越橘属植物中酚类化合物生物活性研究新进展

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摘　要:酚类化合物作为越属植物中主要活性物质之一,具有降血糖、抗炎、保护视力、神经保护、抗菌等生物活性。本文综述近年来越橘属中花青素类和酚类化合物的生物活性的研究进展,旨在为该属植物及其花青素资源的开发利用提供理论参考。

关键词:越橘属;花青素;酚类;生物活性

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Review on bioactivities of phenolic compounds from *Vaccinium* spp.

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Abstract: Phenolic compounds, as main active substances in genus *Vaccinium*, have various biological activities such as hypoglycemic, anti-inflammatory, vision protection, neuroprotection and antibacterial and so on. In this paper, the research progress of some biological activities of anthocyanins and phenolic compounds from *Vaccinium* in recent years were reviewed. It will provide the latest information for further research and resource utilizations of *Vaccinium*.

Key words: *Vaccinium*; anthocyanins; phenolic; bioactivities

越橘(*Vaccinium*)又名越桔,为杜鹃花科植物,本属约 450 种,分布北半球温带、亚热带,美洲和亚洲的热带山区,而以马来西亚地区最为集中,有 235 种以上。我国已知 91 种,24 变种,2 亚种,南、北各地均产,主产西南、华南。本属有一些种的浆果大,味佳,且富含维生素 C,有较高的食用价值。国产有少数种类如南烛、乌鸦果、越橘等的果、根或叶可药用[1]。越橘属植物中含有多种化学成分,如花青素类、黄酮类、萜类、甾体类、有机酸类等化合物,并具有多种生物活性,如降血糖、抗炎、保护视力、神经保护、抗菌等活性,Liu 等[2]2009 年综述进行了总结。对蓝莓的巨大关注,吸引大量学者对越橘属的花青素类等成分活性不断深入研究。近年又有大量的生物活性研究结果发表,为了更好的开发利用越橘属植物资源,本文对越橘属花青素类及酚类成分的生物活性进行了综述。

1　越橘属中花青素类及酚类化合物研究状况

以蓝莓为代表的越橘属植物的花青素类化合物主要由葡萄糖(glucose)、半乳糖(galactose)、鼠李糖(rhamaose)、阿拉伯糖(arabinose)、木糖(xylose)与花色素连接而成,常见的花色素有 6 种,分别是天竺葵素(pelargonidin)(**1**)、矢车菊素(cyanidin)(**2**)、芍药花素(peonidin)(**3**)、飞燕草素(delphinidin)(**4**)、矮牵牛素(petunidin)(**5**)、锦葵花素(malvidin)(**6**)。

对越橘属中花青素的研究始于 1961 年,Suomalainen 等[3]从黑果越橘(*V. myrtillus*)中发现矢车菊素、矢车菊素-3-*O*-阿拉伯糖苷以及矢车菊素-3-*O*-木糖苷。1966 年 Francis 等[4]从矮丛越橘(*V. angustifolium*)中发现矢车菊素-3-*O*-半乳糖苷、矢车菊素-3-*O*-葡萄糖苷、芍药花素-3-*O*-阿拉伯糖苷以及芍药花素-3-*O*-半乳糖苷。Andersen 等[5]利用 HPLC 从越橘(*V. japonicum*)果实中发现天竺葵素 3-*O*-阿拉伯糖苷和天竺葵素 3-*O*-木糖苷,其中天竺葵素 3-*O*-阿拉伯糖苷含量占到 39%。发展至今,越橘属中的花

