天然花青素的抗氧化机制及功能活性研究进展

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摘 要: 花青素是一类广泛存在于被子植物中的天然水溶性色素, 因特殊的化学结构而具有较强的抗氧化活性, 在食品、药品、护肤品等领域广泛应用。花青素的抗氧化性是其生理活性的基础。本文从减少活性氧积累和清除自由基、激活酶抗氧化系统、减少 DNA 损伤、与金属离子发生作用 4 方面综述了花青素可能的抗氧化机制; 从抗肿瘤作用、抑菌作用、对脂类和糖类代谢的调节作用、抗疲劳和抗衰老作用和调节肠道菌群 5 方面介绍了花青素的功能活性, 以期为进一步拓宽花青素的应用领域提供理论参考。

关键词: 花青素; 抗氧化性; 抗氧化机制; 功能活性

Research progress on antioxidant mechanism and functional activity of natural anthocyanin

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ABSTRACT: Anthocyanin is a kind of natural water-soluble pigment widely existing in angiosperms, due to its special chemical structure, anthocyanin has strong antioxidant activity and is widely used in food, medicine, skin care and other fields. The antioxidant activity of anthocyanin is the basis of its physiological activities. This paper reviewed the possible antioxidant mechanisms of anthocyanin from 4 aspects: Reducing the accumulation of reactive oxygen species and scavenging free radicals, activating enzyme antioxidant system, and reducing DNA damage, and interacting with metal ions; the functional activities of anthocyanin were introduced from 5 aspects: Anti-tumor effect, antibacterial effect, regulation of lipid and carbohydrate metabolism, anti-fatigue and anti-aging effect, and regulation of intestinal flora, in order to provide theoretical references for further broadening the application field of anthocyanin.

KEY WORDS: anthocyanin; oxidation resistance; antioxidation mechanism; functional activity

0 引 言

花青素(anthocyanin), 又称花色素, 是花色苷(anthocyanins)水解而得的有颜色的苷元。花青素属于生物类黄酮物质, 是一类水溶性天然色素, 可以随着光照、温度和土壤 pH 等的变化, 使花瓣和果实显示出紫色、红色或蓝色等多种色彩[1]。天然花青素广泛存在于被子植物中, 已知 27 个科、73 个属 7000 余种植物中均含有花青素, 其中以黑枸杞、蓝莓、桑葚等浆果中含量较多[2]。

对花青素的研究始于十九世纪八十年代, 主要集中于花青素的提取和纯化工艺的研究, 开发了超声[3]、酶辅助[4]、微波[5]、双水相[6]、亚临界辅助[7]、超临界流体辅助[8]等提

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取方法, 发展了大孔树脂吸附[9]、高效液相色谱[10]、离心分配色谱[11]、膜吸附[12]等纯化方法。

研究表明, 花青素的高日常膳食摄入量与癌症、心脑血管疾病等多种疾病的发生风险降低有关[13−14], 随着人们对花青素研究的逐渐深入, 其抗肿瘤作用、抑菌作用、对脂类、糖类代谢的调节作用、抗疲劳和抗衰老作用和调节肠道菌群等功能活性已逐步成为研究的热点[15−17]。澳大利亚等国家和地区针对当地特色植物建立花青素数据库, 以指导当地居民的花青素摄入量[18]。本研究从花青素的化学结构出发, 探讨其抗氧化机制, 并对其功能活性进行综述, 以期为进一步拓宽花青素的应用领域提供理论参考。

1 花青素的化学结构

花青素以 C6 (A 环)-C3 (C 环)-C6 (B 环)结构为基本骨架, 基本结构是 2-苯基苯并吡喃阳离子, 如图 1 所示。由于花青素结构中不同碳位上发生的甲基化和羟基化修饰, 即 B 环上 R_1 和 R_2 位置取代基不同, 形成各种各样的花青素。继 1947 年法国 Bordeaux 大学在读博士 Jack Masquelier 在花生仁的包衣中第一次发现花青素[19]以来, 已有 27 类, 超过 700 种的不同花青素被发现和鉴定[20]。自然界中常见的花青素主要有矢车菊素(cyanidin, Cn)、飞燕草素(delphindin, Dp)、天竺葵素(pelargonidin, Pg)、矮牵牛素(petunidin, Pt)、芍药素(peonidin, Pn)、锦葵花素(malvidin, Mv) 6 类。

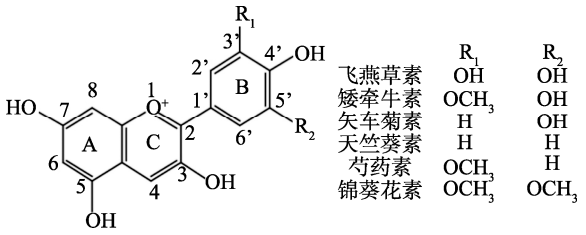

图 1 花青素的基本化学结构

Fig.1 Basic chemical structure of anthocyanin

2 花青素的抗氧化机制

氧化应激与糖尿病、癌症和心血管疾病等人类退行性疾病的发病机制有关[21]。花青素的抗肿瘤、抗衰老、调节代谢、抑菌等生理功能均以其优良的抗氧化能力为基础。花青素的抗氧化机制主要表现在减少活性氧(reactive oxygen species, ROS)积累和清除自由基、激活酶抗氧化系统、减少 DNA 损伤以及与金属离子发生作用等方面。

2.1 花青素的抗氧化机制

2.1.1 减少 ROS 积累, 清除自由基

ROS 是一种含氧中间代谢物, 包括氧自由基和非自由基。氧自由基包括氧的一电子还原产物超氧阴离子自由基($\cdot O_2^-$)、三电子还原产物羟自由基(·OH)、过氧自由基(ROO·)和一氧化氮(NO·)等, 非自由基包括氧的二电子还原产物过氧化氢(H_2O_2)、过亚硝酸盐($ONOO^-$)以及单线态氧($^1O_2$)等, 通过对其他成分的氧化作用将其转变为新的自由基[22−23]。ROS 可以调节宿主体内免疫反应, 对清除死亡细胞和灭杀微生物具有积极的作用, 但体内 ROS 量过多或过少都会产生不利影响, 从细胞水平上损伤机体。

花青素属于多酚类物质, 结构中的多个酚羟基是其强大抗氧化性的基础, 图 2 显示了花青素对活性氧自由基(RO·)清除机制[24]。花青素 B 环上的 3’、4’位邻苯二酚结构能通过 2 个连续的单电子转移反应与 RO·形成稳定的共轭半醌或邻醌式结构, 均匀分布电子云, 降低分子内能; A 环 5 位酚羟基很容易被氧化, 释放 H^+, 对 RO·具有较强的捕捉能力, 3、5、7 位酚羟基进一步与 RO·结合形成假半醌式结构, 并通过酮-烯醇互变异构化反应提高稳定性, 有报道显示每个邻位取代的二酚基团可清除 4 mol RO·[25]; 与其他多酚类物质不同的是, 花青素的 C 环上缺少一个电子, 形成了一个二级氧鎓离子, 即 2-苯基苯并吡喃阳离子, 易于吸引活性氧等自由基的攻击。

天然存在的花青素苷元及其糖苷对于 1,1-二苯基苦味肼自由基(1,1-diphenyl-2-picrylhydrazyl, DPPH·)、·OH、2-联氮-二(3-乙基-苯并噻唑-6-磺酸)二铵盐自由基[2,2'- azinobis (3-ethylbenzothiazoline-6-sulfonic acid ammonium salt), $ABTS^+$]等均具有清除能力, 对 DPPH·和·OH 清除能力略弱于相同浓度的维生素 C (vitamin C, VC), 对 $ABTS^+$的清除能力略强于相同浓度的 VC[26]; 每克黑米和黑色谷壳的花青素冻干粉对 DPPH·清除能力分别相当于 3.694 和 4.208 mmol 维生素 E[27]。花青素的抗氧化活性与纯度和分子结构有关, 分子结构越简单、纯度越高抗氧化活性越强[28]。花青素苷元的抗氧化性高于其糖苷[29], 单糖苷的抗氧化性高于多糖苷[30], 花色苷的抗氧化性高于酰基化的花色苷[29]。

