

基于肠道菌的黄酮类成分代谢特征及药理学思考

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摘要: 肠道菌群参与了机体物质代谢、能量交换等多项重要生理活动, 宿主与肠道微生物的相互作用已经获得了越来越多学者的关注。黄酮类成分是广泛存在于中药的一类多酚类化合物, 具有调节糖脂代谢、抗炎等作用, 但是生物利用度较低, 这对阐明黄酮类成分的药效物质基础和作用机制提出了挑战。目前, 对于黄酮类成分体内代谢行为研究主要集中于肝脏代谢, 而最新研究表明, 人体中的肠道菌群可与黄酮发生相互作用, 一方面肠道菌群对黄酮的化学结构进行生物转化, 产生了新的代谢物可能不同于母药的药理活性; 另一方面, 黄酮成分及其代谢产物又能反过来调节肠道菌群的组成与生理活性, 这似乎对黄酮类成分的药效物质基础研究提供了新的思路。本文总结了关于肠道菌与黄酮类成分相互作用的最新研究进展, 介绍了天然黄酮类成分在肠道菌作用下的转化类型及代谢特征, 同时阐述了黄酮类成分对肠道菌的调节作用; 此外, 本文对肠道菌作用下黄酮多种药理活性进行了讨论, 为深入研究黄酮类成分和其他多酚类天然产物的体内代谢特征及药效作用机制提供了有价值的科学参考。

关键词: 药物代谢; 黄酮; 肠道菌群; 肠道菌代谢物; 天然药物

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Metabolism characteristics and pharmacological insights of flavonoids based on the intestinal bacteria

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Abstract: The gut microbiota takes part in many *in vivo* important physiological activities of host, such as the substance metabolism and energy exchange, etc. The interaction between the host and the intestinal microorganisms has attracted scholars' attention. Flavonoids are a group of polyphenol compounds widely found in natural plants, with the bioactive effect of regulation of glucose and lipid metabolism, anti-inflammation. However, their low bioavailability cause difficulty to clarify the effective substances and the mechanism of flavonoids. Apart from the metabolic effects of liver on flavonoids, recent studies have shown that the gut microbiota can interact with flavonoids. On the one hand, flavonoids can be metabolized by gut microbiota and subsequent metabolites can produce pharmacological activities different from the parent components. On the other hand, flavonoids and their metabolites can in turn regulate the composition and physiological activities of the intestinal flora, which seems to provide a new insight for the research on the effective substances of flavonoids. In this review, we introduced the metabolic characteristics of flavonoids under the actions of intestinal bacteria, and the regulation effects of

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flavonoids on gut microbiota was also summarized. Meanwhile, the therapeutic effect of flavonoids under the action of intestinal bacteria was discussed.

Key words: drug metabolism; flavonoids; gut microbiota; gut microbiota metabolites; natural medicine

黄酮是一类广泛存在于自然界、具有重要生理活性的天然产物。黄酮类成分的基本母核为2-苯基色原酮,它由两个具有酚羟基的苯环(命名为A环与B环)以及连接A、B两环的中央三碳原子组成^[1,2]。图1展示了黄酮类成分的几种母核结构类型,包括黄酮、黄酮醇、二氢黄酮、二氢黄酮醇、异黄酮、3-黄烷醇、二氢查尔酮及花青苷。黄酮类成分具有广泛的药理活性,如调节糖脂代谢、降压、心血管保护、抗炎、抗肝脏毒作用、抗菌抗病毒、雌激素样作用等^[1,3-9]。一般认为,黄酮类成分在肝脏发生广泛代谢,其中儿茶酚-O-甲基转移酶可将黄酮类成分转化成甲基化产物,UDP-葡萄糖醛酸转移酶、硫酸转移酶可将黄酮类成分分别代谢为葡萄糖醛酸结合物或硫酸结合物^[10]。然而,随着近年来肠道菌研究的深入,肠道菌群也被认为参与了黄酮类药物的代谢,进而影响了黄酮类药物的体内过程及药效^[11,12]。本文将围绕黄酮类药物与肠道菌群的相互作用,综述了黄酮类药体内转化、代谢特征、以及药理研究的最新进展并提出思考,以期为本类药物和其他多酚类天然产物的研究与开发提供重要的科学参考。

