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葡萄籽提取物营养成分组成及其生物学功能研究进展

Research progress in nutritional composition and biological function of grape seed extracts

周向辉

ZHOU Xiang-hui

(商丘职业技术学院食品工程学院,河南 商丘 476000)

(*School of Food Engineering, Shangqiu Polytecnic, Shangqiu, Henan* 476000, *China*)

摘要:葡萄籽提取物由于具有较强的抗氧化活性,通常被用作一种营养保健品或膳食补充剂,可用于预防炎症、肿瘤、动脉粥样硬化等代谢疾病。文章综述了葡萄籽提取物中的营养成分组成和生物学功能,总结了葡萄籽提取物中的活性成分在抗氧化、抗炎症、抗肿瘤、抗菌和抗动脉粥样硬化方面取得的最新研究成果,讨论了葡萄籽提取物研究中的不足和未来的研究方向。

关键词:葡萄籽;提取物;多酚;营养成分;生物学功能

Abstract: Grape seed extracts, due to its strong antioxidant activity, is commonly used as a nutritional supplement or dietary supplement. It can be used to prevent metabolic diseases such as inflammation, tumors, and atherosclerosis. This article provides an overview of the nutritional composition and biological functions of grape seed extracts, summarizes the latest research findings on the bioactive ingredients in grape seed extracts in terms of antioxidant, anti-inflammatory, anti-tumor, antimicrobial, and anti-atherosclerosis effects, and discusses the shortcomings and future research directions in grape seed extracts research.

Keywords: grape seed; extracts; polyphenol; nutritional composition; biological function

全球葡萄年产量近 7 800 万 t,其中 57%用于酿造葡萄酒和制造葡萄汁,由此每年产生约 250 万 t 葡萄渣废料[1-2]。其中,葡萄籽占到了近 50%[3]。葡萄籽中含有丰富的膳食纤维、脂质、蛋白质、酚类物质和矿物质[4]。葡萄籽提取物(Grape seed extract,GSE)含有高浓度的多酚化合物,尤其是原花青素,是一种对心血管有益的强抗氧化剂,具有抗氧化、抗炎症、抗肿瘤、抗菌和抗动脉粥样硬化等多种生物活性[5-8]。早在 2011 年,GSE 就被美国食品和药物管理局(FDA)确认为公认安全(GRAS)产品,将它添加至食品中用于营养强化,但目前葡萄籽并未得到充分开发与利用[9]。文章对 GSE 中的化学组成和营养功效展开综述,旨在促进葡萄籽的回收再利用,为葡萄加工副产物的高值化利用提供理论参考。

1 葡萄籽提取物的营养成分组成

1.1 营养成分

葡萄籽(干基)含有蛋白质(11%)、粗纤维(35%)、矿物质(3%)、油脂(7%~20%)和水(7%)[10]。其中蛋白质和油脂主要存在于葡萄籽的胚乳中,而粗纤维主要分布于种皮中。葡萄籽蛋白质中含有所有人体必需的氨基酸,如缬氨酸、甲硫氨酸和苯丙氨酸等[11]。另外葡萄籽蛋白水解液中含有大量疏水氨基酸(占总氨基酸的 38.90%),由于这类氨基酸对血管紧张素转化酶(ACE)活性具有较强抑制作用,可用于加工预防高血压的保健产品[12]。葡萄籽油早在 14 世纪就被西班牙王室作为外用药用于治疗皮肤问题,被誉为"皇家油"或"王室油"[13]。研究[14]发现,葡萄籽油主要的脂肪酸组成为亚油酸(53.6%~69.6%)、油酸(16.2%~31.2%)、棕榈酸(6.9%~12.9%)和硬脂酸(1.4%~4.7%)。葡萄籽油是不饱和脂肪酸的良好来源,其中多不饱和脂肪酸(PUFA)和单不饱和脂肪酸(MUFA)分别占比 56.65%~77.12%和 13.96%~29.63%,其 PUFA 含量明显高于葵籽油、小麦胚芽油、南瓜籽油、芝麻油和米糠油等[15]。

1.2 活性成分

多酚类化合物是整个果实中含量第二多的成分(约

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作者简介:周向辉(1978—),女,商丘职业技术学院讲师,硕士。E-mail:sqzyzxh@126.com

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占29%)[16]，早期研究[17]表明葡萄籽中含有60%～70%的可提取酚类化合物，而葡萄果肉和果皮中只含有10%和28%～35%。目前市场上备受关注的GSE是从葡萄的种子中提取出来的一种多酚物质混合物，其多酚含量多在95%以上[18]，含有15种多酚类化合物，其中主要包括黄烷-3-醇类化合物、黄酮醇类化合物、酚酸类化合物等[19]。