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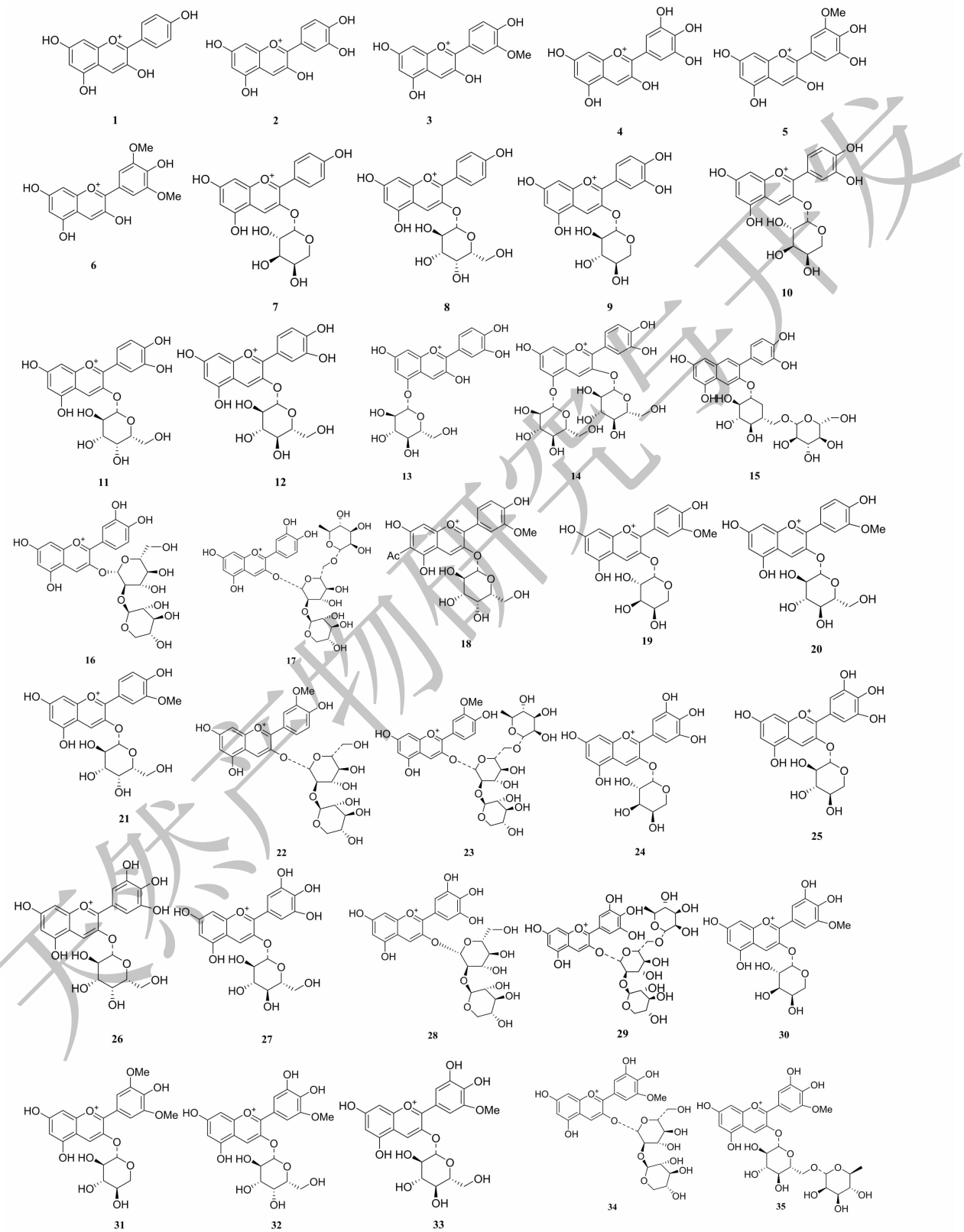
青素类化合物得到极大的丰富,已从该属植物中发现了6中花色素(**1**~**6**),35种花色苷(**7**~**41**)[6],其中含2个天竺葵素糖苷、9个矢车菊素糖苷、6个芍药花素糖苷、6个飞燕草素糖苷、6个矮牵牛素糖苷和6个锦葵花素糖苷,其化学结构见图1。