ALI 等[31]测定了 8 种花青素 Pg、Cn、Dp、Pn、Pt、Mv、芹菜素(apigenin, Ap)、槲皮素(quercetin, Qu)和 7 种花色苷: 天竺葵素-3-葡萄糖苷(pelargonidin -3-glucoside, Pg3G)、矢车菊素-3-葡萄糖苷(cyanidin-3-glucoside, C3G)、飞燕草素-3-葡萄糖苷(delphindin-3-glucoside, D3G)、芍药素-3-葡萄糖苷(peonidin-3-glucoside, Pn3G)、矮牵牛素-3-葡萄糖苷(petunia-3-glucoside, Pt3G)、锦葵花素-3-葡萄糖苷(malvidin-3-glucoside, M3G)、锦葵色素-3-半乳糖苷(malvidin-3-galactoside chloride, Mv-3-gal)的 DPPH·、$ABTS^+$、·OH 的清除率及总抗氧化能力。结果表明, 花青素及其花色苷的抗氧化活性趋势与供电子能力变化趋势一致; 不同类型的糖基结合对活性影响较小。花青素通过降低 ROS 水平, 削弱氧化应激效应介导抗肿瘤作用机制, 富含花青素的黑樱桃提取液在 0~320 μg GAE/mL 的剂量范围内抑制乳腺癌细胞的生长, 但对非癌性 MCF-10A 乳腺上皮细胞无毒性, 说明花青素可以选择性地发挥抗氧化作用机制[15]。

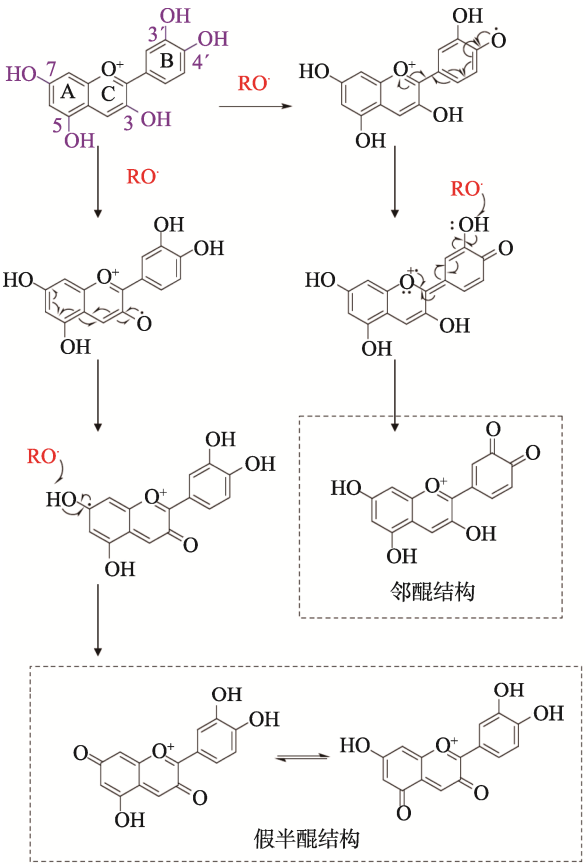

图 2　花青素对活性氧自由基(RO·)清除机制

Fig.2　Clearance mechanism of anthocyanin on active oxygen free radical (RO·)

2.1.2　激活酶抗氧化系统

生物体内的酶抗氧化系统包括超氧化物歧化酶(superoxide dismutase, SOD)、过氧化氢酶(catalase, CAT)、过氧化物酶(peroxidase, POD)、谷胱甘肽过氧化物酶(glutathione peroxidase, GPx)等。抗氧化酶系统的激活可以有效地对抗自由基的生成, 构筑天然生物体内源性抗氧化防御系统[32]。针对 23 项随机对照试验进行元分析结果显示, 可以通过在膳食中添加花青素控制氧化损伤标记物丙二醛(malondialdehyde, MDA)、氧化低密度脂蛋白(oxidized low density lipoprotein, oxLDL)和异前列腺素, 并增加 SOD、GPx 的活性, 与健康受试者相比, 在不健康受试者身上观察的结果更显著[33]。花青素作为信号传递者激活相关因子 2 (NF-E2-related factor 2, Nrf2)抗氧化反应元件(antioxidant reaction element, ARE)信号通路, 见图 3, 顺式调节谷胱甘肽转移酶(glutathione S-transferase, GST)和谷氨酸-半胱氨酸连接酶(glutamate cysteine ligase, GCL)等[34], 提高抗氧化防御系统对抗氧化应激所涉及内源酶活性, 在 ROS 破坏关键细胞大分子之前将其清除, 有效防止氧化应激造成的有害影响。萘普生诱导的氧化性胃溃疡系统, 花青素通过核易位和 Nrf2 结合到胃肠谷胱甘肽过氧化物酶(gastrointestinal-glutathione peroxidase, GI-GPx)启动子 ARE 区域, 提高了 Nrf2 和 GI-GPx 活性, 致硫代巴比妥酸反应物质(thiobarbituric acid reactive substances, TBAR)水平显著降低, CAT、SOD、GPx 水平升高[35]。在高 H_2O_2 触发人克隆结肠腺癌细胞(Caco-2)细胞体系中, 过高的 H_2O_2 对 CAT 具有抑制作用, 花青素激活 CAT 分解外源或内源性 H_2O_2, 但无法将其降低到细胞无害水平; 通过直接抗氧化作用减少 H_2O_2, 使氧化应激达到正常的生物学范围[36]。

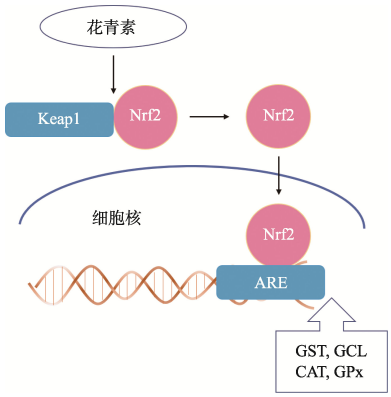

图 3　花青素激活 Nrf2-ARE 信号通路的模式

Fig.3　Patterns of anthocyanin activation in Nrf2-ARE signaling pathway

2.1.3　减少 DNA 损伤

DNA 损伤可能导致细胞毒性、基因毒性和致癌效应[37]。赭曲霉毒素 A (ochratoxin A, OTA)能够剂量依赖地诱导人成纤维细胞产生 ROS 介导 DNA 损伤, 添加 C3G 后 DNA 损伤显著减少, 且单独使用浓度小于 0.250 mmol/L 的 C3G 不会对正常 DNA 造成损伤[38]。蓝莓花色苷使人肝癌细胞(HepG2)中的基因和蛋白质表达水平下降达 24 h, 阻止紫外照射诱导生长阻滞和 DNA 损伤诱生基因 45 (growth arrest and DNA damage inducible protein, *Gadd45*)和鼠双微体基因(murine double minute2, *MDM2*)激活和转录, 通过中断细胞周期的 G_1 期来抑制癌变, 为修复 DNA 损伤提供时间[39]。维生素 E 缺乏大鼠食用添加了 1 g/kg 高度纯化冷杉果球花青素的饲料后血液中脂质过氧化和DNA损伤指标H_2O_2和8-氧代脱氧鸟苷(8-oxo-deoxyguanosine, 8-Oxo-dG)浓度明显降低, 说明食用富含花青素的提取物对肝脏 DNA 具有保护作用[40]。日本三角涡虫暴露于全氟辛酸会导致神经形态缺陷、神经相关基因表达的改变、神经递质水平的改变和 DNA 损伤, 蓝莓花青素通过调节氧化应激生物标志物、三磷酸腺苷(adenosine triphosphate, ATP)含量、DNA 甲基化和 mRNA 表达减轻上述毒性, 使神经递质含量和神经相关基因表达恢复, 减少 DNA 损伤[41–42], 相同机制在日本三角涡虫暴露于全氟辛烷基磺酸实验中得到验证[43]。LAZZE 等[44]使用碱性单细胞凝胶电泳试验研究发现花青素对正丁基过氧化氢诱导的大鼠肝癌细胞 DNA 单链断裂具有保护作用, 该作用与花青素糖苷结构有关。SARMA 等[45]发现芬顿反应中, 在·OH 暴露前形成的 Cn-DNA 复合物可以保护花青素和小

