酚类化合物的吸收特性及对肠道菌群的作用

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摘 要: 作为常见的植物次生代谢产物, 酚类化合物在果蔬、谷物、茶、咖啡等植物性农产品、食品和饮料中广泛存在。酚类已被证明具有多种生物活性, 包括调节血糖血脂、抗肿瘤、抗菌、抗病毒、调节肠道微生态等。酚类复杂混合物的生物利用度与其吸收特性密切相关。本文综述了酚类在消化道小肠和结肠段的吸收规律, 总结了肠道菌群在消化过程中的作用, 并介绍了近年来酚类对肠道菌群调节研究的进展。膳食酚类复杂多样, 与肠道菌群相互作用并相互影响, 且这一过程存在个体差异, 因此酚类的吸收和作用机制研究仍处于起步阶段, 未来可借助宏基因组、转录组、蛋白质组以及高通量代谢组学的发展来不断推进本领域的理论研究。

关键词: 酚类化合物; 生物活性; 吸收; 肠道菌群

Absorption characteristics of phenolic compounds and effects on intestinal flora

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ABSTRACT: As a common plant secondary metabolite, phenol compounds are widely present in vegetable agricultural products such as fruits and vegetables, cereals, tea, coffee, *etc*., as well as in foods and beverages. Phenols have been shown to have a variety of biological activities, including regulating blood glucose and lipids, antitumor, antibacterial, antiviral, and regulating intestinal micro ecology. The bioavailability of various complex mixtures of food introduced phenols is closely related to its absorption characteristics. This article reviewed the absorption patterns of phenols in the small intestine and colon, summarized the roles of the intestinal flora in the digestive process, and introduced the recent research progresses on phenols' regulation roles of intestinal flora. Dietary phenols are complex and diverse, and they interact with intestinal flora and influence each other mutually, which is a individualized procedure. Therefore, research on the absorption and action mechanism of phenols is still in very early stages. With the development of met genomics, transcriptomes, proteome and metabolomics, the theoretical research about phenols' absorption and bioactive mechanism will be promoted in the future.

KEY WORDS: phenolic compounds; bioactivity; absorption; intestinal flora

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1 引 言

酚类是一大类含羟基化合物, 多为植物的次级代谢产物, 普遍存在于水果、蔬菜、谷物、茶、咖啡和葡萄酒等植物性农产品和食品中[1], 其主要通过莽草酸和丙二酸 2 种途径合成, 可以可溶性糖基化形式存在, 也可以不溶性或结合形式存在[2]。酚类在食品、饮料、膳食补充剂和草药中广泛分布, 并且已成为人类饮食中不可或缺的一部分[3], 平均的膳食摄入量约为 1 g/d[4]。

在化学上, 酚类的主要特征在于羟基化的苯基部分。基于它们的化学结构和复杂性(如酚环和取代基团的数量), 通常可分为类黄酮和非类黄酮化合物[5]。类黄酮是我们饮食中最丰富的多酚, 根据氧杂环的氧化程度, 可分为黄酮、黄酮醇、异黄酮、黄烷醇、黄烷酮、花青素和原花色素。非类黄酮又分为酚酸(phenolic acids)、芪类(stilbenes)和木脂素(lignans)。其中酚酸在食物中含量丰富, 最常见的有咖啡酸。酚酸也可与多羟基化合物发生酯化[6], 咖啡酸酯的形式最常见的是绿原酸, 存在于咖啡和许多果蔬中。此外, 阿魏酸可与膳食纤维相关联, 并通过酯键与半纤维素连接, 其主要食物来源之一是麦麸[7]。

目前已有很多报道指出酚类化合物的摄入与机体健康之间存在相关性, 其活性作用机制与这些化合物本身的消化特性相关联。根据结构的复杂程度和聚合程度不同, 酚类可能被小肠吸收(主要为低分子量酚, 如单体和二聚体结构)[8], 或几乎以摄入时的形态到达结肠(低聚和聚合酚类, 分子量可达近 40 kDa)[9−13]。此外, 由于生物利用度较低, 酚类化合物中的大多数最终到达大肠, 可以改变肠道微生物的组成, 并被肠道微生物利用和代谢, 转化为影响宿主健康的生物活性化合物[14,15]。酚类复杂混合物的生物利用度与其吸收特性密切相关, 故本文在概述酚类化合物活性的基础上, 对近年来与其相关的消化代谢和肠道菌群调控研究的进展加以总结。