续图1 Continued Fig.1

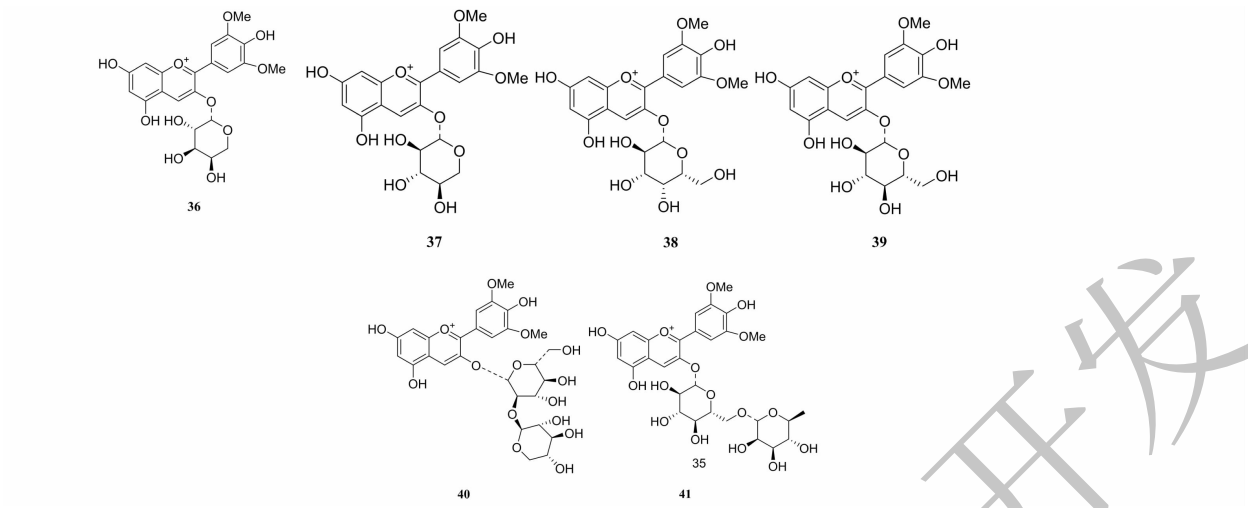


图 1　花青素类化合物的化学结构

Fig. 1　The chemical structures of anthocyanins

2　越橘属化学成分的生物活性

2.1　降血糖

越橘属中含有十分丰富化学化学成分,多种植物在传统医学中被用作抗糖尿病药物。近年来关于其抗糖尿的研究越来越多,充分的实验证据证明,越橘属植物具有良好的降血糖活性。Huang 等[7]采用 D101 大孔树脂柱分离越橘(*V. corymbosum*)果实的甲醇提取物,得到富含奎宁酸衍生物和黄酮类化合物的两个组分,并对提取物进行降血糖活性实验。实验结果显示:葡萄糖转运蛋白-2(GLUT-2)和 PPARγ 的表达在提取物浓度为 400 μg/mL 时显著增加,PPRE 活性也呈剂量依赖的方式增加,此外,越橘提取物还可抑制脂多糖诱导的 NF-κB 活性。*V. cylindraceaeum* 和 *V. padifolium* 越橘治疗Ⅱ型糖尿病实验中,也证明 5-*O*-咖啡基奎宁酸为越橘属抗糖尿病的主要活性成分之一[8]。越橘属植物在降血糖的同时还对血脂、总胆固醇和预防糖尿病引起的视网膜血屏障破裂等具有一定的改善作用,黑果越橘(*V. myrtillus*)叶提取物不仅可降低由链脲佐菌素(STZ)和四氧嘧啶诱导的糖尿病小鼠的血糖,同时还可显著提高胰岛素水平,与糖尿病组小鼠相比,实验组小鼠血浆中低密度脂蛋白水平降低 60.00%、甘油三酯水平降低 40.44%[9,10]。黑果越橘(*V. myrtillus*)提取物在降低 STZ 诱导的糖尿病大鼠的血糖同时,还可下调糖尿病大鼠视网膜血管内皮生长因子(VEGF)表达和降低 zonula occludens-1、occludin、claudin-5 等糖尿病致视网膜病变标志物[11]。南烛(*V. bracteatum*)的多糖同样具有降血糖活性,其降糖机制主要是通过下调 miR-137 来减轻肝脏糖异生,而改善小鼠的葡萄糖代谢[12]。