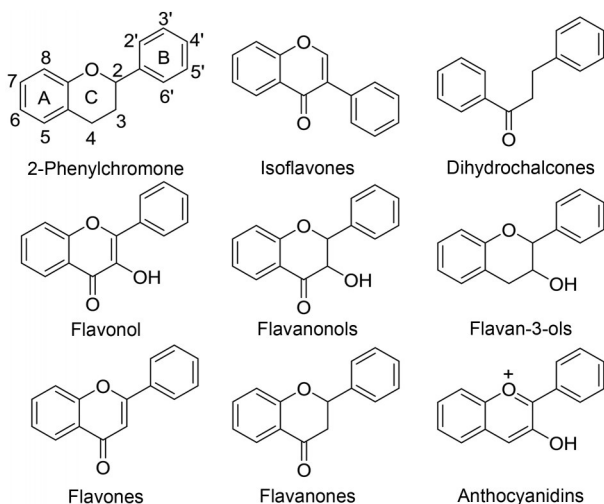


Figure 1 The basic structures of flavonoids

1 肠道菌广泛参与天然药物的代谢

肠道菌群是由寄生在人体肠道中的数万亿、超过1 000余种的细菌、真菌及噬菌体等组成,是肠道微生态系统的核心部分^[13,14]。肠道菌群与宿主细胞进行着物质、能量甚至基因方面的交流,对宿主生理功能的多样性发挥着重要作用;同时,作为人类的第二套基因

组,肠道菌群影响人类的健康与疾病发展,有国外研究者已经提出将肠道菌群作为“人体肝脏以外的第二个代谢性器官”^[15]。肠道菌群中富含大量与物质代谢相关的酶系^[16],因此,肠道菌群对口服药物的生物转化及吸收有重要影响。与肝脏代谢不同,肠道菌群引起的生物转化类型具有一定的独特性,肠道菌对药物的代谢主要包括水解与还原反应^[16-19]。目前,肠道菌群的药物代谢已经被视为机体药物代谢的重要补充^[17,20]。研究显示,人类肠道菌群在门水平上具有一定的稳定性和保守型,而在属和种水平上有较大差异。拥有不同遗传背景、生活习惯的人群中其体内的肠道菌群优势菌属、结构组成等差异非常大,如西方人群中拟杆菌属(*Bacteroides*)是相对含量最多且个体差异最大的菌属,而中国人的肠道菌群中含量较多的菌属为考拉杆菌属(*Phascolarctobacterium*)^[21,22]。因此,受肠道菌群个体差异影响,人体口服天然药物后药物的代谢性质和疗效、作用的机制都可能存在差异^[17]。目前,已经有越来越多的学者开始将肠道菌群的研究纳入到药物的体内过程研究中来,以期更合理地阐明药物的作用机制并指导临床合理用药^[23-25]。

天然药物普遍存在口服后难吸收的特性,比如小檗碱的口服生物利用度约为1%^[26-28]、人参皂苷Rk1为2.87%~4.23%^[29]、水飞蓟宾仅为0.73%^[30],因此,天然药物口服后将不可避免地与肠道菌相互作用,也是被研究较多的一类药物。天然药物是指来源于天然植物、动物或微生物的,对人体疾病状态有改善、消除作用或能够维持人体健康状态的单体化合物及其集合。天然药物化学结构骨架新颖独特、活性好、耐药性低、不良反应少,是我国原创药物的主要来源^[31-33]。据统计,截至2019年,全球超过49.2%的新药是直接来源于天然产物或天然产物的衍生物^[34]。因此,天然药物在新药发现和研究中占有重要地位。其中,黄酮是一类自然界广泛存在的天然产物。目前,已上市黄酮类药物包括黄芩素、儿茶素、水飞蓟宾等。由于黄酮具有2-苯基色原酮的母核结构,同时又具有酚羟基,当黄酮类成分口服进入体内后可能发生广泛代谢,因此,研究黄酮类成分在肠道菌的代谢特征以及药理学作用将具有重要的科学意义。

