蓝莓的主要化学成分及生物活性

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摘要: 越橘属的蓝莓含有花青苷 (花青素或酚配基, 与糖的结合体)、绿原酸、黄酮素、亚麻油酸、蝶二苯乙烯 (紫檀芪)、白藜芦醇及不同维生素等生物活性成分。花青苷口服后可分布到不同器官及可穿越血脑屏障而分布到脑。很早就报道蓝莓所含花青苷可加速视紫素的再生而有益于视力及眼部健康。近年的研究显示蓝莓因具有抗压力、抗氧化、抗发炎、抗血管新生而对癌症、糖尿病、高血脂、高血压、神经退化、肥胖、骨质疏松等老化有关的慢性病有益处。蓝莓有杀菌作用, 可用于处理妇女泌尿道感染。因此蓝莓被认为是最有营养价值的食物之一。

关键词: 蓝莓; 越橘属; 花青苷; 抗氧化; 慢性病

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Chemical principles and bioactivities of blueberry

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Abstract: The bioactive principles contained in blueberries (Vaccinium) are various kind of anthocyanins (anthocyanidins, or phenolic aglycone, conjugated with sugar), chlorogenic acid, flavonids, *α*-linolenic acid, pterostilbene, resveratrol, and vitamins. After oral administration, anthocyanins can pass through blood-brain barrier and thus appear in various organs and brain. Improve visual function by increasing rhodopsin regeneration and ocular health is the earliest reported bioactivities of anthocyanin. Recent studies demonstrated the benefit of blueberries to prevent the age-related chronic diseases such as cancer, diabeties, hyperlipidemia, hypertension, neurodegeneration, obesity, and osteoporosis through its apoptosis, antioxidant, antiinflammation, and antiangiogenesis effects. Blueberries can eradicate microorganisms for the prevention of symptomatic urinary tract infections in women. Thus, blueberries are recognized as one of the most nutritious foods and cultivated worldwide. However, how to prolong the shelving time of fresh fruit, well utilize the leaf and stem to isolate the bioactive chemicals, improve quality consistency of juicy and dry products, all should be further concerned.

Key words: blueberry; Vaccinium; anthocyanins; antioxidation; chronic diseases

1 基源

蓝莓为越橘属, 约有 450 种, 主要者约 18 种, 分布于全世界亚寒带、温带及亚热带, 高 30 cm 至 4 m。中国的大、小兴安岭山区有野生蓝莓, 近年已进行人工驯化栽培。而源生于北美洲者泛称美国蓝莓, 约百年前由 F. V. Coville 开始人工栽培。

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2 基因库及基因转植

Alkharouf 等[1]在 2007 年发表了他们所建立的蓝莓基因组数据库 (blueberry genomics database) 的信息, 此数据库含有基因表达顺序码 (expressed sequence tag)、微列阵 (microarry) 及寒冷环境及冷冻下蓝莓基因表达的数据, 可由此了解部分蓝莓的基因与基因表达的相关性, 如低温下, 哪些基因的表达被提升或抑制, 或蓝莓花蕾在低温下有哪些耐受冷的基因。

Song & Sink[2]也叙述 4 种基因转植北方高丛蓝莓 (*Vaccinium corybosum* L.) 的方式。

3 化学成分

Somerset 及 Johannor[3]报道, 蓝莓含有飞燕草素、锦葵花素、芍药素、矮牵牛素等花青素 (图 1)。Hosseinian 及 Beta[4]测定了 6 种加拿大曼尼托巴省所产的莓的总花青苷 (anthocyanins) 含量, 发现矮丛蓝莓含最高量, 100 g 蓝莓含总花青苷 558.3 mg、含飞燕草素-3-葡萄糖苷 84.4 mg、含锦葵花素-3-半乳糖苷 139.6 mg。Harris 等[5]分析矮丛蓝莓叶、果、茎、根 95%乙醇提取物中的化学成分。发现叶中含最高量的绿原酸, 占了提取物的 1/10, 在果及茎中含有槲皮素糖苷。Srivastava 等[6]发现蓝莓主要的花青苷为飞燕草素、矢车菊素、芍药素、矮牵牛素、锦葵花素。花青苷使凋亡增加, 使 glutathione-s-transferase 和 quinone reductase 降低, 此与防癌有关。Mattila 等[7], 发现蓝莓果皮每 100 g 含酚酸为 85 mg。Bere[8]发现蓝莓含有人体必需脂肪酸亚麻油酸 (图 1), 含量约 0.25 g·(100 g)$^{-1}$, 脂肪则占 0.75 g·(100 g)$^{-1}$。

