着组学分析技术的快速发展, 早期的提取分离方法已不能满足多种成分精准鉴定的需求。基于高分辨质谱分析的代谢组学技术可针对多种代谢产物进行定性和定量分析, 液相色谱-质谱联用(LC-MS)代谢可以检测出相对高分子量化合物(Roessner等2001; Dunn等2008; Becker等2012), 进一步为药用化合物的精准分析奠定基础(Wu等2018; Pang等2016; Wang等2015)。本研究采用LC-MS代谢组学分析白玉兰花蕾和盛花期花朵的代谢物, 深入挖掘白玉兰中具有药用价值的化合物, 通过聚类分析比较不同类别药用化合物在花蕾和花朵中的差异, 对质谱图谱进行深入解析, 为白玉兰药用成分的深入研究提供理论依据。

1 材料与方法

1.1 试验材料

白玉兰(*Magnolia denudata* Desr.)新鲜花蕾及盛开花朵取自北京林业大学校园(40°00'03"N, 116°20'25"E)的白玉兰样株, 树木生长状态良好, 开花时间为3月中旬至4月初。在花期同一时间段内采集其花蕾(B)和花朵(F), 每组6个生物学重复, 立即置于液氮中冷冻, 用于提取及上机检测。

1.2 试验方法

1.2.1 样品制备

白玉兰花蕾、花朵样品各称取80 mg, 加入内标(0.3 $g\cdot L^{-1}$ L-2-氯苯丙氨酸; 0.01 $g\cdot L^{-1}$ Lyso PC17:0, 均为甲醇配置)各20 μL和1 mL的甲醇:水(V:V=7:3); 在–20°C放置2 min预冷, 研磨(60 Hz, 2 min), 超声提取30 min, –20°C静置20 min, 离心10 min (12 000×g, 4°C), 取300 μL上清液挥干, 然后用400 μL甲醇-水(V:V=1:4)复合溶液, 涡旋30 s, 超声2 min。将混合物离心(4°C, 12 000×g, 10 min), 吸取上清, 用有机相针孔过滤器(0.22 μm)过滤样品, 并转移到LC进样小瓶, 进行LC-MS分析。

1.2.2 色谱分析

所有色谱分离均使用AB ExionLC超高效液相(AB Sciex)串联QE高分辨质谱仪(赛默飞世尔科技公司)组成的液质联用系统进行, 色谱柱(100 mm×2.1 mm, 1.8 μm, Waters公司的ACQUITY UPLC HSS T3)进行分离。流动相: A相为超纯水(含0.1%甲酸), B相为乙腈(含0.1%甲酸), 流速0.35 $mL\cdot min^{-1}$。柱温40°C, 进样量5 μL。

1.2.3 质谱分析

样品质谱信号采集分别采用正负离子扫描模式。数据采集采用全扫描模式(m/z范围, 100~1 200)。质谱分析参数为毛细管温度320°C (+)和320°C (−); 离子喷雾电压3 800 V(+)和3 200 V (−); 鞘层气体流量为40 Arb; 辅助气体流量15 Arb; 辅助气体加热器温度, 350°C (+)和350°C (−)。

1.3 数据分析

使用Progenesis QI (Waters公司)对LC-MS数据进行分析, 内标的检测参数根据峰RT比对结果选择并排除同位素峰, 每个离子通过RT和m/z对进行识别, 将60%以上的样品中没有离子信号的峰去除, 采用三维集(质荷比m/z、保留时间RT和峰值强度)获取原始数据组。每个色谱峰的峰面积代表对应物质的相对含量, 对所有数据进行归一化处理, 代谢产物解析根据质谱数据及质谱图谱解析并参照NIST20及本课题组数据库。