1.2.1 黄烷-3-醇类化合物 黄烷醇类多酚是GSE中主要的类黄酮代谢产物，其基本结构母核为2-苯基氧杂萘，由于黄烷醇均在C环3号位上发生羟化，又被称为黄烷-3-醇类化合物。它的单体结构如图1(a)所示，主要包括：(＋)-儿茶素、(－)-表儿茶素、(－)-表儿茶素3-没食子酸酯、(＋)-没食子儿茶素、(－)-表没食子儿茶素、(＋)-没食子儿茶素3-没食子酸酯、(－)-表没食子儿茶素3-没食子酸酯等[22]。原花青素是由若干个黄烷3-醇类化合物单元通过不同键链接，聚合而成的水溶性多酚类物质，按聚合度大小不同，可分为原花青素单体、低聚体和高聚体。原花青素单体是构成原花青素的主要结构单元，其聚合度为1，而聚合度在1～3的被称为原花青素低聚体，聚合度超过4的被称为原花青素高聚体[23]。

A型原花青素[如图1(b)]由(＋)-儿茶素、(－)-表儿茶素、(－)-表儿茶素3-没食子酸酯或(－)-表没食子儿茶素通过C2—O—C7或C2—O—C5键连接聚合而成，而B型原花青素[如图1(c)]通过C4—C8或C4—C6键连接聚合形成。GSE中的原花青素大多属于B型，且C4—C8键较C4—C6键丰富。而仅有一项研究[24]表明，通过串联质谱分析，白色葡萄品种(霞多丽)中存在A型原花青素。原花青素含量的高低是决定GSE产品质量的关键指标，葡萄籽中原花青素的含量高达30%左右，是葡萄皮中原花青素的2倍[25]。

1.2.2 黄酮醇类化合物 GSE中的黄酮醇类化合物以游离态或与糖结合成苷的形式(*O*-糖苷)存在，具有C6—C3—C6的基本结构，主要包括黄烷酮、黄酮、黄酮醇三大类物质[26]，如橙皮素、柚皮素、槲皮素、山奈酚等(如图2所示)。研究[28]发现，在Noble、Carlos两个品种的葡