2.2　抗炎

越橘属植物具有良好的抗炎活性。在小鼠饲料中加入蔓越莓(*V. macrocarpon*)粉,用来治疗氮氧甲烷(AOM)和硫酸葡聚糖钠(DSS)诱导的大肠炎小鼠结肠肿瘤,发现与阳性对照小鼠相比,饲料中添加 1.5% 的蔓越莓干粉可显著降低小鼠的肿瘤发生率(50% *vs* 80%)、肿瘤多样性(2.77 ± 0.88 *vs* 5.91 ± 1.01)、肿瘤负荷(4.64 ± 1.26 *vs* 17.69 ± 2.48)和平均肿瘤大小(10.28 ± 1.33 *vs* 18.78 ± 1.89),从而显著抑制结肠肿瘤的发生,此外还可降低 AOM 和 DSS 诱导小鼠的 IL-1β、IL-6、TNF-α 的表达水平[13]。越橘(*V. vitis-idaea*)果实抑制 3T3-L1 脂肪细胞和 RAW264.7 巨噬细胞炎症的实验中,发现其提取物可以显著降低 IL-6、MCP-1、IL-1β 和 COX-2 的表达水平[14]。Pandir 等[15]使用含 42.04% 花色苷的越桔提取物对痤疮丙酸杆菌和 LPS 诱导的小鼠肝损伤和巴豆油诱导的小鼠耳部水肿的抗炎作用实验中,发现其提取物可以有效抑制巴豆油引起的耳部水肿和痤痤疮丙酸杆菌、LPS 引起的肝脏炎症反应。Pereira 等[16]将越橘(*V. corymbosum*)提取物中富含花青素的组分和 5-氨基水杨酸的抗炎强度作了比较,结果表明越橘提取物可降低促炎介质和 ROS 的产生,其作用强于 5-氨基水杨酸。临床实验发现蔓越莓(*V. macrocarpon*)提取物对类风湿关节炎有一定抑制作用,但作用机制目前尚未阐明。对细胞抗炎的作用机制被认为是越橘提取物通过抑制 NF-κB

信号通路来发挥抗炎作用[17-20]。

2.3 保护视力

越橘属植物富含多酚类物质。在一项对受试者进行问卷进行弱视评估的临床试验中,受试者通过口服越橘(*V. uliginosum*)提取物 1 000 mg/天 4 周后,实验组通过口服越橘提取物口服能有效缓解平板电脑观看引起的视疲劳症状[21]。笃斯越橘(*V. uliginosum*)的多酚提取物通过抑制 m-钙蛋白酶介导的晶状体蛋白水解和氧化应激,对硒诱导的大鼠晶状体白内障形成起保护作用[22]。老年性黄斑变性(AMD)是导致老年人视力下降和失明的主要原因,而 A2E 过度积累导致视网膜色素(RPE)凋亡是 AMD 的重要决定因素。多项实验表明,越橘(*V. uliginosum*)提取物不仅具有抑制蓝光诱导的光氧化作用,还能抑制细胞内 A2E 的积累,使 RPE 细胞在蓝光照射下存活,可以减少和预防蓝光诱导的视网膜损伤[23-25]。