牛胸腺 DNA (calf thymus DNA, ctDNA)免受氧化损伤, 推测 Cn-DNA 复制可能是 DNA 氧化损伤的一种可能的防御机制[46], 其机理如图 4 所示, Cn 通过电子转移作用在相邻碱基对之间形成三明治状复合物。

2.1.4 与金属离子发生作用

人体内游离的金属离子, 如 Fe^{2+}、Mg^{2+}、Cu^{2+}等可以催化加速自由基的形成, 花青素中含有间苯二酚和没食子酸结构, 能够提供孤对电子[47], 可与上述金属离子形成无催化活性的花青素-金属络合物, 阻止或减少自由基的形成。NODA 等[48]从茄子皮中得到飞燕草素-3-(p-酰化芸香糖苷)-5-葡萄糖苷(nasunin), 在大鼠主动脉环实验中, nasunin 与 Fe^{3+}络合清除·OH, 并通过抑制内皮细胞增殖而发挥抗微血管生成的作用。在氧和金属离子的存在下, 抗坏血酸(ascorbic acid, AsA)能够使非酶促反应中的芳香环羟基化, 防止坏血病的发生。花青素对 AsA 氧化的保护机制可能存在 2 种途径, 如图 5 所示, 一是在 AsA 和 Cu^{2+}存在下, 花青素与 Cu^{2+}螯合作用增强, 形成花青素与 Cu^{2+}螯合物保护 AsA; 二是可能形成 AsA-Cu^{2+}-花青素络合物[49]。

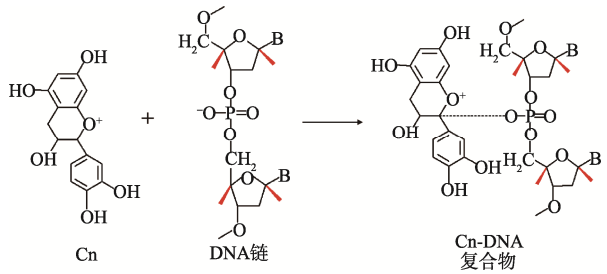

图 4 花青素-DNA 复合物的形成

Fig.4 Formation of cyaniding-DNA complex

综上所述, 花青素抗氧化可能的机理包括减少 ROS 积累和清除自由基、激活酶抗氧化系统、减少 DNA 损伤、与金属离子发生作用。花青素以剂量、时间依赖的方式选择性地抗氧化, 对正常细胞和机体无毒性。花青素抗氧化能力与其纯度和结构有关, 苷元、糖基、甲基和酰化酸的类型、糖基化、甲基化和酰化的位置和程度对其抗氧化能力均有影响, 符合构效关系。

3 花青素的功能活性

3.1 抗肿瘤作用

作为具有抗肿瘤功能的天然产物, 花青素及其衍生物对乳腺癌、结肠癌、肝癌、口腔癌等多种肿瘤具有抑制作用(作用机制见表 1), 且能够减少手术、放疗和化学疗法等方法对患者造成的伤害, 为抗肿瘤临床药物的研发提供了新的思路。

花青素的抗肿瘤作用具有选择性[50−54], 与肿瘤的发生阶段密切相关, 且可能与其他酚类形成协同效应[50]。肿瘤发展初期(前 5 周)在大鼠饮食中添加花青素后, 乳腺二羟基甲基丁酸(dihydroxymethyl butyric acid, DMBA)-DNA 加合物的形成量明显降低了 34%和 56%, 内源性抗氧化酶 GPx、POD 被显著激活, 说明紫葡萄花青素能够在乳腺肿瘤发生初期降低细胞对诱发剂的敏感性[51]。内蒙古野生蓝莓花青素对人口腔癌(KB)细胞增殖具有剂量依赖的抑制作用, 质量浓度为 200 g/mL 时抑制率大于 60%, 24 h 诱导 KB 细胞凋亡率达 32.56%, 并能够将 KB 细胞周期阻滞在 G_2/M 期[52]。野生笃斯越桔花青素质量浓度为 200 μg/mL 时对人肺腺癌早期细胞(SPCA-1)凋亡率达 39.5%, 凋亡细胞周期主要为 G_0/G_1 期[53]。4-甲基亚硝胺基-1-3-吡啶基-1-丁酮前体 4(乙酰氧基甲基)亚硝胺基-1(3-吡啶基)-1-丁酮是烟草中主要肺癌致癌因子, 蓝靛果花青素显著降低其诱导的人肺上皮(BEAS-2B)细胞 DNA 损伤、断裂和 ROS 水平, 上调毛细血管扩张性共济失调症突变激酶(ataxia-telangiectasiamutation, ATM)依赖的 DNA 损伤修复级联反应, 且在测试浓度范围对正常 BEAS-2B 细胞无细胞毒性[54]。

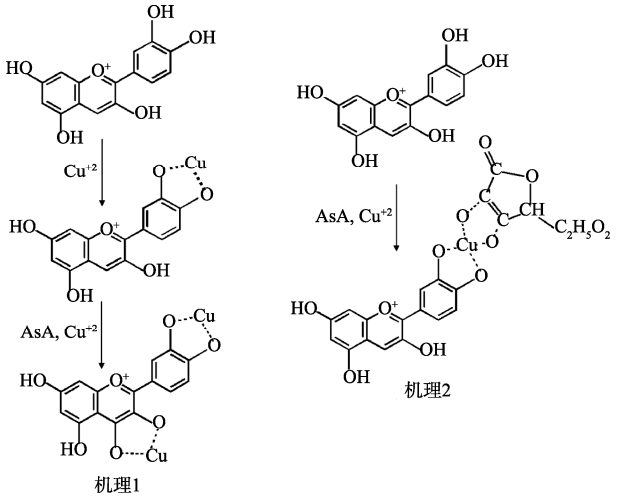

图 5 花青素对 AsA 氧化的保护机制

Fig.5 Protective mechanism of anthocyanin on AsA oxidation

花青素能够参与多条抗肿瘤信号途径, 通过抗氧化、抗炎、促进肿瘤细胞凋亡、增强免疫监视、抑制肿瘤细胞转移和血管生成发挥抗肿瘤效应。Dp 对骨肉瘤细胞具有时间和浓度依赖的细胞毒性, 可诱导自噬体的形成和自噬相关蛋白(light chain 3, LC3-II)转化水平的提高, 通过抑制自噬破坏细胞保护机制允许 ROS 积累, 促进骨肉瘤细胞凋亡[55]。C3G 通过增强白介素 4 (interleukin-4, IL-4)刺激的小鼠骨髓巨噬细胞(bone marrow-derived macrophages, BMDM)抑炎细胞因子 mRNA 表达与蛋白生成, 调控 BMDM 极化, 影响 BMDM 炎性反应[56]。P3G 显著降低肿瘤坏死因子 *α* (tumor necrosis factor-*α*, TNF-*α*)和 IL-6 水平, 抑制 NF-*κ*B (nuclear factor-*kappa* B)和激活蛋白-1 (activator protein-1, AP-1)活化, 减少抑制性卡巴蛋白(NF-*κ*B

inhibitor-*α*, IkB-*α*)的激活、降低 c-Jun 氨基末端激酶/丝裂原活化蛋白激酶 JNK MAPK (c-jun-n-terminal kinase, JNK; mitogen activated protein kinase, MAPK)的磷酸化, 减少由于 Toll 样受体 4 (toll-like receptor 4, TLR4)的激活触发的炎症反应[57]。C3G、矢车菊素-3-O-芸香糖苷(cyanidin-3-O-rutoside, C3R)均能够促进天冬氨酸特异性的半胱氨酸蛋白水解酶(cysteine-caspase, C-cas3、C-cas9)和促凋亡基因 *Bax* 的表达, 抑制抗凋亡基因 *Bcl-2* 的表达[58–59]。花青素对致癌物与 DNA 的加合反应具有阻断作用[60], 或抑制癌细胞谷胱甘肽转移酶 *π* (GST-*π*)的 mRNA 水平, 减少 GST-*π* 的表达, 且对腺癌和鳞癌 GST-*π* 表达具有相同抑制效果[61]。花青素对黑色素瘤细胞 B16-F1 的生长、肺转移和肿瘤血管生成具有抑制作用, 该作用是通过磷脂酰肌醇 3 激酶/苏氨酸蛋白激酶(phosphatidylinositol 3-kinase/serine-threonine kinase, PI3K/Akt)和 Ras/MAPK 级联途径介导, 下游效应因子血管内皮生长因子(vascular endothelial growth factor, VEGF)和抑制基质金属蛋白酶(matrix metalloproteinase-2/-9, MMP-2/-9)明显减少[62]。白藜芦果实花青素对人结肠癌细胞具有抗侵袭活性, 通过抑制抗磷酸化抗体核因子抑制蛋白(inhibitor *kappa* B *alpha*, IκB*α*)磷酸化而抑制由 TNF-*α* 触发的 NF-*κ*B 的激活, 进而抑制 NF-*κ*B 调节蛋白的表达[63]。与糖基化形式相比, 苷元形式对细胞外信号调节激酶(extracellular regulated kinase, ERK)/MAPK 和 NF-*κ*B 信号转导有较强的抑制作用, Pn3G 对 p38/MAPK 有轻微的抑制作用[64]。