2 实验结果

2.1 白玉兰花蕾和花朵的代谢物分析

2.1.1 白玉兰花蕾和花朵代谢物主成分分析

为更加完整检测不同种类化合物, 使用正负离子模式检测白玉兰花蕾和花朵代谢物, 结果显示其色谱特征不同, 保留时间具有重现性和稳定性, 表明本研究代谢组分分析具有可靠性和有效性。实验组的离子峰和RT值高度相似, 峰高与峰面积表现出明显差异, 表明不同实验组样品含有代谢物的种类相似, 但相同物质的含量具差异。

使用无监督投影法对花蕾与花朵代谢物进行主成分分析(principal component analysis, PCA), 得到的第一主成分和第二主成分在总方差中所占的比重分别为34.8%和12.8% (图1), 所建立的PCA模型参数为R^2X=0.583, Q^2=0.8, 两者的值均大于50%, 表明模型建立良好。结果显示, 组内样品聚集程度较好, 不同实验组间能被完全分离, 两组之间差异显著。

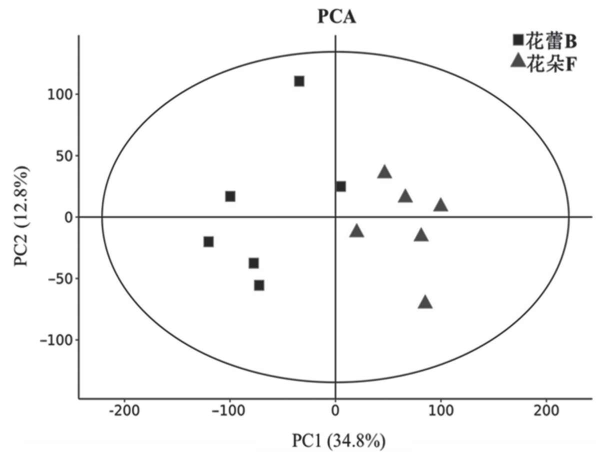

图1 白玉兰花蕾和花朵代谢物主成分分析(PCA)

Fig. 1 Principal component analysis (PCA) of bud and flower metabolites in *M. denudata*

图中每个点对应一个样品, 同一形状的点表示相同的实验组, B、F分别表示白玉兰花蕾、花朵。

2.1.2 白玉兰花蕾和花朵代谢物种类分布

以变量重要性投影值(variable importance in projection, VIP)>1和P<0.05为标准, 筛选得到492种代谢物(表1), 它们分属苯丙素类化合物、萜类化合物、生物碱类化合物、有机酸化合物、有机氧化合物、有机杂环化合物和有机硫化合物。其中数目最多的苯丙素类化合物和萜类化合物占到总数的47.56%, 需予以重点关注。

2.2 白玉兰药用化合物聚类情况分析

在白玉兰花蕾和花朵中共检测到代谢物8类492种(VIP>1, P<0.05), 鉴定出具有药用价值且结构明确的化合物22种, 其在花蕾和花朵的含量差异如图2所示。其中苯丙素类化合物、生物碱类化合物、萜类化合物间苯三酚三聚体A和有机酸化合物谷氨酰胺色氨酸在花蕾中含量普遍较高, 萜类化合物睡茄内酯和有机酸化合物奎宁酸药用成分在花朵中表达较高。苯丙素类中有7种化合物在花朵中上调, 10种化合物在花蕾中上调。

表1 白玉兰代谢物的类别、数目与百分比

Table 1 Metabolites types, numbers and relative percentages of *M. denudata*

类别	数目	百分比/%
苯丙素类化合物(phenylpropanoids)	186	37.80
萜类化合物(terpenoids)	48	9.76
生物碱类化合物(alkaloids)	23	4.67
有机酸化合物(organic acids compounds)	13	2.64
含氧有机化合物(oxygen-containing organic compounds)	30	6.10
有机杂环化合物(organoheterocyclic compounds)	12	2.44
有机硫化合物(organosulfur compounds)	2	0.41
未分类物质(unclassified substances)	178	36.18
总计	492	100.00