2.4 神经保护作用

近年来越橘植物的神经保护作用研究明显增多。Shukla 等[26]用 mk-801 诱导小鼠致精神病,然后给予越橘(*V. macrocarpon*)水提物(1 和 2 g/kg)治疗 14 天,之后检测发现 mk-801 诱导的小鼠大脑中 DA、5-HT 和 NA 水平显著升高,GABA、谷氨酸和甘氨酸水平下降,表明越橘水提物可明显改善实验性精神病患者的行为症状,具有神经调节、降低氧化应激作用。对东莨菪碱诱导的小鼠失忆模型给予口服越橘(*V. crymbosum*)提取物 7 天,对小鼠使用迷宫行为测试,口服越橘提取物组的小鼠行为表现出明显的认知功能恢复,并证明了提取物对东莨菪碱致小鼠健忘症模型有改善作用,其作用与脑源性神经营养因子(BDNF)/cAMP 反应元件结合蛋白(CREB)/丝氨酸苏氨酸激酶(AKT)信号通路的激活有关[27]。南烛(*V. bracteatum*)的提取物通过激活 5-HT1A 受体介导的细胞内 Ca^{2+} 和 ERK1/2 磷酸化,在 5-HT1A 受体上表现出强烈的激动作用,具有镇静催眠、抗抑郁的作用[28,29]。兔眼蓝莓(*V. virgatum*)的提取物经 HPLC 分析主要成分为飞燕草素,其提取物对三甲基锡(TMT)诱导的小鼠神经毒性的体外神经保护作用和体内学习记忆作用的研究中中发现,提取物通过抑制脂质过氧化作用降低了 TMT 诱导的记忆损伤水平[30]。

2.5 抗菌

越橘属植物的挥发油及果实和叶的提取物均有抑菌作用,近年来较多研究是对大肠杆菌的抑制作用。Bayar 等[31]从越橘(*V. myrtillus*)挥发油中鉴定出 22 种成分,并进行抑菌实验,发现越桔挥发油对菌核病菌、黑斑病菌、红孢镰刀菌菌丝生长有抑制作用。Susana 等[32]发现,越橘(*V. floribundum*)果实和叶片的提取物的抗菌实验发现,对革兰氏阴性细菌如寒沙门氏菌,弧菌、鳗弧菌、创伤弧菌、大肠杆菌的生长具有显著抑制作用。Silva 等[33]发现槲皮素-3-葡萄糖苷、绿原酸和咖啡酸是越橘(*V. corymbosum*)水提物的主要成分,用其叶片和果实的提取物分别以 12.5 和 50 mg/mL 的浓度,可以抑制金黄色葡萄球菌的生长。Rodríguez-Pérez 等[34]从蔓越莓(*V. macrocarpon*)提取物中对大肠杆菌具有较强的抗菌活性,从中分离出 13 个酚类化合物,显示出不同的抑菌活性作用。与对照组比较,杨梅素和槲皮苷能够显著降低大肠杆菌生物膜的形成,而二氢阿魏酸葡糖苷、原花青素 A 二聚体、槲皮素葡糖苷、杨梅素则能够显著降低大肠杆菌表面疏水性。蔓越莓提取物对大肠杆菌还具有抗粘附活性[35]。腺齿越橘(*V. uliginosum*)和樟叶越橘(*V. vitis-idaea*)等也有一些抑菌研究报道,其提取物能够抑制嗜干真菌和非嗜干真菌可见菌落的生长[36-39]。

2.6 对内脏器官保护作用

越橘属植物对肾脏、肝脏、卵巢以及心血管等有一定保护作用。Akbari 等[40]发现,越橘(*V. arctostaphylos*)果实提取物具有对庆大霉素致大鼠肾毒性的保护作用。在喂饲越橘水提物 30 天后,小鼠心脏抽取血液样本中测定血清肌酐(Cr)、尿素氮(BUN)、钠、钾水平。结果表明:越橘果实水提物显著增加血清尿素、肌酐、近曲小管体积、远曲小管体积、肾小球,显著减少血管体积和间质组织,并且在提取物浓度为 400 mg/kg 时影响最大,表明越橘果实提取物对庆大霉素引起的肾脏损害具有保护作用。Zhang 等[41]发现,南烛(*V. bracteatum*)的部分提取物,具有对 $KBrO_3$ 诱导的肾脏损伤具有保护作用,从中分离鉴定出 isoorientin (**1**)、orientin(**2**)、牡荆素(**3**)、isovitexin(**4**)、异槲皮苷(**5**)、quercetin-3-*O*-*α*-*L*-rhamnoside(**6**)和 chrysoeriol-7-*O*-*β*-*D*-glucopyranoside(**7**)等 7 个化合物。Gong 等[42]发现,越橘提取物(*V. corymbosum*)对镉致小鼠肝毒性具有保护作用,提取物能以剂量依赖方式恢复肝脏抗氧化防御系统的活性,使镉中毒引起的形态学改变恢复到接近正常水平,并且可与肝脏中的镉螯合以减轻镉的水平。黑