3.2　抑菌作用

花青素对除肺炎克雷伯菌外几乎所有的革兰氏阴性菌(大肠杆菌、铜绿假单胞菌、肠炎沙门氏菌、松内志贺氏菌、寻常变形杆菌)和革兰氏阳性菌(产气荚膜梭菌、枯草芽孢杆菌、金黄色葡萄球菌、因诺卡氏李斯特菌)均有一定程度的抑制作用[65]; 对食源性细菌(金黄色葡萄球菌、蜡样芽孢杆菌、单核细胞增生李斯特菌、大肠杆菌、鼠伤寒沙门氏菌、阴沟肠杆菌)和食源性真菌(烟曲霉、曲霉、花色曲霉、索状青霉、金黄色青霉、木霉)表现出良好抑制特性[66]; 与细菌相比, 花色苷对于黑曲霉、白色念珠菌等真菌具有更强的抑制效果[67–68]。花青素可能的抑菌机制包括: (1)破坏细胞壁的结构和完整性, 细胞膜去极化, 影响细胞膜的通透性, 造成细胞穿孔、崩解而死亡[69]; (2)抑制细菌 DNA、RNA 和蛋白质的生物合成, 减少细菌代谢速率, 导致细菌死亡[70]; (3)抑制病原菌碱性磷酸酶、ATP 和 SOD 活性[71]; (4)减弱细菌对三羧酸循环的影响, 抑制细菌胞外蛋白酶活性, 减轻细菌的致病作用, 花青素对细菌胞外蛋白酶的抑制作用源于多酚对基质金属蛋白酶活力的抑制[72]。有研究表明, 花青素的抑菌作用为上述多个机制共同作用的结果[73]。

3.3　对脂类、糖类代谢的调节作用

花青素通过抑制肝脏糖异生作用降低高血糖; 抑制消化酶, 调节肠促胰岛素分泌水平和肠道生态失调; 调节胰岛素水平, 保护胰腺细胞, 减少胰岛素抵抗、炎症和氧化应激, 减少糖尿病相关疾病。过氧化物酶体增殖物激活受体–*γ*-共激活因子 1-*α* (proliferator-activated receptor *gamma* coactivator 1*α*, PGC-1*α*)、磷酸烯醇丙酮酸羧激酶和葡萄糖-6-磷酸酶 mRNA 表达下调可能是 C3G 的抑制肝脏糖异生作用主要原因[74]。花青素主要通过抑制 *α*-淀粉酶降低白米的消化率, 抑制 *α*-葡萄糖苷酶来调节餐后高血糖, 而其他酚类物质则调节唾液-淀粉酶、葡萄糖摄取和糖转运[75–76]; 越桔花青素通过非共价键结合酶分子实现对 *α*-葡萄糖苷酶和 *α*-淀粉酶的可逆抑制, 且具有混合竞争性, *α*-葡萄糖苷酶可能比 *α*-淀粉酶对其更敏感[77]; 花青素通过增加糖原合成酶激酶 3*β* (glycogen synthase kinase-3*β*, GSK-3*β*)的磷酸化和糖原合成酶 2 (glycogen synthase, GYS2)的表达促进糖原合成[16]。C3G 保护胰腺 *β* 细胞, 下调视黄醇结合蛋白 4 (retinol binding protein 4, RBP4)的表达, 提高胰岛素敏感性, 防止胰岛素抵抗[16], 且对雌性大鼠的作用强于雄性大鼠[78]。C3G 经发酵消化后的代谢产物能够改善高糖+棕榈酸诱导的 HepG2 细胞的葡萄糖消耗量和糖原含量, 说明 C3G 经发酵消化后的代谢产物对预防、改善糖尿病具有一定效果[79]。

花青素通过抑制胰腺脂酶减少脂质的分解代谢[80]; 激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)信号通路减弱细胞脂质积聚; 膳食花青素可以改变肠道菌群, 降低肠道总胆固醇; 激活 Akt 和 ERK/MAPK 信号通路, 提高棕色脂肪组织(brown adipose tissue, BAT)活性, 促进碳水化合物和脂肪代谢。高脂饮食导致 ROS 激增, 上调回肠中 p65 蛋白、ERK1/2 磷酸化水平、回肠肌球蛋白轻链磷酸化水平, 花青素通过激活 AMPK 减弱 HepG2 细胞中的脂质积聚, 抑制烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)氧化酶 1/4 (NADPH oxidases, NOX1/4)和诱导型一氧化氮合酶(inducible nitric oxide synthase, NOS2)表达增加, 健康雄性 C57BL/6J 小鼠补充 40 mg/kg 体重的花青素可有效减轻高脂饮食引起的肥胖、血脂异常和胰岛素抵抗, 减轻肝脏脂质沉积和炎症[81–82], 并能阻断脂肪合成酶的关键酶乙酰辅酶 A 羧化酶活性[83]。C3G 改善小鼠脂肪细胞(3T3-L1)功能紊乱, 恢复胰岛素受体底物-1 (insulin receptor substrate-1, IRS-1)/PI3K/Akt 途径, 改善由于高脂饮食导致的肥胖和代谢综合征[84]。枸杞花色苷重塑受损肠道菌群、调节动脉炎症 NF-*κ*B 和肝脏脂质代谢中甾醇调节元件结合蛋白(sterol regulatory element-binding protein, SREBP-2)的信号通路, 改善动脉粥样硬化[85]。C3G 和 C3R 激活 Akt 和 ERK-MAPK 信号通路, 提高 BAT 活性, 并提高线粒体拷贝数量及相关蛋白 PGC-1*α*、线粒体转录因子 A (mitochondrial

transcription factor A, TFAM)和 Nrf2, 上调脂肪酸氧化相关基因蛋白解偶联蛋白 1 (uncoupling protein, UCP1)、PGC1a 和 PRDM16 (PR domain containing 16)的表达水平, 提高产热, 促进碳水化合物和脂肪代谢[86]。

3.4 抗疲劳、抗衰老作用

花青素调整代谢、延长运动时间和水平; 维持细胞活力、恢复细胞形态、减轻细胞周期阻滞; 部分逆转淀粉样 β 斑块(amyloid beta, Aβ)相关基因的突变和神经纤维缠结; 抑制氧化应激, 从细胞尺度上修复神经细胞损伤, 恢复相关记忆蛋白的表达。小鼠补充花青素负重强迫游泳和转棒时间显著延长, 乳酸脱氢酶、血乳酸、血尿素氮水平降低, 肝糖原、肌糖原含量增加[87]; MDA、SOD 水平增加、TNF-α、IL-1β、IL-6 波动下调, 骨骼肌 PGC-1α 和过氧化物酶体增殖物激活受体 α (peroxisome proliferator-activated receptor α, PPARα)的 mRNA 表达上调[16]。

摄入一定量的花青素后, 老年人在非病理性记忆衰退和轻度认知障碍中的认知能力得到改善[88]。体外试验表明, C3G 浓度为 100 μmol/L 时, 可逆转 10 μmol/L A$\beta_{25\text{-}35}$ 对人神经母细胞瘤细胞(SH-SY5Y)细胞造成的损伤, 部分逆转 Aβ 相关基因突变和神经纤维缠结, 细胞存活率提高了 72.26%[89]。蓝莓花青素提取物能增强暴露于极低频电磁场的大鼠的认知能力, 受试大鼠海马神经元细胞 NO、MDA 和 Ca^{2+}水平降低, 抗氧化酶群数量提高[90]。紫薯花青素增强雌激素受体 α 介导的线粒体生物合成信号, 抑制小鼠内质网应激诱导的细胞凋亡, 恢复相关记忆蛋白的表达[91]。花青素诱导细胞自噬保护 PC12 细胞免受 $CoCl_2$ 诱导的缺氧损伤[92]。