4 药物动力学

Bränning 等[9]发现大鼠服用蓝莓果皮有 61%在直肠发酵, 增加粪便中纤维及蛋白质的排出及排便量, 在盲肠的羧基酸 (carboxylic acid) 量也升高, 而加入益生菌则使盲肠的羧基酸下降, 丙酸上升。蓝莓皮与益生菌使血中丙酸、丁酸高于只吃蓝莓皮者, 表示益生菌促使这两种有机酸在肠道的吸收。果皮使盲肠内的乳酸菌、双益菌、肠杆菌降低, 血中氨 (ammonia) 降低。所以果皮与益生菌对大肠道内的发酵的影响是不同的。这对发展具保健效用的食物具有重要性。

Toromanović 等[10]通过 10 位健康人 (5 男 5 女) 服用蓝莓汁研究发现, 服用大量蓝莓汁 (300 g) 后尿中马尿酸升高一倍。马尿酸量的增加与蓝莓汁服用量

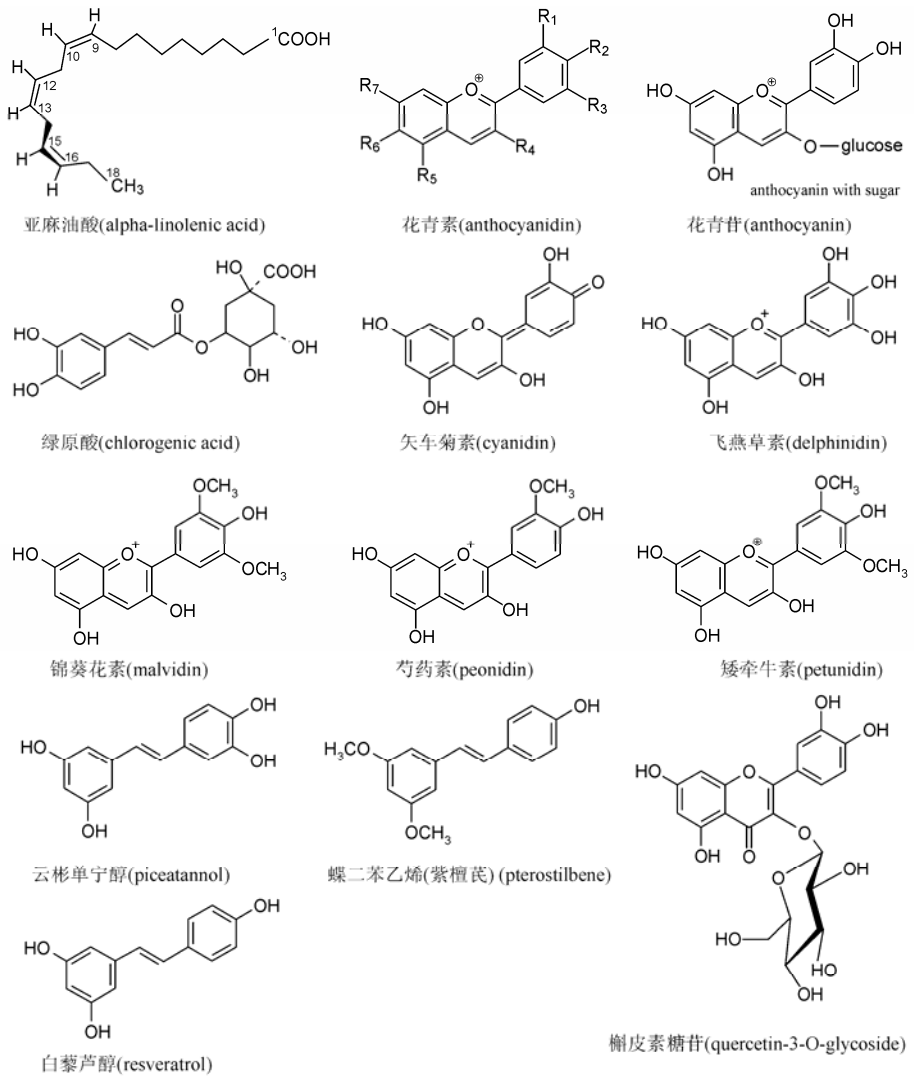

图 1 蓝莓生物活性成分的化学结构式

有关。已知安息香酸及柳酸在肝中与甘氨酸结合成马尿酸, 这是评估肝功能的方法之一。Kalt 等[11]发现猪服用蓝莓后, 其肝、眼、脑均出现花青苷。所以花青苷可以穿越血脑屏障。Collins 等[12]发现蓝莓等不同水果具有抗癌作用, 在离体肠细胞的研究中发现, 花青苷在肠的吸收只有 3%～4%, 比多酚糖苷低。含与葡萄醣结合的花青苷吸收程度高于与半乳糖结合者。他用维生素 E、辅酶、蓝莓、银杏、白藜芦醇在线虫上验证老化之自由基理论。Kay 等[13]发现人服用含花青苷的棠梨 (Chokeberry) 后, 0、0.5、1 及 2 h 抽血, 于 0、4～5、22～24 h 收集尿, 发现在血浆及尿中至少有 10 个花青苷代谢物。Mazza 等[14]发现人吃高脂食物及冷冻含有 25 种花青苷的蓝莓粉末后, 在血中出现其中 19 种, 血中抗氧化量和花青苷总量相关, 这表示人类可以吸收这些花青苷或酰化 (acylated) 的花青苷。Wu 等[15]发现老年女性服用含有 24 种花青苷的篮莓后, 有 32 种花青苷及代谢物在血中出现, 并证明人可将矢车菊素甲基化成为芍药素及进行葡萄糖醛酸化。但也显示和其他黄酮类相比, 花青苷的吸收及排泄均偏低。Andres-Lacueva 等[16]发现 19 个月龄老年大鼠服用蓝莓 8 周后, 可翻转其神经信息传递及认知行为失常。