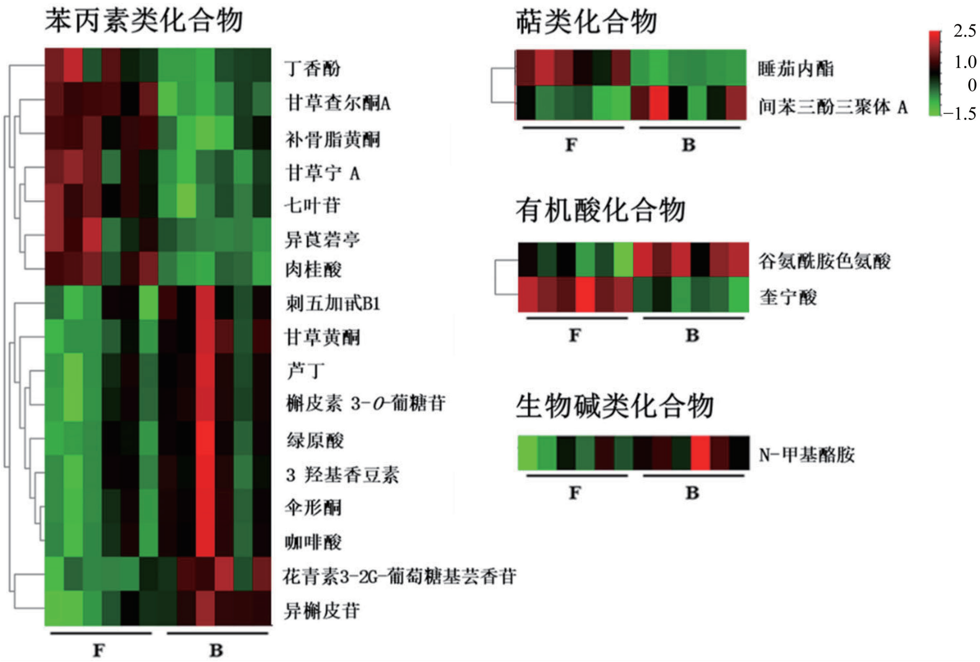

图2 白玉兰花蕾和花朵药用代谢化合物聚类分析

Fig. 2 Cluster analysis of medicinal metabolites in flower bud and blooming flower of *M. denudata*

图中B、F分别表示白玉兰花蕾、花朵。每行表示不同药用代谢化合物在不同样本中的表达量情况, 每列表示不同样品中药用代谢化合物的表达量情况。树状分支表示对不同样本不同代谢物的聚类分析结果, 每部分颜色与代谢物变化的显著性成正比, 其中红色表示上调, 绿色表示下调。

2.3 白玉兰药用化合物化学结构

有药用价值的22种化合物, 属于4个不同种类, 其中苯丙素类化合物最多, 达17种(图3); 萜类化合物2种, 有机酸化合物2种, 生物碱类化合物1种(图4)。

2.4 白玉兰药用化合物药用价值分析

白玉兰花蕾和花朵中含量最多的是苯丙素类化合物, 共计17种, 占所鉴定药用化合物的77.3%。其中具药用价值的苯丙素类主要为芦丁、花青素3-2G-葡萄糖基芸香苷、伞形酮、3-羟基香豆素和槲皮素3-*O*-葡糖苷等, 其在抗氧化、抗癌、抗肿瘤、护肝、抗炎、免疫调节和治疗糖尿病等方面有潜在药用价值。此外, 药用活性物质绿原酸和甘草黄酮等物质在抗氧化、抗流感、抗菌、护肝、护心、抗炎、解热、神经保护、抗肥胖、抗病毒、抗微生物和抗高血压等多种重要作用(表2)。

此外, 白玉兰花中的萜类化合物、有机酸化合物和生物碱类化合物三类药用化合物一共5种, 其中生物碱类化合物中的N-甲基酪胺具促进消化功能。萜类化合物中的睡茄内酯和间苯三酚三聚体 A具抗肿瘤等重要作用。有机酸及其衍生化合物中的奎宁酸具有抗流感功能, 谷氨酰胺色氨酸在与甘草酸联合研制抗流感药物中具重要功效(表2)。