3.5 调节肠道菌群

花青素能够调节肠道特定菌群种类、增加有益菌群数量。以每天 200 mg/kg 枸杞花色素苷连续饲喂 12 周后, 小鼠肝脏抗氧化酶系统被激活, 肠屏障封闭带-1 (zonula occludens 1, Zo-1)、闭合蛋白、紧密连接蛋白和粘蛋白-1 的 mRNA 表达显著增加, 肠道微生物群厌氧属(*Barnesiella*)、另枝菌属(*Alistipes*)等均得到调节[93]。高纯蓝莓花色苷(纯度为 96.8%)可以影响人体肠道菌群微生物的多样性, 体外厌氧发酵 12 h 后, 能够提高双歧杆菌、瘤胃球菌、IV型梭状芽孢杆菌、变形菌门等特定菌群的相对丰度, 该作用对于双歧杆菌等益生菌尤其明显, 24 h 后上调瘤胃球菌属、IV型梭状芽孢杆菌属等菌群相对丰度的作用依然存在, 但对双歧杆菌的上调作用不再明显, 该研究表明合理使用蓝莓花色苷可以提高肠道益生菌活性[94]。蔓越莓提取物对由动物性饮食导致的肠道益生菌数量下降有较为显著的改善, 在饮食中补充冻干蔓越莓增加了拟杆菌门、类杆菌纲和拟杆菌目等菌群的相对丰度和属的数量, 减少了厚壁菌门、梭状芽孢杆菌纲和原杆菌属的相对丰度[95]。CHEN 等[96]发现 C3G 对大鼠肠道菌群均匀性和丰富度改善调节作用与肠道位置有关, 花青素显著增加了回肠中罗姆布茨菌、毛螺菌科 NK4A136 组、罗斯氏菌的相对丰度; 增加了结肠中放线杆菌的相对数量, 减少了类杆菌和螺杆菌的相对数量; 但对于结肠粘膜中的微生物影响不显著, 其主要原因可能是肠道菌群对 C3G 的快速利用可能导致到达黏膜的 C3G 数量减少。

YAN 等[97]比较了芦苇花色苷和菊粉对人体肠道菌群的影响, 发现芦苇花色苷对人体肠道菌群的影响强于菌粉, 将肥胖的生物标记物厚壁菌门/拟杆菌的比例由 0.57 降低至 0.28, 并显著提高双歧杆菌和阿里松氏菌的相对丰度, 降低了普氏菌、小类杆菌、巨单胞菌和梭状芽孢杆菌的相对丰度; 与菌粉相似, 芦苇花色素苷通过促进短链脂肪酸, 如乙酸、丙酸和丁酸的形成发挥类似于益生元的作用。ZARY-SIKORSKA 等[98]发现与富含胡萝卜素的橙色胡萝卜提取物相比, 富含花青素的紫色胡萝卜提取物对雄性大鼠肠道菌群的影响更显著, 该作用是通过提高盲肠中丙酸、丁酸和 β-葡萄糖醛酸酶的活性实现的。OWOLABI 等[99]发现紫米花青素通过抑制 α-淀粉酶而抑制淀粉消化, 为肠道益生菌群提供能量。

4 结束语

目前, 关于花青素抗氧化机制的理论研究已经取得了较大的进展, 可能的机理包括减少活性氧积累和清除自由基、激活酶抗氧化系统、减少 DNA 损伤、与金属离子发生作用等。花青素以剂量、时间依赖的方式选择性地抗氧化, 其抗氧化能力与其纯度和结构有关, 苷元、糖基、甲基和酰化酸的类型、糖基化、甲基化和酰化的位置和程度对其抗氧化能力均有影响, 符合构效关系。花青素优良的抗氧化能力使其具有抗肿瘤、抗衰老、抑菌、调节糖类、脂肪代谢和调节肠道菌群等多种功能, 并在体外和动物试验中得到较多验证。然而, 花青素的功能活性在人体内的作用机制研究较少且机理不明, 需要进一步深入研究。

由于花青素具有水溶性强而脂溶性差、稳定性差、对细胞膜的透过性较差等特性, 导致其生物利用度低, 临床药效低于体外试验结果。采用结构修饰对其改性可以提高花青素的稳定性, 制备微胶囊、纳米颗粒、脂质体等将其包埋可以提高花青素生物利用度, 使其能够到达靶向位置, 可以预测这将成为花青素的应用领域中新的研究热点。

参考文献

[1] AZUMA A, YAHUSHIJI H, SATO A. Postharvest light irradiation and appropriate temperature treatment increase anthocyanin accumulation in grape berry skin [J]. Postharvest Biol Technol, 2019, 147(1): 89–99.

[2] 由璐, 隋茜茜, 赵艳雪, 等. 花色苷分子结构修饰及其生理活性研究进展[J]. 食品科学, 2019, 40(11): 351–359.
YOU L, SUI QQ, ZHAO YX, *et al*. Recent progress in structural modification and physiological activity of anthocyanins [J]. Food Sci, 2019, 40(11): 351–359.

[3] ANDRADE TA, HAMERSKI F, LOPEZ FDE, *et al*. Ultrasound-assisted

pressurized liquid extraction of anthocyanins from *Aronia melanocarpa* pomace [J]. Sep Purif Technol, 2021, 267(12): 119290.

[4] KUMAR M, DAHUJA A, SACHDEV A, *et al*. Evaluation of enzyme and microwave-assisted conditions on extraction of anthocyanins and total phenolics from black soybean (*Glycine max* L.) seed coat [J]. Int J Biol Macromol, 2019, 135(8): 1070–1081.

[5] FERREIRA FL, MINUZZI NM, RODRIGUES RF, *et al*. Citric acid water-based solution for blueberry bagasse anthocyanins recovery: Optimization and comparisons with microwave-assisted extraction (MAE) [J]. LWT, 2020, 133(11): 110064.

[6] ODABAS HI, KOCA I. Simultaneous separation and preliminary purification of anthocyanins from *Rosa pimpinellifolia* L. fruits by microwave assisted aqueous two-phase extraction [J]. Food Bioprod Process, 2021, 125(1): 170–180.

[7] WANG YW, LUAN GX, ZHOU W, *et al*. Subcritical water extraction, UPLC-Triple-TOF/MS analysis and antioxidant activity of anthocyanins from *Lycium ruthenicum* Murr [J]. Food Chem, 2018, 249: 119–126.

[8] MARTINEZ AS, KORNPOINTNER C, HASELMAIR GC, *et al*. Dynamic streamlined extraction of iridoids, anthocyanins and lipids from haskap berries [J]. LWT-Food Sci Technol, 2021, 138(3): 110633.

[9] LIU P, LI WR, HU ZZ, *et al*. Isolation, purification, identification, and stability of anthocyanins from *Lycium ruthenicum* Murr [J]. LWT, 2020, 126(5): 109334.

[10] ZHAO X, ZHANG SS, ZHANG XK, *et al*. An effective method for the semi-preparative isolation of high-purity anthocyanin monomers from grape pomace [J]. Food Chem, 2020, 310(4): 125830.

[11] LIMA AS, OLIVEIRA BS, SHABUDIN SV, *et al*. Purification of anthocyanins from grape pomace by centrifugal partition chromatography [J]. J Mol Liq, 2021, 326(3): 115324.

[12] VALENCIA AJA, HERNANDEZ BGI, CERON MGI, *et al*. Enhanced process integration for the extraction, concentration and purification of di-acylated cyanidin from red cabbage [J]. Sep Purif Technol, 2020, 238(5): 116492.

[13] GUO Y, ZHANG PW, LIU YJ, *et al*. A dose-response evaluation of purified anthocyanins on inflammatory and oxidative biomarkers and metabolic risk factors in healthy young adults: A randomized controlled trial [J]. Nutrition, 2020, 74(6): 110745.

[14] ROSARIO VA, CHANG C, SPENCER J, *et al*. Anthocyanins attenuate vascular and inflammatory responses to a high fat high energy meal challenge in overweight older adults: A cross-over, randomized, double-blind clinical trial [J]. Clin Nutr, 2021, 40(3): 879–889.