不同花青苷 (cyanidin-3-*O*-beta-galactoside, cyanidin-3-*O*-beta-glucoside, cyanidin-3-*O*-beta-arabinose, malvidin-3-*O*-beta-galactoside, malvidin-3-*O*-beta-glucoside, malvidin-3-*O*-beta-arabinose, peonidin-3-*O*-beta-arabinose and delphinidin-3-*D*-beta-galactoside) 在小脑、大脑皮层、海马回、纹状体均可发现而产生抗氧化作用及改善信息传递的作用。

5 保健作用

5.1 回顾性论文的报道 蓝莓的花青苷可以使眼睛视网膜上维生素 A 与视紫蛋白 (opsin) 构成的视紫素 (rhodopsin) 受光刺激分解及再合成更活泼有效, 而益于视力。甚至对近视、远视、老花眼、视网膜退化、夜盲、青光眼、老年白内障都有帮助, 此为较早被注意的生物活性。

自 2005 年以来, 有 7 篇以上与蓝莓相关的回顾性文献发表。Svarcova 等[17]的回顾性论文, 收集 1935～2007 的有关资料, 认为蓝莓富含酚酸、花青苷与前花青素及黄酮素, 为可促进健康的食物, 如可处理糖尿病、心血管疾病、癌症等慢性病。Ramassamy[18]认为蓝莓提取物所含的多酚类物质, 因具抗氧化及其他作用机制而具有保护神经的作用。Neto[19]指出在动物实验及临床上显示蔓越莓及蓝莓可抑制血管硬化、失血性中风、老年神经退化, 其生物活性化学成分为花青苷、黄酮醇、前花青素、桂皮酸及二苯乙烯、三萜类化合物 (熊果酸 ursolic acid) 等黄酮素。其作用机制与对抗氧化压力、发炎、调节大分子物质间的相互作用及疾病过程中基因的表达有关。Zafra-stone 等[20]收集的文献认为天然的花青苷抗氧化剂对心血管病、老年的氧化压力、发炎、神经退化有广泛疗效。花青苷可改善神经及认知功能、不同的退化性疾病、眼科疾病, 具有保护 DNA 的完整、抗血管新生、抗血管硬化、抑制幽门杆菌等作用。Melzig 及 Funke 的论文[21]指出, 多酚类化合物为植物来源的淀粉酶 (*α*-amylase) 抑制剂, 而可能用于处理 2 型糖尿病。