2 酚类化合物活性概述

酚类化合物除了显著的抗氧化作用之外, 还具有抗癌、抗神经退行性疾病的作用[16−18], 且已有许多体内介入和流行病学研究证实了膳食多酚具有抗炎、抗脂肪生成、抗糖尿病、抗心血管疾病等活性[19−25]。

2.1 血糖血脂调节作用

Lordan 等[26]对 5 种褐藻提取物的 α-淀粉酶和 α-葡萄糖苷酶的抑制作用进行了研究, 发现抑制效果与提取物的酚含量和抗氧化活性呈正相关。茶多酚对原发高血压、高血脂有较好的防治作用[27], 在以犬类为模型的实验中, 绿茶粉和茶多酚表现出调节脂代谢的作用, 在犬日粮中添加 1%绿茶粉和 0.25%茶多酚能够控制犬的体重, 降低犬血浆粘度和血液粘度[28]。韦芳媚等[29]研究表明桑叶提取物、茶多酚及其复配物均能促进糖尿病关键酶的抑制效果, 具有协同降血糖的作用。Kuttan 等[30]发现酚类化合物可以抑制大鼠服用葡萄糖后血糖的升高, 显著提高其葡萄糖耐量, 而糖尿病大鼠灌服 18 d 后, 其血糖水平有显著下降。

2.2 抗肿瘤作用

Amakura 等[31]对麻黄提取物的抗肿瘤活性进行了研究, 其中的草质素(herbacetin)(一种黄酮类化合物)是与抗肿瘤活性相关的成分之一。田福忠等[32]从抑制增殖、诱导凋亡、抑制迁移及侵袭、抑制新生血管形成、引发免疫反应等有关方面综述了近年来报道的丹皮酚的抗肿瘤作用及其机制。从大量的研究成果中可以发现, 丹皮酚对食管癌、胃癌、前列腺癌、肝癌、肠癌、骨癌、乳腺癌、皮肤癌等癌症均有治疗作用。

2.3 抗菌、抗病毒作用

由于酚基团的毒性, 酚类化合物常表现出抗菌作用, 其机制包括对细菌的基本发育和代谢、细胞膜功能和细菌能量代谢的干扰。黄酮醇和黄酮可抑制细菌解旋酶活性并增加葡萄球菌(*Staphylococcus*)的膜细胞质通透性。Flavan-3-ol 类, 例如表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG), 可与细菌膜形成复合物, 减少菌膜形成; 对于粪肠球菌(*E. faecalis*)可降低毒力因子和胶原结合抗原的表达; 还可下调肺炎克雷伯菌(*K. pneumoniae*)的能量代谢和蛋白生物合成[33−35]。EGGG 所属的茶多酚类化合物还表现出广泛的抗菌、抗病毒活性[36], 如对幽门螺杆菌[37]、单核细胞增生性李斯特菌、耐甲氧西林金黄色葡萄球菌[38,39]、铜绿假单胞菌[40]、丙型肝炎病毒[41]、流感病毒[42]、HIV[43−45]和念珠菌属真菌[46]的抑制作用。

2.4 肠道微生态调节作用

多酚现已被视为除益生元、益生菌外维护肠道健康的第 3 大调节因子[47]。研究者发现植物多酚有利于维持肠道微环境的稳态[48], 其可以刺激共生和有益微生物群的生长, 同时抑制致病菌株[49]。Lee 等[50]研究表明, 茶多酚类物质及其衍生物对某些致病细菌如产气荚膜梭菌(*Clostridium perfringens*)、艰难梭菌(*C. difficile*)和拟杆菌属(*Bacteroides spp*)的生长具有显着抑制作用, 而共生厌氧菌, 如(梭状芽胞杆菌、双歧杆菌属)和益生菌乳酸杆菌等受到的影响较小。

2.5 其他活性

褐藻 *Ecklonia cava* 的正丁醇提取组分富含多酚化合物, 具有较好的抗脂肪生成活性, 可增加 3T3-L1 脂肪细胞的甘油分泌并降低其葡萄糖消耗水平[51]。