[15] LAGE NN, LAYOSA MAA, ARBIZU S, *et al*. Dark sweet cherry (*Prunus avium*) phenolics enriched in anthocyanins exhibit enhanced activity against the most aggressive breast cancer subtypes without toxicity to normal breast cells [J]. J Funct Foods, 2020, 64(1): 103710.

[16] SPINOLA V, PINTO J, LLORENT-MARTINE EJ, *et al*. Evaluation of *Rubus grandifolius* L. (wild blackberries) activities targeting management of type-2 diabetes and obesity using *in vitro* models [J]. Food Chem Toxicol, 2019, 123(1): 443–452.

[17] HU M, DU J, DU LD, *et al*. Anti-fatigue activity of purified anthocyanins prepared from purple passion fruit (*P. edulis* Sim) epicarp in mice [J]. J Funct Foods, 2020, 65(2): 103725.

[18] IGWE E, NEALE E, CHARLTON KE, *et al*. First stage development of an Australian anthocyanin food composition database for dietary studies-A systematic process and its challenges [J]. J Food Compos Anal, 2017, 64(1): 33–38.

[19] WESELER AR, BAST A. Masquelier's grape seed extract: From basic flavonoid research to a well-characterized food supplement with health benefits [J]. Nutr J, 2017, 16(5): 1–19.

[20] ADAKU C, SKAAR I, BERLAND H, *et al*. Anthocyanins from mauve flowers of *Erlangea tomentosa* (*Bothriocline longipes*) based on erlangidin-the first reported natural anthocyanidin with C-ring methoxylation [J]. Phytochem Lett, 2019, 29(2): 225–230.

[21] 魏伊蓝, 董航明, 谢哲凡, 等. 活性氧在低氧诱导非小细胞肺癌转移中的作用[J]. 中华医学杂志, 2017, 97(40): 3174–3178.
WEI YL, DONG HM, XIE ZF, *et al.* Role of reactive oxygen species in hypoxia-induced non-small cell lung cancer migration [J]. Nat Med J China, 2017, 97(40): 3174–3178.

[22] SUN Y, LU YF, SAREDY J, *et al*. ROS systems are a new integrated network for sensing homeostasis and alarming stresses in organelle metabolic processes [J]. Redox Biol, 2020, 37(10): 101696.

[23] BAUER G. Intercellular singlet oxygen-mediated bystander signaling triggered by long-lived species of cold atmospheric plasma and plasma-activated medium [J]. Redox Biol, 2019, 26(9): 101301.

[24] MATTIOLI R, FRANCIOSO A, MOSCA L, *et al*. Anthocyanins: A comprehensive review of their chemical properties and health effects on cardiovascular and neurodegenerative diseases [J]. Molecules, 2020, 25(17): 3809.

[25] SHAHIDI F, AMBIGAIPALAN P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects-A review [J]. J Funct Foods, 2015, 18(B): 820–897.

[26] 王晗, 朱华平, 李文钊, 等. 桑葚提取物中花青素分析及其体外抗氧化活性研究[J]. 食品与发酵工业, 2019, 45(15): 170–175.
WANG H, ZHU HP, LI WZ, *et al*. Anthocyanins in mulberry extract and their *in vitro* antioxidant activity [J]. Food Ferment Ind, 2019, 45(15): 170–175.

[27] 张欧玲, 向珣朝, 颜李梅, 等. 不同黑稻品种黑米和谷壳的花青素产量及其抗氧化性比较[J]. 西北植物学报, 2020, 40(3): 510–518.
ZHANG OUL, XIANG XC, YAN LM, *et al*. Comparison of yield and antioxidant activity of anthocyanin from grains and husks among different black rice varieties [J]. Acta Botanica Boreali-Occident Sin, 2020, 40(3): 510–518.

[28] CAVALCANTI RN, SANTOS DT, MEIRELES MAA. Non-thermal stabilization mechanisms of anthocyanins in model and food systems-An overview [J]. Food Res Int, 2011, 44(2): 499–509.

[29] TSUDA T, WATANABE M, OHSHIMA K, *et al*. Antioxidative activity of the anthocyanin pigments cyanidin-3-O-beta-d-glucoside and cyaniding [J]. J Agric Food Chem, 1994, 42(11): 2407–2410.

[30] JING P, BOMSER JA, SCHWARTZ SJ, *et al*. Structure-function relationships of anthocyanins from various anthocyanin-rich extracts on the inhibition of colon cancer cell growth [J]. J Agric Food Chem, 2008, 56(20): 9391–9398.

[31] ALI HM, ALMAGRIBI W, AL-RASHIDI MN. Antiradical and reductant activities of anthocyanidins and anthocyanins, structure-activity relationship and synthesis [J]. Food Chem, 2016, 194(3): 1275–1282.

[32] 曾小峰, 曾志红, 曾顺德, 等. 不同抗性诱导剂对金针菇抗氧化酶系统的影响[J]. 西南大学学报(自然科学版), 2019, 41(10): 22–27.
ZENG XF, ZENG ZH, ZENG SD, *et al*. Effects of different resistance inducers on the antioxidant enzyme system in *Flammulina velutipes* [J]. J Southwest Univ (Nat Sci Ed), 2019, 41(10): 22–27.

[33] FALLAH AA, SARMAST E, JAFARI T. Effect of dietary anthocyanins on biomarkers of oxidative stress and antioxidative capacity: A systematic review and meta-analysis of randomized controlled trials [J]. J Funct Foods, 2020, 68(3): 103912.

[34] JAFARI T, FEIZI A, ASKARI G, *et al*. Parenteral immunonutrition in patients with acute pancreatitis: A systematic review and meta-analysis [J]. Clin Nutr, 2015, 34(1): 35–43.

[35] KIM SJ, KIM JM, SHIM SH, *et al*. Anthocyanins accelerate the healing of naproxen-induced gastric ulcer in rats by activating antioxidant enzymes via modulation of Nrf2 [J]. J Funct Foods, 2014, 7(3): 569–579.

[36] ZHANG H, LIU RH, TSAO R. Anthocyanin-rich phenolic extracts of purple root vegetables inhibit pro-inflammatory cytokines induced by H_2O_2 and enhance antioxidant enzyme activities in Caco-2 cells [J]. J Funct Foods, 2016, 22(4): 363–375.

[37] STEFANOWICZ HJ, GUCWA M, MONIUSZKO SB, *et al*. Bersaldegenin-1,3,5-orthoacetate induces caspase-independent cell death,

DNA damage and cell cycle arrest in human cervical cancer HeLa cells [J]. Pharm Biol, 2021, 59(1): 54–65.

[38] RUSSO A, FAUCI LL, ACQUAVIVA R, *et al*. Ochratoxin a-induced DNA damage in human fibroblast: Protective effect of cyanidin 3-O-*β*-d-glucoside [J]. J Nutr Biochem, 2005, 16(1): 31–37.

[39] LIU W, LU XY, HE GY, *et al*. Protective roles of Gadd45 and MDM2 in blueberry anthocyanins mediated DNA repair of fragmented and non-fragmented DNA damage in UV-irradiated HepG2 cells [J]. Int J Mol Sci, 2013, 14(11): 21447–21462.

[40] RAMIREZ TC, ANDERSEN M, GARDNER PT, *et al*. Anthocyanin-rich extract decreases indices of lipid peroxidation and DNA damage in vitamin E-depleted rats. [J]. Free Radical Biol Med, 2001, 31(9): 1033–1037.

[41] ZHANG JY, WANG B, ZHAO BS, *et al*. Blueberry anthocyanin alleviate perfluorooctanoic acid-induced toxicity in planarian (*Dugesia japonica*) by regulating oxidative stress biomarkers, ATP contents, DNA methylation and mRNA expression [J]. Environ Pollut, 2019, 245(2): 957–964.

[42] ZHANG JY, SHAO XX, ZHAO BY, *et al*. Neurotoxicity of perfluorooctanoic acid and post-exposure recovery due to blueberry anthocyanins in the planarians *Dugesia japonica* [J]. Environ Pollut, 2020, 263(8): 114471.

[43] SHAO XX, ZHAO BY, WANG B, *et al*. Neuroprotective effects of blueberry anthocyanins against perfluorooctanoic sulfonate on planarian *Dugesia japonica* [J]. Ecotox Environ Saf, 2019, 175(7): 39–47.