5.2 抗氧化性作用 抗氧化作用是蓝莓所产生不同作用的根本。Joseph 等[22, 23]发现蓝莓及其他含高量氧化剂的莓提取物, 降低乙型类糖蛋白与多巴胺在转殖有 muscarinic M1, M3 接受器的细胞 (COS-7) 所引起的钙内流失常及蛋白激酶等蛋白质的活化。Kolosova 等[24]证明在先天性易发生白内障的大鼠 (OXYS rats) 的实验中, 蓝莓可以使血中脑过氧化物降低, 并减少白内障。Rimando 等[25]发现在不同蓝莓果中有抗氧化作用的癌化学预防物, 如白藜芦醇、蝶二苯乙烯 (紫檀芪)、云杉单宁醇等二苯乙烯的存在。Goyarzu 等[26]发现服用 4 个月富含抗氧化剂的添加 2%蓝莓的饲料, 可预防老年大鼠 (Fischer-344 rats) 的认知失常, 并提升反应氧化压力的蛋白质, 降低脑中 NF-kappa B。Mansour[27]发现矮丛蓝莓 (*Vaccinium amgustifolium*) 可以抑制北极鲑鱼精液由硫酸亚铁引起的脂质过氧化。Barros 等[28]在鼷鼠上的实验说明蓝莓含的多酚, 包括花青苷具有抗氧化和基因保护作用, 因而可改善记忆及保护对 DNA 的伤害。Williams 等[29]证明在动物实验中, 含 2% 蓝莓的饲料喂食 12 周, 可改善记忆与加强激酶 (ERK1/2) 活性, 活性 (REB) 蛋白质与脑神经作用因子 (BDNF) 有关。Sakagami 等[30]证明鼷鼠浸在 25 ℃水中 8 h 后, 此氧化压力引起血中脂过氧化物浓度上升 1 倍, 蓝莓汁对此脂过氧化物的清除作用高于桑葚。McGuire 等[31]证实, 饲料中加 2% 蓝莓提取物可以使移植到老年鼷鼠脑部多巴胺神经细胞存活更久。由于多巴胺神经细胞对氧 化压力的敏感性高, 所以其存活延长是抗氧化作用的结果。Wolfe 及 Liu 等[32]在人类肝癌细胞中测定将 dichlorofluorescin 氧化成 dichlorofluorescein 而呈现荧光的研究中, 发现在不同水果中, 蓝莓的抗氧化能力最高, 其次为小红莓 (Cranberry)、苹果及红葡萄, 再次为绿葡萄。在 25 种水果中, 石榴及蓝莓的抗氧化作用最好, 香蕉及瓜类则较差。Wang 等[33, 34]

认为蓝莓的挥发油, 可以预防蓝莓的腐烂, 加强绿原酸及花青苷的抗氧化作用。而有机栽培可使高丛蓝莓的总多酚、总花青苷及抗氧化活性增加。Shukitt-Hale 等[35]使用 4 个月大的雄性 Fischer-344 大鼠, 服用含 20%饲料 8 周后, 发现蓝莓的多酚类物质可对抗海人草酸局部注射至海马回 20 周后在大鼠所引起的认知降低及抑制发炎基因的表达。