3 讨论

3.1 白玉兰花蕾与花朵的药用成分差异

白玉兰花中成分分析结果显示, 花蕾和花朵的化合物含量存在明显差异。其中芦丁、咖啡酸和异槲皮苷等代谢物在花蕾中的表达量明显高于花朵, 而奎宁酸和肉桂酸等成分表达量在花朵中较高。最近有研究发现苯丙素类中的黄酮类化合物是甲虫潜在的拒食化合物(Austel等2021), 而玉兰花蕾中芦丁、咖啡酸和异槲皮苷的大量产生, 很可能起到防御害虫啃食以保证花蕾顺利发育的功能; 而随着花朵绽放执行繁育功能, 这类化合物含量

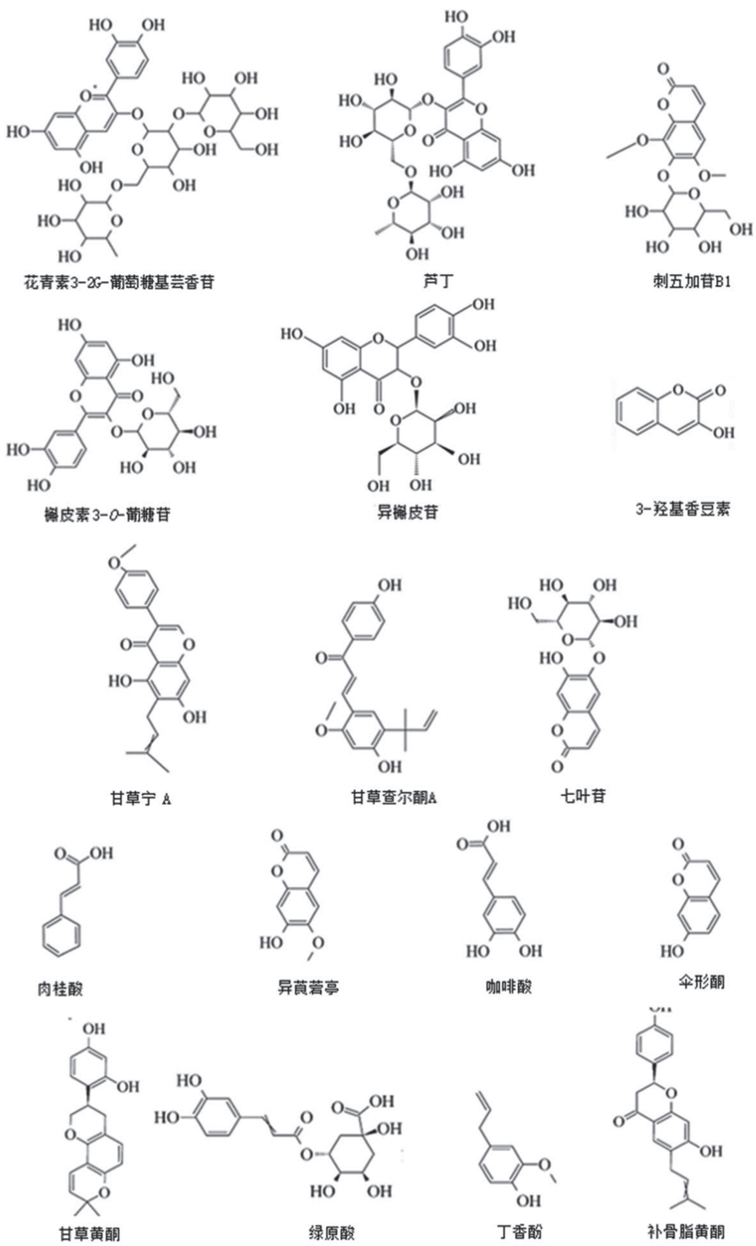

图3 白玉兰苯丙素类药用化合物的化学结构

Fig. 3 Chemical structures of medicinal phenylpropanoids of *M. denudata*

逐渐降低, 睡茄内酯和奎宁酸这两种活性成分开始明显积累。本课题组在前期对木兰科*M. springeri*研究中, 也发现不同阶段代谢成分的明显变化(Wang等2014), 而近期亦有研究发现萜类化合物与植物开花过程中花蜜形成有关, 可保障植物正常授粉(Stpiczyńska等2021)。综上, 我们认为花蕾与盛开花朵在各阶段执行的功能不同, 造成其代谢物存在明显差异, 花蕾与花朵的药用成分及干燥与新鲜材料的药用成分亦存在明显差异, 在研究与应用中需要严格区分。此外, 在发酵后的白玉兰花瓣中还发现了大量酚类物质, 可作为天然抗氧化剂和抗癌剂(Park等2015)。以上研究均证明白玉兰花具有重要的潜在药用价值, 亟待深入研究与分析。