总的来说, 酚类化合物对人体有多种有益活性, 其活性作用机制与肠道微生物的组成密不可分, 其膳食摄入量

与健康益处息息相关。

3　酚类化合物的吸收特性

多酚的生物活性高度依赖于其吸收特性。通过饮食摄入的各种酚类的复杂混合物, 进入胃肠道后可以被部分地释放和吸收, 以原型、甲基化、硫酸化和葡糖醛酸化衍生物的形式出现在血浆中; 也可在胃肠道消化后存活并到达结肠, 通过结肠吸收并且在血浆中出现上述衍生物或对应的甘氨酸衍生物[3]或通过粪便排泄[14]。此外, 很多酚类到达结肠后通过肠中的微生物转化为其他形式的代谢产物[52]。因此了解酚类的消化吸收过程以及其与肠道微生物的相互作用将促进其生物利用度的研究, 更多地了解其对健康的影响[53]。

3.1　小肠中的吸收

大多数多酚以酯、糖苷或聚合物的形式存在于食品中, 其不能以其天然形式被吸收, 这些物质在被吸收之前必须通过肠酶或结肠微生物区系进行水解[54]。据估计, 只有5%~10%的膳食多酚(主要是具有单体和二聚体结构的)直接在小肠中被吸收, 通常发生在去结合反应如去糖基化之后。这些简单酚类可以先后在肠细胞和肝细胞中进行广泛的 I 相和 II 相反应, 产生一系列水溶性的代谢物(甲基化、葡糖苷酸化和硫酸化衍生物), 释放到体循环中, 并进一步分配到器官和尿液中排泄。剩余的大部分的膳食酚类(占总摄入量的 90%~95%)未经小肠吸收, 进入结肠后被吸收或累积, 或经受肠道微生物分泌的酶的作用[4,55,56]。

3.2　结肠中的吸收

在小肠中未被吸收的酚, 以及吸收后经肝脏处置并通过胆汁排泄的酚类代谢物, 将进入结肠。除了少量酚可直接被结肠细胞直接吸收外, 大部分都将参与到肠道菌群的代谢中。有报道经尿液排出的微生物来源的酚类代谢物, 占所摄入的多酚量的最大比例[57]。另据报道食物中酚类被结肠微生物分解后的代谢物可能才是富含多酚食物有益健康的实际化合物, 而不是食物中的原始酚类[55]。

通常多酚降解的第一步通过微生物糖苷酶和酯酶释放糖苷配基和寡聚物, 部分释放的小分子酚酸或单体酚可以在肠道中直接被吸收, 或者与细胞表面的特定或非特定受体结合, 通过影响多个基因的表达和信号转导发挥生理功能[58−60]; 另有些 II 相代谢产物通过胆汁排出, 经微生物葡糖醛酸酶和硫酸酯酶解解聚后也可实现再吸收。此外, 来自结肠细菌的酶在剩余的未吸收多酚的多酚骨架进行酶促反应, 依次产生具有不同生理意义的代谢物[56], 例如由细枝真杆菌导致的环裂变, 产生不同生物活性的对人类健康有益的代谢物[61]。无法被微生物利用或被吸收的酚类及其酚类的代谢物, 将以粪便的形式排出体外。

Juana 等[14]对他人的研究进行了总结, 推测酚类化合物的第一次微生物转化导致初始代谢物的积累, 该初始代谢物与原始化合物具有相似的结构特征(特别是保留其官能团), 并且被认为是早期发酵阶段的标志物。初始代谢物持续暴露于微生物群会导致其分解为最终代谢产物。一些代谢产物的积累增加表明它们与某些微生物共有的主要代谢途径相关。相反, 以较小浓度存在的代谢物可能与能够激活次级代谢途径的特定微生物群组成有关。

体外和体内研究对于构建酚类化合物的结肠代谢途径至关重要。体外研究包括厌氧接种培养, 使用含酚类化合物的基质进行菌液、人或动物粪便的接种培养。在这些研究中使用的酚类底物包括纯标准物、分离得到的化合物, 酚类提取物以及食物或预消化的食物[62−78]。体外实验已广泛被用于研究黄烷-3-醇(flavan-3-ols), 二苯乙烯(estilbenes), 木脂素(lignans)和异黄酮(isoflavones)的结肠降解[79]。对于收集得到的代谢物可辅以肠细胞的体外培养, 以判断其生理活性作用[80]。