[44] LAZZE MC, PIZZALA R, SAVIO M, *et al*. Anthocyanins protect against DNA damage induced by tert-butyl-hydroperoxide in rat smooth muscle and hepatoma cells [J]. Mutat Res, 2003, 535(1): 103–115.

[45] SARMA SR, SHARMA R. Anthocyanin-DNA copigmentation complex: Mutual protection against oxidative damage [J]. Phytochemistry, 1999, 52(7): 1313–1318.

[46] JALDAPPAGARI S, MOTOHASHI N, GANGEENAHALLI MP, *et al*. Bioactive mechanism of interaction between anthocyanins and macromolecules like DNA and proteins [M]. New York: Springer Berlin Heidelberg, 2008.

[47] XU W, ZHANG N, ZHANG ZT, *et al*. Effects of dietary cyanidin-3-diglucoside-5-glucoside complexes with rutin/Mg(II) against H_2O_2-induced cellular oxidative stress [J]. Food Res Int, 2019, 126(7): 108591.

[48] NODA Y, KANEYUKI T, IGARASHI K, *et al*. Antiangiogenic activity of nasunin, an antioxidant anthocyanin, in eggplant [J]. Res Commun Mol Pathol Path, 1998, 102(2): 175–187.

[49] SARMA AD, SREELAKSHMI Y, SHARMA R. Antioxidant ability of anthocyanins against ascorbic acid oxidation [J]. Phytochemistry, 1997, 45(4): 671–674.

[50] MAZEWSKI C, LIANG K, MEJIA EGD. Comparison of the effect of chemical composition of anthocyanin-rich plant extracts on colon cancer cell proliferation and their potential mechanism of action using *in vitro*, in silico, and biochemical assays [J]. Food Chem, 2018, 242(3): 378–388.

[51] JUNG KJ, WALLIG MA, SINGLETARY KW, *et al*. Purple grape juice inhibits 7,12-dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumorigenesis and *in vivo* DMBA-DNA adduct formation [J]. Cancer Lett, 2006, 233(2): 279–288.

[52] 陈琦, 李少伟, 贾宇臣, 等. 蓝莓花青素通过下调 p53 基因 DNA 甲基化抑制口腔癌 KB 细胞增殖及诱导细胞凋亡[J]. 遗传, 2014, 36(6): 566–573.
CHEN Q, LI SW, JIA YC, *et al*. Blueberry anthocyanins induce G2/M cell cycle arrest and apoptosis of oral cancer KB cells through down-regulation methylation of p53 [J]. Hereditas, 2014, 36(6): 566–573.

[53] 姜浩瀚, 吕留庄, 景志行, 等. 野生笃斯越桔总花青素对 SPCA-1 细胞活力抑制及机理[J]. 食品与生物技术学报, 2019, 38(6): 102–108.
JIANG HH, LV LZ, JING ZX, *et al*. Inhibition of Chinese wild vaccinium *Uliginosum Linn*. anthocyanins on SPCA-1 cell viability and its mechanism [J]. J Food Sci Biotechnol, 2019, 38(6): 102–108.

[54] AMARARATHNA M, HOSKIN DW, RUPASINGHE HPV. Anthocyanin-rich haskap (*Lonicera caerulea* L.) berry extracts reduce nitrosamine-induced DNA damage in human normal lung epithelial cells *in vitro* [J]. Food Chem Toxicol, 2020, 141(7): 111404.

[55] LEE DY, PARK YJ, HWANG SC, *et al*. Cytotoxic effects of delphinidin in human osteosarcoma cells [J]. Acta Orthop Traumato, 2018, 52(1): 58–64.

[56] 张晓静, 崔梦珂, 辛广远, 等. 花青素 Cyanidin-3-O-glucoside 对脂多糖和白介素-4 刺激的小鼠骨髓巨噬细胞极化的影响[J]. 中国免疫学杂志, 2019, 35(11): 1320–1324.
ZHANG XJ, CUI MK, XIN GY, *et al*. Effect of anthocyanin cyanidin-3-O-glucoside on bone marrow derived macrophages polarization induced by lipopolysaccharide or IL-4 in mice [J]. Chin J Immunol, 2019, 35(11): 1320–1324.

[57] DUARTE LJ, CHAVES VC, VINICIUS PDSNM, *et al*. Molecular mechanism of action of pelargonidin-3-O-glucoside, the main anthocyanin responsible for the anti-inflammatory effect of strawberry fruits [J]. Food Chem, 2018, 247(3): 56–65.

[58] 杨霞, 陈琦, 王利. 蓝莓花青素诱导口腔癌 KB 细胞凋亡的实验研究[J]. 北京中医药大学学报, 2019, 42(4): 312–317.
YANG X, CHEN Q, WANG L. Blueberry anthocyanin induces apoptosis in oral cancer KB cells: An laboratory study [J]. J Beijing Univ Tradit Chin Med, 2019, 42(4): 312–317.

[59] BISHAYEE A, MBIMBA T, THOPPIL RJ, *et al*. Anthocyanin-rich black currant (*Ribes nigrum* L.) extract affords chemoprevention against diethylnitrosamine-induced hepatocellular carcinogenesis in rats [J]. J Nutr Biochem, 2010, 22(11): 1035–1046.

[60] SINGLETARY KW, JUNG KJ, GIUSTI M. Anthocyanin-rich grape extract blocks breast cell DNA damage [J]. J Med Food, 2007, 10(2): 244–251.

[61] 秦朝, 官立萍, 司艳莉, 等. 花青素对非小细胞肺癌组织细胞 GST-*π* 表达的影响[J]. 中成药, 2017, 39(5): 1075–1077.
QIN C, GUAN LP, SI YL, *et al*. Effect of anthocyanin on GST-*π* expression in non-small cell lung cancer cells [J]. Chin Tradit Patent Med, 2017, 39(5): 1075–1077.

[62] SU CC, WANG CJ, HUANG KH, *et al*. Anthocyanins from *Hibiscus sabdariffa* calyx attenuate *in vitro* and *in vivo* melanoma cancer metastasis [J]. J Funct Foods, 2018, 48(9): 614–631.

[63] YUN JW, LEE WS, KIM MJ, *et al*. Characterization of a profile of the anthocyanins isolated from *Vitis coignetiae* Pulliat and their anti-invasive activity on HT-29 human colon cancer cells [J]. Food Chem Toxicol, 2010, 48(3): 903–909.

[64] WONGWICHAI T, TEEYAKASEM P, PRUKSAKORN D, *et al*. Anthocyanins and metabolites from purple rice inhibit IL-1*β*-induced matrix metalloproteinases expression in human articular chondrocytes through the NF-*κ*B and ERK/MAPK pathway [J]. Biomed Pharmacother, 2019, 112(4): 108610.

[65] VELICKOVIC J, KOSTIC D, STOJANOVIC G, *et al*. Phenolic composition, antioxidant and antimicrobial activity of the extracts from *Prunus spinosa* L. fruit [J]. Hem Ind, 2014, 68(3): 297–303.

[66] SAMPAIO SL, LONCHAMP J, DIAS MI, *et al*. Anthocyanin-rich extracts from purple and red potatoes as natural colourants: Bioactive properties, application in a soft drink formulation and sensory analysis [J]. Food Chem, 2021, 342(4): 128526.

[67] SABATINI L, FRATERNALE D, GIACOMO BD, *et al*. Chemical composition, antioxidant, antimicrobial and anti-inflammatory activity of *Prunus spinosa* L. fruit ethanol extract [J]. J Funct Foods, 2020, 67(4): 103885.

[68] SUCHETA, CHATURVEDI K, YADAV SK. Ultrasonication assisted salt-spices impregnation in black carrots to attain anthocyanins stability, quality retention and antimicrobial efficacy on hot-air convective drying [J]. Ultrason Sonochem, 2019, 58(11): 104661.