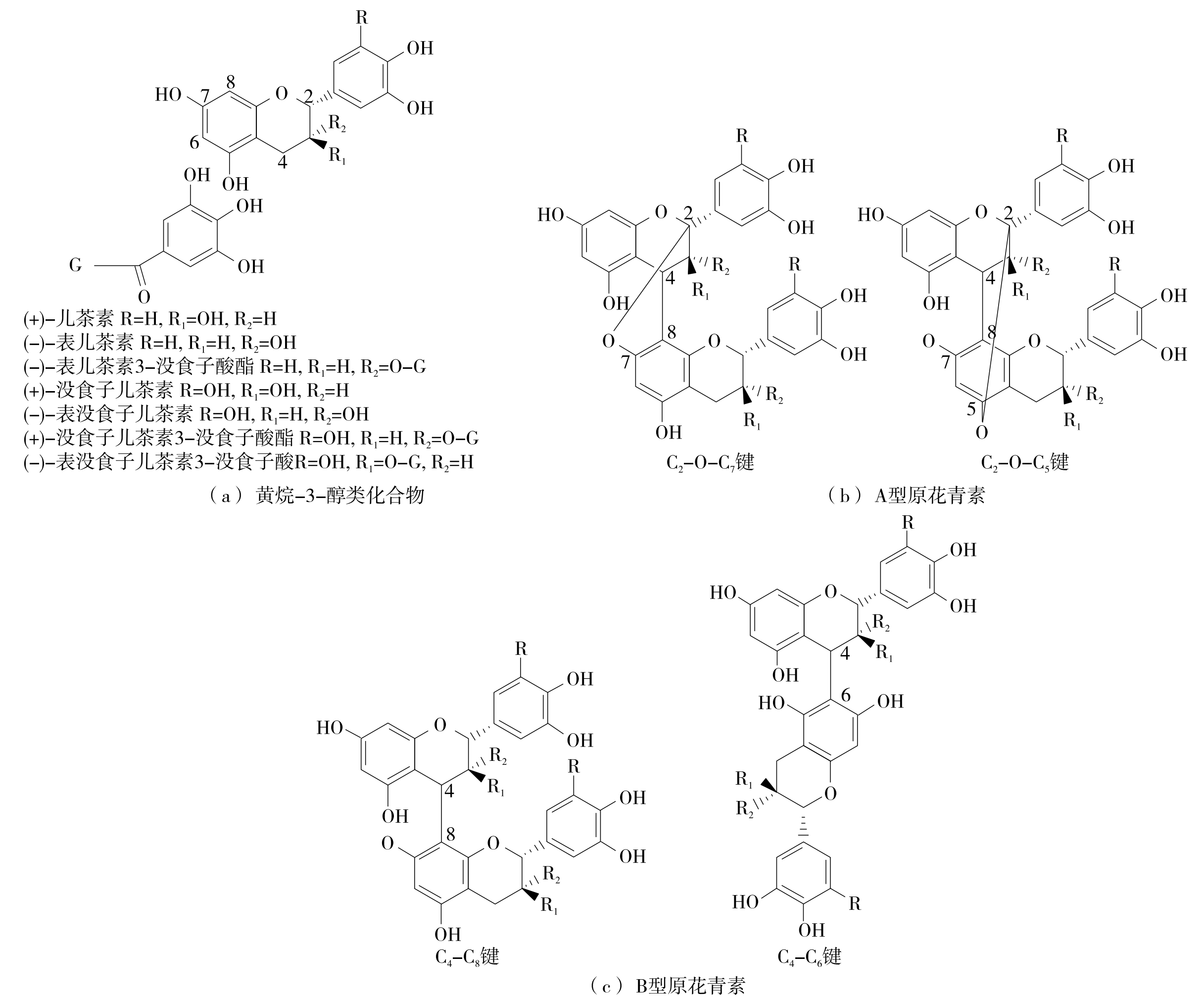


图1 葡萄籽提取物中黄烷-3-醇类化合物的结构式[20－21]

Figure 1 Structure formula of flavane-3-alcohols in grape seed extracts

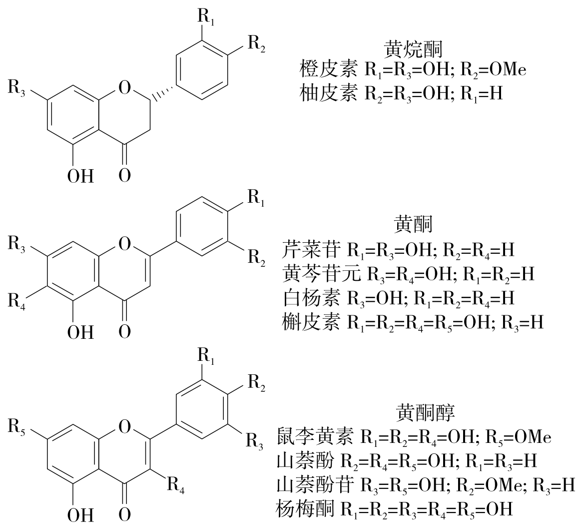


图 2　葡萄籽提取物中黄酮醇类化合物的结构式[27]

Figure 2　Structural formula of flavonols in grape seed extracts

萄籽中检测到 23 种黄酮醇，其中有 8 种槲皮素类、6 种杨梅酮类、6 种山柰酚类，而赤霞珠、雷司令两个品种中共有 21 种黄酮醇。槲皮素衍生物（如槲皮素-3-*O*-半乳糖苷、双脱氢槲皮素）均是葡萄籽中含量最丰富的黄酮醇类型。

1.2.3　酚酸　目前发现 GSE 中的酚酸主要分为 C6—C1 酚酸（具有羟基苯甲酸骨架）和 C6—C3 酚酸（具有羟基肉桂酸骨架）两类（如表 1 所示），前者主要包括水杨酸、*p*-羟基苯甲酸、原儿茶酸、没食子酸、香草酸和丁香酸等；后者主要包括肉桂酸、*p*-香豆酸、咖啡酸、阿魏酸、芥子酸等[30]。酚酸结构简单，分子量较小，20%～25%的酚酸都以游离形式存在，主要贮存在葡萄籽细胞的液泡中。研究[31]显示不同来源的葡萄籽中没食子酸的含量因葡萄品种、地理位置、成熟度、气候条件和采后处理的不同而存在差异，梅洛、霞多丽、圆叶葡萄（*Vitis rotundifolia*）3 个品种葡萄籽中没食子酸含量分别为 10，15，99 mg/100 g。在加利西亚 6 种白葡萄籽提取物中，主要含有没食子酸、原儿茶酸和咖啡酸，其中没食子酸和原儿茶酸在 Treixadura 品种的葡萄籽中含量最高，咖啡酸在 Caiño 品种的葡萄籽中含量最高[32]。