但总体而言, 体外模型对于体内真实消化的代表性有限, 如体外温育不包括肠肝循环、结肠细胞吸收、与粘膜相关的微生物群以及运输期间的生理状况变化。体内研究是体外研究的理想补充。有报道酚类化合物会被快速吸收, 在摄入后 0.5~4 h 之间达到血浆浓度峰值, 对应于胃和/或小肠吸收, 而结肠代谢物之后才出现在血浆中, 表明它们逐渐发生结肠生物转化, 在某些情况下, 4 h 后显示血浆浓度第 2 次升高[14,71,81−83]。

4　酚类对肠道菌群的调节作用

酚类化合物进入结肠后可被肠道菌群利用, 同时这些化合物及其代谢产物也将反作用于肠道菌, 改变菌群的组成比例。目前已有较多文献报道了通过体外发酵实验考察酚类对肠道菌群的调节作用。有学者使用体外发酵模型分析了葡萄籽中黄烷-3-醇类对肠细菌群生长的影响。他们发现特定食物来源的黄烷-3-醇谱可影响菌群的组成, 促进乳酸杆菌(*Lactobacillus*)和肠球菌(*Enterococcus*)的生长, 降低梭状芽胞杆菌(*Clostridium histolyticum*)的比例及其分解代谢活性, 从而引发这些化合物的生物利用度和潜在的生物活性的变化。类似地, Fogliano 等[84]在体外模型中发现, 水不溶性可可组分的细菌发酵与双歧杆菌和乳酸杆菌以及丁酸盐产生的增加有关。成焕等[85]的研究表明槟榔籽多酚可以提高其肠道菌群的物种多样性水平, 改变变形菌门(*Proteobacteria*)与厚壁菌门(*Firmicutes*)相对丰度比值, 其中柔嫩梭菌属(*Faecalibacterium*)增加幅度最大, 拟杆菌属(*Bacteroides*)和双歧杆菌属(*Bifidobacterium*)的相对丰度也有小幅增加。另据许奇等[86]报道, 在一定的浓度范围内, 茶多酚的浓度和其对肠道致病菌的生长抑制效果呈正相关,

当浓度达到 2.5%时抑菌效果达到最大。

除了采用体外发酵的方式来考察酚类对肠道菌群的调节作用之外，体内实验更能真实地反映酚类对肠道菌群的作用效果，这类实验多采用啮齿类为模型动物。根据各类报道，富含多酚的饮食较为普遍地表现出益生元的作用效果，使得动物肠道中乳酸杆菌、双歧杆菌属的微生物比例增加[87,88]；此外还多表现出梭菌类微生物比例下降的规律[87,89,90]。除啮齿类外，在对猪及肉鸡肠道菌群研究中，茶多酚的饲喂也表现出提高乳酸菌比例的效果[91]。在关于人体肠道益生功能的研究方面，Yamakoshi 等[92]报道了健康成人摄入富含原花青素的葡萄籽提取物，2 周后检测结果表明双歧杆菌(*Bifidobacteria*)的数量显著增加。

5 展 望

饮食中酚类化合物促进了有益代谢产物的产生，避免或阻碍了消化道有害化合物的产生和发挥作用，保护和延长肠内稳态[14]。酚类在饮食中类别多样但含量较低，尽管已有研究初步揭示了酚类的吸收规律和活性功能，但他们的确切作用机制尚未完全确立。对酚类的吸收和活性作用机制的深入研究需要综合考虑化合物的分子结构，消化道酶和肠道菌群分泌的酶的作用，化合物原型以及在酶作用下结构改变后进入细胞的能力，以及进入体循环后再次代谢等影响因素。除了每日摄入多酚的个体间差异外，肠道微生物群组成的个体间差异也将导致多酚及其代谢物的生物利用度和生物效力的差异[93,94]。因此在研究中个体间的差异性，以及酚与肠道菌群之间的双向改变作用，都将增加研究的难度和不确定性。随着宏基因组、转录组、蛋白质组以及高通量代谢组学的不断发展和完善，基于整体的实验技术将对多酚-微生物群相互作用的复杂性提供更详尽的描述，对酚类的代谢途径和生理相关性提供更全面的见解，并最终促进我们理解酚类的功能活性作用机制[95]。

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