果越橘(*V. myrtillus*)提取物对大鼠卵巢缺血再灌注损伤以及一些重金属如镉、铂所致的卵巢损伤有保护作用[43];再灌注损伤试验 10 天后,重金属组的大鼠其卵巢组织出现严重水肿、血管充血、出血、卵泡变性等病理损害;而越橘提取物组的大鼠卵巢组织中丙二醛含量明显增加,超氧化物歧化酶、过氧化氢酶、谷胱甘肽过氧化物酶和谷胱甘肽-S-转移酶(GST)活性下降。越橘能降低铂、镉诱导的卵巢毒性,从而减轻自由基损伤,但并不能完全保护大鼠卵巢组织[44,45]。越橘对大鼠心血管的作用主要体现在保护软膜的微循环,防止血管收缩、微血管通透性,减少白细胞粘附方面[46,47]。

2.7　抗肥胖

越橘在抗肥胖同时还可对肥胖引起的并发症如高血脂、高血压等有改善作用。越橘(*V. ashei*)的花青素对高脂饮食诱导的肥胖雄性 C57BL/6 小鼠的抗肥胖实验中,发现当花青素浓度为 200 mg/kg 时,八周后可降低小鼠体重 19.4%,并有效地降低血清葡萄糖,减弱附睾的脂肪细胞,改善血脂水平,并显著抑制 TNF-α、IL-6、PPARγ 和 FAS 的表达[48]。蔓越莓(*V. macrocarpon*)提取物可降低高脂饮食小鼠体重,其脂质过氧化、蛋白羰基化(肝脏和脂肪组织)和肝脂肪积累都相对较低[49]。黑果越橘(*V. myrtillus*)叶提取物能显著降低肥胖鼠体重增加和内脏脂肪量积累,而且血清中三酰甘油、游离脂肪酸、总胆固醇和低密度脂蛋白胆固醇水平也显著降低[50]。越橘(*V. arctostaphylos*)提取物可改善肥胖患者的高血压,并无相关的不良反应,具有一定的安全性和耐受性[51]。因此,越橘提取物在用于治疗肥胖或肥胖相关的疾病应用有巨大的前景。

2.8　抗氧化

HPLC 对黑果越橘(*V. myrtillus*)提取物的分析中发现,含量最高的酚类物质为绿原酸,其次是其原儿茶酚酸、白藜芦醇等;其提取物具有显著抗氧化活性,而且其抗氧化活性主要取决于多酚类物的含量[52]。研究发现:大果越橘(*V. macrocarpon*)果实的正丁醇萃取组分是抗氧化活性最强的部分,其 DPPH 清除活性达 87.0% ± 1.15%[53]。Šaponjac 等[54]发现:黑果越橘(*V. myrtillus*)提取物分成三个组分,第三个组分中分离鉴定了 8 种酚酸,对香豆酸含量最高,为 57.87 mg/100g,其自由基清除作用最强。近年研究还特别关注外界因素对越橘植物抗氧化能力的影响,如镉可增加越橘中绿原酸含量,进一步增强抗氧化能力[55]。在 5 月、7 月和 9 月收获的越橘(*V. myrtillus*)叶中熊果苷和茎中黄烷醇的含量最高,而 7 月采收的越橘表现出最强的抗氧化能力[56,57]。

3　展望

我国越橘属植物种类丰富,分布广泛,其化学成分以酚类化合物为主,而其中的花青素又是研究最为广泛和深入的酚类化合物之一,多年的研究已经表明其具有抗氧化、抗炎、抗菌等生物活性。而近年来对越橘属的多项研究结果也表明,越桔属植物在抗肥胖、降血糖、保护视力等亚健康疾病上表现出良好的治疗效果,但还有大量的研究空白和广阔的空间。该属植物在未来在食品、化妆品、医药等方面都具有巨大的研究开发前景,值得大力推进。

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