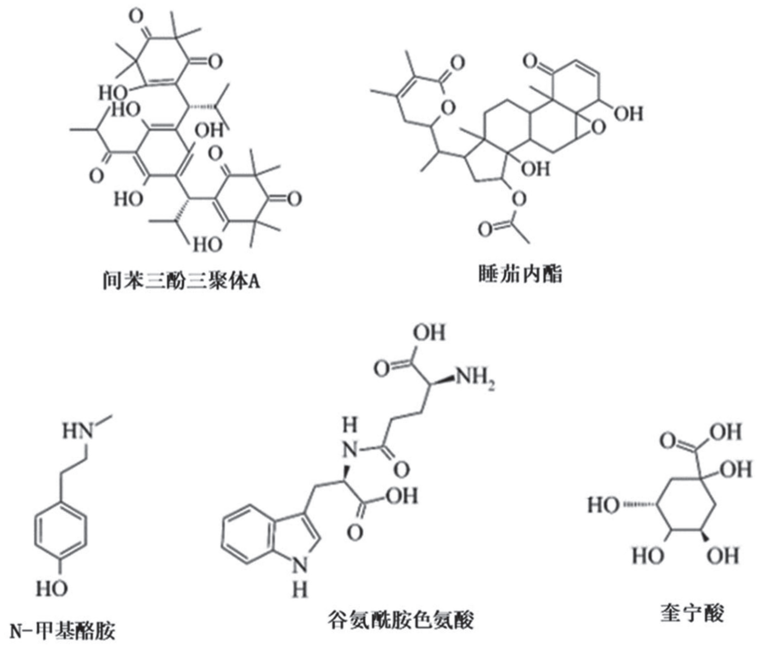

图4 白玉兰其他类药用化合物的化学结构

Fig. 4 Chemical structures of other medicinal compounds of *M. denudata*

3.2 白玉兰花药用化合物潜在价值

本研究筛选并获得492种代谢化合物(表1), 初步解析得到具有潜在药用价值的化合物22种, 涉及苯丙素类化合物、萜类化合物、生物碱类化合物和有机酸化合物4类。以下将针对白玉兰花蕾和花朵中成分进行分类讨论, 以期对玉兰花的药用开发提供依据。

诸多研究表明: 芦丁、伞形酮、槲皮素3-*O*-葡糖苷、异槲皮苷、绿原酸和咖啡酸等10种化合物具有较强的抗氧化作用, 其中芦丁、异槲皮苷和绿原酸等化合物已被证实兼具有抗炎效果(Ghorbani 2017; Mullen等2002; Garg等2020; Orfali等2016; Panda和Kar 2007; Załuski等2018; Shaw等2003; Olas 2020)。本研究发现芦丁等物质多存在于花蕾中, 表明白玉兰花蕾在抗氧化及抗炎和治疗糖尿病中有更大潜在应用。