5.3 抗发炎作用 细菌、霉菌、病毒的感染, 外来的物理及化学物包括自由基都会引起身体保护性的发炎现象, 但过分的发炎及过久的发炎则对身体造成伤害。Han 等[36]证明蓝莓提取液可抑制正常人类内皮细胞 (CRL-2606) 因脂多糖体引起前列腺素 E2 的产生, 而具抗氧化及抗发炎作用。Lau 等[37]发现蓝莓提取物可以抑制脂多糖引导小神经胶质细胞制造一氧化氮、白细胞介质及肿瘤胚死因子, 所以可用于处理中枢神经的发炎。Torri 等[38]证明蓝莓在角叉菜胶、组织胺、甲醛引起的大鼠的局部发炎、及醋酸注射引起的腹部疼痛实验, 不同发炎实验模式, 均有抗炎及止痛作用。Osman 等[39]发现内毒素及 *D*-氨基半乳糖引致的大鼠肝损伤, 可被益生菌 (乳酸菌, 双义杆菌) 及蓝莓降低。

5.4 抗老化 从很多报告可知, 老年所引起的神经及行为衰退是氧化压力及发炎造成的, 因而可用抗氧化剂减轻其症状。Strőmberg[40]以神经毒 6-羟基多巴胺 (6-hydroxydopamine) 注射到大鼠的纹状回, 引起多巴神经细胞的死亡, 发现含蓝莓的饲料可以增强多巴神经细胞的恢复及活化小神经胶质细胞。Joseph 等[16, 22, 23, 26, 31, 41−46]用草莓、菠菜及蓝莓饲养 19 个月龄大鼠, 观察这些大鼠脑部从纹状体释放多巴胺及神经细胞交接处的活动情况、副交感神经刺激剂碳酰胆碱 (carbachol) 引起的 GAPase 活性增强及不同活动行为, 发现除抗癌、抗心脏病、抗老化引起的神经及行为退化、对抗模式性老年痴呆及促进空间的记忆等作用外, 也增加神经细胞的活动。以蓝莓所含的花青苷最有效, 而且不同的花青苷也在脑内被发现。Wang 等[47]在大鼠实验中证明蓝莓可降低暂时性结扎右中脑动脉脑缺血引起的神经细胞凋亡及脑梗塞。Willis 等[48, 49]认为蓝莓有助于脑部的发育。他们更进一步证明蓝莓可使神经及血管增生, 将胎儿海马回组织移植到年轻及中年母鼠眼前腔, 蓝莓可以增加神经的生长, 但血管不增生。Ramirez 等[28, 50]对成年大鼠服用冷冻干燥的蓝莓, 每天每 kg 体重 3.2 mg 的剂量口服给予花青苷, 30 天后发现对老年痴呆出现的短期记忆失常有改善作用。Zhu 等[51]认为小神经胶质细胞分泌发炎前细胞素及类淀粉蛋白质 (amyloid) 在神经细胞上的堆聚, 与老年痴呆关系密切。而在老年痴呆实验模式鼷鼠的实验中证明服用蓝莓可以抑制小神经胶质细胞的活化, 清除类淀粉蛋白质, 并防止其聚集, 故应有助于老年痴呆病人。

5.5 抗糖尿病 Martineau 等[52]发现蓝莓的根、茎、叶乙醇提取物加强C2C12肌肉细胞对葡萄糖的摄取。对 3T3-L1 脂肪细胞, 根、茎提取物可加强对葡萄糖的吸收, 叶及茎提取物加强葡萄糖刺激 Tc-tet 胰岛 beta 细胞的胰岛素分泌。果提取物刺激 DNA 的合成 (thymidine incorporation)。根、茎、叶提取物促进 3T3-L1 脂肪细胞脂质的聚集。根、叶、果提取物抑制大量葡萄糖引起的 PC12 细胞凋亡。所以蓝莓含有似胰岛素或胰岛素增敏剂格列酮性质的物质而可对抗葡萄糖的毒性、加强胰岛 beta 细胞的增生。Abidov 等[53]用含 250 mg 蓝莓叶提取物 (含 50 mg 绿原酸、50 mg 杨梅树皮素) 对 2 型糖尿病病人进行临床疗效评估。在 4 周过程中, 病人每天服用 3 次, 分别在饭前以 100 mL 水同时给予, 发现血糖从 143 下降到 104 $mg\cdot L^{-1}$, 血中发炎性 C 反应蛋白 (C-reactive protein) 也从 5.18 下降到 2.14 $mg\cdot L^{-1}$, 同时丙氨酸转氨酶、天门冬氨酸转氨酶也下降。Melzig 及 Funke[22]在一篇综述文章提及植物中多酚类物质是抑制淀粉酶而有降血糖作用的主要成分。Vuong 等[54]发现加拿大矮丛蓝莓具有抗糖尿病作用, 以一种细菌 *Serratia vaccinii* bacterium 发酵的蓝莓汁, 其酚类物质会转化而增强抗氧化作用, 如使肌细胞摄取葡萄糖的能力加大 48%, 对脂肪细胞则增加 142%。不过绿原酸及没食子酸虽然是发酵蓝莓汁的主要成分, 并无上述作用。所以发酵的蓝莓汁可抗糖尿病。