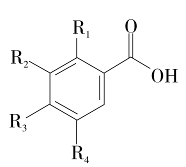
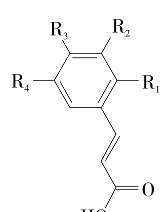
2　葡萄籽提取物的生物学功能

2.1　抗氧化作用

当人体受到外界物理、化学或生物因素的刺激时，会产生自由基。自由基积累过多会加快衰老和诱发一些退行性疾病（如心血管功能障碍、胃肠不适、神经系统疾病、胰腺炎等）。研究[33]发现，葡萄籽原花青素提取物（GSPE）能增强细胞活力，避免高糖诱导的胞内氧化还原代谢紊乱和线粒体功能障碍，其主要原因就在于 GSPE 增强了细胞线粒体功能，调节超氧化物歧化酶（SOD）活性，降低氧化应激，避免高糖诱导的细胞凋亡。GSE 能减轻大脑皮层和海马体的认知功能障碍、神经细胞凋亡和线粒体氧化应激，对保护神经元氧化损伤具有明显的效果。Sun 等[34]研究发现，GSPE 通过增强 Ser9 位点的糖原合酶激酶 3β（GSK-3β）的磷酸化来抑制小鼠线粒体通透性转换孔（mPTP）的打开，减少线粒体超氧化物的产生，防止神经元凋亡。此外，体外试验[35]表明，GSPE 不仅减少了乙醇诱导的人肝癌细胞（HepG2 细胞）中活性氧（ROS）形成和细胞色素 P450 2E1（CYP2E1）的表达，而且还增强了过氧化氢酶（CAT）、SOD 和谷胱甘肽过氧化物酶（GSH-Px）等抗氧化酶的活性，显示出较强的肝脏保护能力。

表 1　葡萄籽中酚酸的分类和化学结构[29]

Table 1　Classification and chemical structure of phenolic acids in grape seed extracts

分类	名称	R_1	R_2	R_3	R_4
 C6—C1 酚酸（羟基苯甲酸骨架）	水杨酸	OH	H	H	H
	p-羟基苯甲酸	H	H	OH	H
	原儿茶酸	H	H	OH	OH
	没食子酸	H	OH	OH	OH
	香草酸	H	OCH_3	OH	H
	丁香酸	H	OCH_3	OH	OCH_3
 C6—C3 酚酸（羟基肉桂酸骨架）	2-羟基肉桂酸	OH	H	H	H
	3-羟基肉桂酸	H	OH	H	H
	p-香豆酸	H	H	OH	H
	咖啡酸	H	OH	OH	H
	阿魏酸	H	OCH_3	OH	H
	芥子酸	H	OCH_3	OH	OCH_3

2.2 抗炎症作用

炎症反应是宿主应对感染和组织损伤而产生的一种保护机制。在此过程中，先天免疫细胞，如白细胞、单核细胞和巨噬细胞等增多[36]，尤其是巨噬细胞在先天性免疫系统中发挥着重要作用[37]。GSE显著地抑制了LPS诱导的RAW264.7细胞中肿瘤坏死因子-α（TNF-α）、白细胞介素-6（IL-6）、诱导型一氧化氮合成酶（iNOS）和一氧化氮（NO）的基因表达和蛋白分泌，这些指标的减少与炎症信号分子丝裂原活化蛋白激酶（MAPK）、核转录因子（NF-κB）的下调有关[38]。炎症是一个内在的生理过程，常伴有多器官的进行性损伤和生理功能障碍，与常见的慢性代谢疾病如胰岛素抵抗、神经退行性疾病、结肠炎、肥胖和糖尿病等密切相关[39]。GSE能够减轻小鼠腹泻、血便、黏膜损伤和炎症浸润等不良症状，潜在机制主要是通过下调炎性细胞因子IL-6、白细胞介素-1β（IL-1β）和TNF-α的mRNA表达以及转录子STAT3的磷酸化，改善小肠上皮细胞的凋亡[40]。

2.3 抗肿瘤作用

天然化合物构成了一个潜在的抗肿瘤药物库，大约60%的抗癌药物都来自天然化合物[41]。GSE中的酚类化合物（尤其是表没食子儿茶素和原花青素）被证明具有抗肿瘤和细胞周期调节活性[42-43]。在体外肿瘤细胞培养试验[44]中，表没食子儿茶素和原花青素能够促进肿瘤细胞凋亡且抑制其生长。GSE在质量浓度为100 μg/mL时可抑制前列腺癌细胞的生长和细胞活力；1.5～15.0 μg/mL时，能显著降低前列腺癌细胞系中DU145细胞和PC3M细胞的群落形成和创面愈合能力；1.5 μg/mL以下时，可降低侵袭性前列腺癌细胞的迁移[45]。GSE的抗肿瘤活性可能主要是通过诱导程序性间皮细胞凋亡产生的。由B细胞淋巴瘤-2（BCL-2）家族蛋白中X蛋白（BAX）提高了线粒体膜通透性，加速了线粒体的破坏，增强细胞色素C的释放，促进细胞凋亡的发生[42]。