芦丁可预防结肠癌和前列腺癌等多种疾病(Abdel-Naim等2018), 甘草查尔酮A有抗肺癌和口腔癌的作用(陈康等2021; Shen等2014), 3-羟基香豆素、异槲皮苷和肉桂酸也被证明具有一定抗癌作用(Orfali等2016; Luo等2019; Mousa和Petersen 2009)。以上成分在白玉兰花蕾和花朵均存在, 表明白玉兰花蕾和花朵在抗癌与抗肿瘤中均有潜在应用价值。

有研究发现槲皮素3-*O*-葡糖苷可抗真菌(Safwat等2018), 刺五加苷B1有抗流感作用, 可预防和治疗甲型流感病毒介导的感染(Yan等2018, 2020), 咖啡酸有抗冠状病毒的潜力(Garcia和Spyropoulos 2008; Mani等2020)。以上药用化合物在花蕾和花朵中均有表达, 其在抗流感与抗菌中均具有潜在应用意义。

芦丁、槲皮素3-*O*-葡糖苷、甘草宁A和异槲皮苷被用于治疗糖尿病(Ghorbani 2017; Makino等2013; Cao等2021; Verma等2013), 以上化合物在白玉兰花蕾中表达更多, 花蕾可作为糖尿病天然药用化合物的提取来源。

香豆素类物质已被证实在木兰科植物中存在, 如从朴茨茅斯产荷花玉兰(广玉兰)中分离得到2种香豆素类化合物, 分别为6-甲氧基-7-羟基香豆素和6,8-二甲氧基-7-羟基香豆素(Yang等1994); 从日本厚朴木兰分离出6-烯丙基-8-(5′-烯丙基-2′-羟基苯基)香豆素(Youn等2008); 从柳叶木兰(*Magnolia*

表2 白玉兰主要药用化合物成分

Table 2 Main medicinal compounds of *M. denudata*

化合物类型	化合物名称	VIP值	潜在药用价值	参考文献
苯丙素类	芦丁(rutin)	11.83	抗糖尿病, 抗炎, 抗氧化, 神经保护, 有肾保护和肝保护作用; 抗肿瘤和抗微生物作用; 治疗肠道疾病、阿尔茨海默氏病; 增强骨细胞中的增殖和骨化标记; 清除自由基、刺激成骨细胞生长、降低血糖; 预防结肠癌和前列腺癌等多种疾病; 调节血压; 促进皮肤伤口愈合; 可作为甲醇诱导的结肠肿瘤的抑制剂	Ghorbani 2017; Budzynska等2019; Habtemariam和Belai 2018; Habtemariam 2016; Abdel-Naim等2018; 李玉山2013; Olaleye等2014; Almeida等2012; Deschner等1991
	甘草黄酮(glabridin)	11.22	抗氧化	Carmeli和Fogelman 2009
	绿原酸(chlorogenic acid)	8.06	抗氧化, 抗菌, 心脏保护, 抗炎, 神经保护, 抗肥胖, 抗病毒, 抗微生物, 抗高血压, 清除自由基和刺激中枢神经系统	Naveed等2018; 邢丽娜等2015
	花青素3-2G-葡萄糖基芸香苷[cyanidin 3-(2G-glucosylrutinoside)]	4.46	抗氧化和预防血管舒张	Mullen等2002
	伞形酮(umbelliferone)	3.37	降血脂和抗肿瘤作用抗氧化性能, 保护细胞DNA免受氧化损伤	Sarker和Nahar 2017; Garg等2020
	3-羟基香豆(3-hydroxycoumarin)	3.19	抗癌	Orfali等2016
	槲皮素3-*O*-葡萄糖苷(quercetin 3-*O*-glucoside)	3.11	对巴豆油所致水肿有明显的缓解作用; 具有抗胰腺癌转移治疗的潜力; 抗过敏作用; 抗糖尿病和抗氧化作用; 抑制肿瘤生长因子诱导的胰腺癌细胞迁移; 可抑制谷氨酰胺合成酶和抗真菌活性	Amroun等2021; Lee等2015; Makino等2013; Panda和Kar 2007; Lee等2016; Safwat等2018
	肉桂酸(cinnamic acid)	2.16	抗癌; 治疗静脉血栓栓塞	Mousa和Petersen 2009; Garcia和Spyropoulos 2008
	异槲皮苷(isoquercitrin)	1.86	抗氧化剂, 抗增殖, 抗炎, 抗高血压和抗糖尿病, 抗癌及抗肿瘤; 抗疲劳作用; 对氧化应激, 癌症, 心血管疾病, 糖尿病和过敏反应均显示出多种化学保护作用	Orfali等2016; Luo等2019; Valentová等2014
	刺五加苷B1 (eleutheroside B1)	1.80	抗流感; 预防和治疗甲型流感病毒介导的感染	Załuski等2018; Yan等2018, 2020
	补骨脂黄酮(bavachin)	1.54	抗血管生成和抗肿瘤活性	Nepal等2012
	甘草宁A (gancaonin A)	1.46	治疗糖尿病	Cao等2021
	咖啡酸(caffeic acid)	1.23	抗冠状病毒; 抗氧化剂和抗血小板的潜力	Mani等2020; Olas 2020
	甘草查尔酮A (licochalcone A)	1.16	抗肺癌作用; 抗肿瘤, 抗发炎, 抗细菌和抗寄生虫; 对口腔癌的抗转移作用	陈康等2021; 赵虹等2013; Shen等2014
	七叶苷(aesculin)	1.13	有效降低血尿酸; 利尿活性; 预防结肠炎	Qun等2016; Martín等1990; Tian等2019