5.6 降血压 Norton 等[55]发现喂食含蓝莓的饮料给大鼠 13 周后, 测量大鼠主动脉的收缩力, 发现蓝莓可抑制甲型交感神经接受器致活剂脱氧肾上腺素引起的血管收缩, 此作用与内皮细胞有关。Kalea 等[56]发现蓝莓可以降低大鼠主动脉的氨基葡聚糖及蛋白多糖, Sakaida 等[57]发现蓝莓的果可以抑制血管紧张肽素转换酶的活性, 并对自发性高血压大鼠有降血压作用, 因而可以防止冠状动脉病及中风。

5.7 降胆固醇、降血脂 Abidov 等[58]对不胖、不抽烟、无糖尿病的高血脂男性, 作口服含有蓝莓的 8 种基本水果的降胆固醇随机、双盲、安慰剂对照的临床评估。病人每天在餐前服用 900 mg 的基本水果提取物, 发现病人的总胆固醇从 (280 ± 23) 降至 (250 ± 11) $mg\cdot dL^{-1}$, 低密度脂蛋白从 (195 ± 23) 降为 (169 ± 21)

mg·dL^{-1}, 高密度脂蛋白增加 (3.2 ± 0.6) %。尿中与发炎有关前列腺素 (8-epi-PGF2, 11-dehydro-TXB2) 下降。Kalt 等[59]发现以 70% 大豆、燕麦、大麦及 1%、2%、4% 蓝莓饲料喂食的猪, 其总胆固醇、低密度脂蛋白、高密度脂蛋白与不含蓝莓者比较均降低, 而以含 2% 为最好, 分别降低 11.7%、15.1% 及 8.3%。Prior 等[60]研究蓝莓、草莓冰冻干燥粉, 从蓝莓及草莓纯化的花青苷, 对肥胖鼠饲养以低脂 (10% 的热量源自脂肪) 及高脂 (45% 及 60% 的热量源自脂肪) 的饲料。发现只有纯化的花青苷具减肥作用。Nagao 等[61]发现蓝莓叶可使肥胖大鼠降低血脂、三硝基甘油, 其降血脂作用与降低脂肪生成及加强在肝的脂肪分解有关。