2.4 抗菌作用

GSE具有广谱的抗菌性能，能够抑制革兰氏阳性菌（如蜡状芽孢杆菌、金黄色葡萄球菌、凝结芽孢杆菌和枯草芽孢杆菌等）、革兰氏阴性菌（如铜绿假单胞菌、大肠杆菌等）的生长繁殖[46]，且对于革兰氏阳性菌更有效[47]。酚类物质包括白藜芦醇、酚酸类、原花青素、槲皮素和儿茶素等是GSE能够发挥抗菌特性的物质基础。白藜芦醇显示出对金黄色葡萄球菌、铜绿假单胞菌和粪肠球菌等多种致病菌良好的抑制活性，在小鼠正常皮肤表面使用白藜芦醇可诱导抗菌肽的产生，抑制金黄色葡萄球菌的生长，阻止菌体侵入皮肤[48]。而从含量而言，儿茶素和原花青素是主要酚类物质，占GSE中总酚类化合物的77.6%，其可能是GSE的主要抑菌成分[49]。此外，在GSE中表没食子儿茶素没食子酸酯（EGCG）和表儿茶素没食子酸酯（ECG）被证明是对单核增生李斯特菌、鼠伤寒沙门氏菌、大肠杆菌O157:H7、空肠弯曲杆菌等病原菌最有效的抗菌剂。其潜在机制主要归因于EGCG和ECG的结构中存在没食子酰基，它能够抑制细胞成脂分化[50]。研究[51-52]发现，GSE中的酚酸的抗菌机制可能是酚酸的解离使得菌体细胞膜发生过度酸化，改变细胞膜电位，影响细胞渗透压，从而破坏细胞质膜，导致细胞成分渗漏，同时影响ATP合成中涉及的钠—钾ATP酶，干扰胞内能量代谢。

2.5 抗动脉粥样硬化作用

心血管疾病是造成全球发病率和死亡率持续升高的主要原因。据统计[53]，到2030年，全球将有近2 330万人死于心血管疾病。动脉粥样硬化是心血管疾病的主要病理基础，大中型动脉内皮下内膜血管中脂蛋白慢性积聚产生阻塞斑块，导致血管狭窄，限制血液流动并导致严重的组织缺氧，造成心肌梗塞、中风和血栓等一系列临床并发症甚至导致死亡[54-55]。有研究[56]显示，动脉粥样硬化与膳食多酚的摄入呈明显负相关。多酚的抗氧化、抗炎症和其他生物活性能够有效调节免疫系统，促进血管扩张，降低心血管疾病风险[57]。将一种GSE标准补充剂（ECOVITIS®）用于处于早期亚临床动脉粥样硬化的女性，结果显示6个月之后，受试人群的总胆固醇和甘油三酯显著降低，高密度脂蛋白胆固醇显著增加[58]。同样，无症状颈动脉斑块或游离颈动脉内膜中层厚度（CIMT）异常的患者在服用GSPE后，抑制了CIMT的升高，消除了颈动脉斑块，促进颈动脉斑块的稳定，且随着治疗时间的延长，GSPE的抗动脉粥样硬化作用越显著[59]。

3 展望

葡萄加工会产生大量的废弃物即葡萄籽，它富含膳食纤维、蛋白质、油脂和多酚类化合物等多种营养成分，GSE是含有这些丰富的营养成分和活性成分的混合物，具有多种生物学功能。近年来，对食品加工副产物中天然活性成分的研究越来越深入，未来的研究工作可以从以下两个方面开展：① 深化GSE生物学功能及其潜在机制研究。目前关于GSE生物活性的研究基本上还是通过动物模型或体外试验开展的，人群干预试验数据支撑不足，潜在机制不明确。接下来要紧紧围绕临床试验，研究GSE的营养成分和健康功效之间的潜在联系，以助推新型GSE产品的开发。② 进一步提升葡萄加工副产物综合利用水平。葡萄皮渣是具有高营养成分和高经济价值的副产物，除了对葡萄籽中功能性成分利用之外，葡萄皮中仍含有较多的多酚类物质，未来可以集中于全面利用葡萄皮渣，促进葡萄及其加工剩余物的高值化利用。

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