表2 (续)

化合物类型	化合物名称	VIP值	潜在药用价值	参考文献
苯丙素类	丁香酚(eugenol)	1.10	抗氧化和抗菌活性	Ogata 2008
	异莨菪亭(isoscopoletin)	1.06	抗抑郁、抗氧化、抗甲状腺降血糖和护肝作用; 抗关节炎作用; 免疫调节作用; 抑制蛋白质糖基化、醛糖还原酶和白内障; 发生; 降血糖和降血脂作用	Capra等2010; Shaw等2003; Panda和Kar 2006; Kang等1998; Pan等2010; Manuele等2006; Lee等2010; Verma等2013
萜类	睡茄内酯(physapubenolide)	3.27	抗肿瘤	Ma等2016
	间苯三酚三聚体A (myrtucommulone A)	1.28	抗癌	Iskender等2016
有机酸	奎宁酸(quinic acid)	3.99	抗流感	Zhang等2020
	谷氨酰胺色氨酸 (glutamyl tryptophan)	1.15	抗病毒感染	Smirnov等2012
生物碱类	N-甲基酪胺 (N-methyltyramine)	4.22	促进消化	Stohs和Hartman 2015

salicifolia)中发现了香豆素类物质(Tsuruga等1991)。本研究发现在白玉兰花蕾与花朵中存在2种香豆素类化合物, 分别是伞形酮和3-羟基香豆素(图3)。香豆素类物质具有较强的抗氧化性能, 可作用于ROS的形成与清除, 进而影响自由基介导的氧化损伤。最新研究还发现该类化合物可保护细胞DNA免受氧化损伤(Sarker和Nahar 2017; Garg等2020), 并证实在降血脂和抗肿瘤方面具有潜在的药用功能。

白玉兰是我国具重要研究潜力的树种之一, 本研究对其花蕾与花朵中药用化合物进行了提取与鉴定分析, 对研究该树种潜在药用价值具有重要的科学意义。花朵作为植物的繁殖器官, 其代谢物成分非常丰富, 在抗癌与抗肿瘤、抗流感与抗菌中均有重要的潜在应用, 白玉兰花蕾在抗氧化及抗炎和糖尿病治疗中有更大潜在作用。综上, 本研究揭示了白玉兰花蕾和花朵的特殊药用成分及其药用价值, 并对花蕾及花朵的药用成分差异进行了对比, 为白玉兰的药用开发提供了数据支撑。

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