5.8 抗癌作用 癌组织的增长需要有充分营养或者血液的供应, 所以抑制新血管增生是抑制癌组织的方法之一。Schmidt 等[62]发现矮丛蓝莓具有抗人类前列腺癌分裂及抗细胞黏着的作用, 而高分子的前花青素是活性成分。该成分对依赖男性素的前列腺癌有选择性的抑制作用。Hope 等[63]发现蓝莓汁可以抑制致突变物质 methylmethanesulfonate 及 benzo[a]pyrene 引起的突变。Wilms 等[64]实验证明女性志愿者服用富含槲皮素的蓝莓苹果汁可以保护人类淋巴细胞的 DNA 不被过氧化氢及 benzo[a]pyrene 破坏, 而用以说明其抗癌作用。在观察人服用蓝莓汁 4 周后, 测定 168 位服用者的槲皮素、维生素 C、抗氧化能力、过氧化氢引起的 DNA 损伤及 benzo[a]pyerne-diol-epoxide (BPDE) 与 DNA 的结合, 发现前 3 项增加, DNA 损伤降低, BPDE 与 DNA 结合增加。而 CyplB15 基因变异者的淋巴细胞 DNA, 其被果汁保护的更好, COMT 基因变异者则反应不好, 甚至有不良反应[65]。所以建议对人的基因图谱加以分类, 以找出对营养品效果更好的人。Skupién 等[66]发现蓝莓可以强烈地抑制具有抗药性的 HL60/VINC 及 HL60/DOX 白血症细胞。Matchett 等[67, 68]发现矮丛蓝莓所含的黄酮类物质可以抑制前列腺癌细胞基质金属蛋白酶 (matrix metalloproteinases)。Srivastava 及 Yi 等[6, 69]发现蓝莓的多酚可以抑制两种大肠癌细胞株 HT-29 及 Caco-2 的增生并使其凋亡。Bickford 等[70]发现蓝莓与其他天然营养物的相互作用可以加强骨髓造血干细胞的分化。Kahle 等[71]发现蓝莓的花青苷可以在人类回肠引流液出现 85% 以上, 所以应可到达大肠用以预防直肠疾病。Seeram 等[72]根据不同莓含有抗氧化、抗癌、抗神经退化及抗发炎的植物成分的不同, 而进一步分析不同莓所含的多酚物 (花青苷、黄酮醇、黄烷醇、并没食子鞣质、没食子鞣质、前花青素、酚酸), 并测定对人类口腔、乳、大肠、前列腺癌细胞株的作用, 发现在 25～200 μg·mL^{-1} 浓度下对不同癌有不同程度的抑制作用。Suh 及 Boateng 等[73, 74]发现蓝莓所含的蝶二苯乙烯 (紫檀芪), 对雄 Fisher 344 大鼠因化学致癌物 (azoxymethane) 引起的大肠癌 (畸型腺管病) 有抑制作用。Boivin 等[75]发现矮丛及紫叶蓝莓可抑制胃、前列腺、肠、乳癌细胞株的生长 (高丛蓝莓抑制作用不高), 其抑制作用的原因为抑制细胞周期。Pan 等[76]发现蓝莓成分蝶二苯乙烯可使人类胃癌细胞凋亡, 阻断细胞周期的 G1, 增加 p53、p21、p27、p16 蛋白, 降低周期素 (cyclin) A、E 及周期素依赖性激酶 (cyclin-dependent kinase, CDK2, 4, 6)。

5.9 骨质疏松 Derareddy[77]发现服用 5% 蓝莓 (*w*/*w*) 100 天, 可以抑制 6 个月大的雌性大鼠切除卵巢后的骨质疏松。

5.10 抗菌作用 Chatterjee 等[78]发现包括蓝莓在内的不同莓, 对 clarithromycin 有抗药性的幽门杆菌 (49503) 有抑制作用, 或加强对 clarithromycin 的敏感性。Anthony 等[79]发现蓝莓提取物对十二指肠梨形鞭毛虫 (*Giardia duodenalis*) 滋养子 (trophozoite) 有抑制作用, 改变小粒隐形胞子虫 (*Cryptosporidium parvum*) 的型态。Bränning 及 Osman 等[9, 80]证明, 益生菌和蓝莓可以降低糊精硫酸钠所引起的大肠炎, 降低肠道细菌转移到肠系膜, 降低淋巴结的细菌, 肠道细菌也减少, 肠道内羧基酸、丙酸量升高。

6 展望

“自由基学说”认为体内自由基过多是引起老化及不同慢性病的根本原因, 这一学说亦被大多数医学界人士认同。而有清除自由基、抗氧化作用的天然物, 如越橘属的蓝莓, 有关他的研究也是最多的。蓝莓的保健功能被证实最多的是抗氧化作用, 如动物或人服用后血中抗氧化量增加或不同器官出现花青苷及其代谢物, 其次为抗炎、抗癌、抗老化、降血压、降胆固醇、抗菌、抗骨质疏松、降血糖作用。临床观察的结果, 要考虑不同蓝莓产品及其含有生物活性成分的不同, 还要考虑是否在随机、双盲、有安慰剂为对照的情况下进行的。其生物活性成分的 作用机制已在基因及分子层次证明。蓝莓的培育也从基因层次去开发出适合在不同环境中生长的品种。产品的质量管理也是重点。

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