[69] GARZON GA, SOTO CY, MARCELA LR, *et al*. Phenolic profile, *in vitro* antimicrobial activity and antioxidant capacity of *Vaccinium meridionale*

swartz pomace [J]. Heliyon, 2020, 6(5): e04272.
[70] GONG SY, FEI P, SUN Q, *et al*. Action mode of cranberry anthocyanin on physiological and morphological properties of *Staphylococcus aureus* and its application in cooked meat [J]. Food Microbiol, 2021, 94(4): 103632.
[71] SUN XH, ZHOU TT, ZHOU CH, *et al*. Antibacterial effect and mechanism of anthocyanin rich Chinese wild blueberry extract on various foodborne pathogens [J]. Food Control, 2018, 94(12): 115–161.
[72] 朱泓, 赵慧芳, 吴文龙, 等. 黑莓、蓝莓冻干粉的的抑菌抗炎活性研究[J]. 现代食品科技, 2013, 29(10): 2410–2414, 2430.
ZHU H, ZHAO HF, WU WL, *et al*. Anti-proteus mirabilis effect of freeze-dried powder of polyphenolic enriched berry [J]. Mod Food Sci Technol, 2013, 29(10): 2410–2414, 2430.
[73] DENG HT, ZHU JY, TONG YQ, *et al*. Antibacterial characteristics and mechanisms of action of *Aronia melanocarpa* anthocyanins against *Escherichia coli* [J]. LWT, 2021, 150(10): 112018.
[74] ZHANG XN, HUANG HZ, ZHAO XY, *et al*. Effects of flavonoids-rich Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) pulp extracts on glucose consumption in human HepG2 cells [J]. J Funct Foods, 2015, 14(4): 144–153.
[75] BARIK SK, RUSSELL RW, MOAR MK, *et al*. The anthocyanins in black currants regulate postprandial hyperglycaemia primarily by inhibiting α-glucosidase while other phenolics modulate salivary α-amylase, glucose uptake and sugar transporters [J]. J Nutr Biochem, 2020, 78(4): 108325.
[76] LEE JJL, CHAN B, CHUN C, *et al*. A preparation of β-glucans and anthocyanins (LoGiCarb™) lowers the *in vitro* digestibility and *in vivo* glycemic index of white rice [J]. Rsc Adv, 2020, 10(9): 5129–5133.
[77] JI YL, LIU D, JIN Y, *et al*. *In vitro* and *in vivo* inhibitory effect of anthocyanin-rich bilberry extract on α-glucosidase and α-amylase [J]. LWT, 2021, 145(6): 111484.
[78] BISPO KP, AMUSQUIVAR E, GARCIA SD, *et al*. Supplementing diet with blackberry extract causes a catabolic response with increments in insulin sensitivity in rats [J]. Plant Food Hum Nutr, 2015, 70(2): 170–175.
[79] GOWD V, BAO T, WANG L, *et al*. Antioxidant and antidiabetic activity of blackberry after gastrointestinal digestion and human gut microbiota fermentation [J]. Food Chem, 2018, 269(12): 618–627.
[80] PENG JM, JIA Y, DU X, *et al*. Study of physicochemical stability of anthocyanin extracts from black peanut skin and their digestion enzyme and adipogenesis inhibitory activities [J]. LWT, 2019, 107(6): 107–116.
[81] CREMONINI E, DAVERI E, MASTALOUDIS A, *et al*. Anthocyanins protect the gastrointestinal tract from high fat diet-induced alterations in redox signaling, barrier integrity and dysbiosis [J]. Redox Biol, 2019, 26(9): 2213–2317.
[82] DAVERI E, CREMONINI E, MASTALOUDIS A, *et al*. Cyanidin and delphinidin modulate inflammation and altered redox signaling improving insulin resistance in high fat-fed mice [J]. Redox Biol, 2018, 18(9): 16-24.
[83] ZHOU L, ZHANG CQ, QIANG Y, *et al*. Anthocyanin from purple sweet potato attenuates lead-induced reproductive toxicity mediated by JNK signaling pathway in male mice [J]. J Funct Foods, 2021, 224(11): 112683.
[84] MOLONIA MS, OCCHIUTO C, MUSCARA C, *et al*. yanidin-3-O-glucoside restores insulin signaling and reduces inflammation in hypertrophic adipocytes [J]. Arch Biochem Biophys, 2020, 691(9): 108488.
[85] LUO Y, FANG JL, YUAN K, *et al*. Ameliorative effect of purified anthocyanin from *Lycium ruthenicum* on atherosclerosis in rats through synergistic modulation of the gut microbiota and NF-κB/SREBP-2 pathways [J]. J Funct Foods, 2019, 59(8): 223–233.
[86] YOU YL, LIANG C, HAN X, *et al*. Mulberry anthocyanins, cyanidin 3-glucoside and cyanidin 3-rutinoside, increase the quantity of mitochondria during brown adipogenesis [J]. J Funct Foods, 2017, 36(9): 348–356.
[87] 张卓睿, 毛迪锐, 高晗, 等. 蓝莓花青素对小鼠抗疲劳及体内抗氧化作用[J]. 食品科学, 2017, 38(21): 207–211.
ZHANG ZR, MAO DR, GAO H, *et al*. Anti-fatigue and antioxidant effects of anthocyanins from blueberry in mice [J]. Food Sci, 2017, 38(21): 207–211.
[88] KRIKORIAN R, KALT W, JANE E, *et al*. Cognitive performance in relation to urinary anthocyanins and their flavonoid-based products following blueberry supplementation in older adults at risk for dementia [J]. J Funct Foods, 2020, 64(1): 103667.
[89] 刘伟, 贺源, 王紫玉, 等. 花色苷对 A$\beta_{25\text{-}35}$ 损伤 SH-SY5Y 细胞保护作用的研究[J]. 营养学报, 2016, 38(1): 63–66.
LIU W, HE Y, WANG ZY, *et al*. Protective effect of anthocyanin against injury induced by A$\beta_{25\text{-}35}$ in SH-SY5Y cells [J]. Acta Nutr Sin, 2016, 38(1): 63–66.
[90] CHEN J, LI HY, WANG D, *et al*. Delphinidin protects β2m-/Thy1+bone marrow-derived hepatocyte stem cells against TGF-β1-induced oxidative stress and apoptosis through the PI3K/Akt pathway *in vitro* [J]. Chem Biol Interact, 2019, 297(1): 109–118.
[91] LU J, WU DM, ZHENG YL, *et al*. Purple sweet potato color attenuates domoic acid-induced cognitive deficits by promoting estrogen receptor-α-mediated mitochondrial biogenesis signaling in mice [J]. Free Radical Biol Med, 2012, 52(3): 646–659.
[92] ZHANG YZ, YIN LQ, HUANG L, *et al*. Composition, antioxidant activity, and neuroprotective effects of anthocyanin-rich extract from purple highland barley bran and its promotion on autophagy [J]. Food Chem, 2021, 339(3): 127849.
[93] PENG YJ, YAN YM, WAN P, *et al*. Effects of long-term intake of anthocyanins from *Lycium ruthenicum* Murray on the organism health and gut microbiota *in vivo* [J]. Food Res Int, 2020, 130(4): 108952.
[94] ZHOU L, XIE MH, YANG F, *et al*. Antioxidant activity of high purity blueberry anthocyanins and the effects on human intestinal microbiota [J]. LWT, 2020, 117(1): 108621.
[95] JOSE RM, MATTHAN NR, JIN L, *et al*. Cranberries attenuate animal-based diet-induced changes in microbiota composition and functionality: A randomized crossover controlled feeding trial [J]. J Nutr Biochem, 2018, 62(12): 76–86.
[96] CHEN GW, WANG G, ZHU CJ, *et al*. Effects of cyanidin-3-O-glucoside on 3-chloro-1,2-propanediol induced intestinal microbiota dysbiosis in rats [J]. Food Chem Toxicol, 2019, 133(11): 110767.
[97] YAN YM, PENG YJ, TANG JL, *et al*. Effects of anthocyanins from the fruit of *Lycium ruthenicum* Murray on intestinal microbiota [J]. J Funct Foods, 2018, 48(9): 533–541.
[98] ZARY-SIKORSKA E, FOTSCHKI B, FOTSCHKI J, *et al.* Preparations from purple carrots containing anthocyanins improved intestine microbial activity, serum lipid profile and antioxidant status in rats [J]. J Funct Foods, 2019, 60(9): 103442.
[99] OWOLABI OL, DAT-ARUN P, TAKAHASHI YC, *et al.* Gut microbiota metabolism of functional carbohydrates and phenolic compounds from soaked and germinated purple rice [J]. J Funct Foods, 2020, 66(3): 103787.

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