2 肠道菌转化黄酮类化合物的反应类型

与黄酮类药物在肝里的代谢类型不同,肠道菌的

黄酮代谢几乎不涉及氧气^[35]。在肝脏中, 黄酮类成分主要发生结合型反应, 如儿茶酚-*O*-甲基转移酶可将黄酮类成分转化成甲基化产物, UDP-葡萄糖醛酸转移酶、硫酸转移酶可将黄酮类成分分别代谢为葡萄糖醛酸结合物或硫酸结合物^[10]。而肠道菌的代谢类型一般包括去糖基化反应、去甲基化反应、脱羟基化反应、还原反应以及环裂变反应等^[36-40]。肠道菌可将外源性黄酮类化合物作为自身碳源维持自身生长, 同时肠道菌对某些具有抑菌作用的黄酮类分解反应也缓解了自身生长的压力, 对保证本种菌属的存活有积极意义^[41]。

2.1 去糖基化反应 除黄烷醇类型结构的黄酮外, 大多数黄酮类化合物均以*O*-糖苷或*C*-糖苷形式存在, 而人体口服黄酮类药物或含黄酮类成分的中药后, 在血浆中检测到的糖苷含量大大降低, 说明黄酮在肠道中发生了显著的去糖基化反应。去糖基化在大肠和小肠中均会发生, 而不同类型的黄酮糖苷被不同部位的酶或肠道菌代谢。在肠细胞中, 存在两种可以水解黄酮类单糖苷的 β -葡萄糖苷酶, 包括乳糖酶-根皮苷水解酶复合物以及胞浆 β -葡萄糖苷酶, 可将如槲皮素-3-*O*-葡萄糖苷和槲皮素-4'-*O*-葡萄糖苷等黄酮类单糖苷水解为相应的苷元^[42-44]。

而对于大部分黄酮非单糖苷类, 人体自身的酶类无法对寡糖链进行有效水解。而盲肠和大肠中的专性或兼性厌氧菌可利用黄酮, 尤其是黄酮苷类作为自身生长的唯一碳源^[41]。因此, 肠道菌不仅可以对黄酮单糖苷进行水解反应, 也可以对黄酮非单糖苷, 如芦丁等, 进行水解产生苷元^[45]。黄酮醇、黄酮、黄烷酮、二氢查耳酮、异黄酮和花青素的*O*-糖苷均可被特定人类肠道细菌进行*O*-去糖基化反应^[45]。此外, 肠道细菌还可对黄酮-*C*-糖苷进行去糖基化反应^[46,47]。肠道菌中也广泛存在具有 β -葡萄糖苷酶活性的酶类, 如肠道菌中优势种属如双歧杆菌属(*bifidobacteria*)与乳杆菌属(*lactobacillus*)等就存在相关酶系^[48]。而对于非单糖苷类化合物, 肠道菌中某些菌属进化成特异性水解其他糖苷键的酶, 如嗜酸乳杆菌(*Lactobacillus acidophilus*)

等菌属中已经出现可以水解鼠李糖苷键的 α -*L*-鼠李糖苷酶, 可用于对芦丁、异橙皮苷等进行去糖基化反应^[35,36]。目前对黄酮-*C*-糖苷的去糖基化反应研究仍然较少, 有研究报道, 对于黄酮和异黄酮-*C*-糖苷, 毛螺菌科(*Lachnospiraceae*)、肠球菌科(*Enterococcaceae*)、链球菌科(*Streptococcaceae*)中存在一些成员可以参与这些黄酮-*C*-糖苷的分解作用, 这些菌属同时也可以与相应苷元的*O*-糖苷发生相互作用产生对应苷元^[49-52]。图2展示了几种黄酮类物质被肠道菌代谢发生去糖基化反应的示例。

2.2 去甲基化和脱羟基化反应 当黄酮糖苷通过去糖基化反应生成苷元后, 除一部分被肠细胞吸收进入体内外, 黄酮母核上(如黄酮、异黄酮或异戊烯基黄烷酮)的取代基如甲氧基或羟基也可进一步被肠道菌中的相应酶类修饰, 生成脱甲基或脱羟基化的产物(图3)^[37]。此类反应一般发生在黄酮母核的A环或B环, 一些真杆菌属(*Eubacterium*)、伊格尔兹氏属(*Eggerthella*)等菌属的成员如黏液杆菌(*Eubacterium limosum*)可以介导此类反应^[38,53,54]。

2.3 还原反应和环裂变反应 黄酮的分子结构决定了其可以作为一个电子受体, 可以与电子供体如氢原子自由基发生还原反应而被重新氧化。肠道微生物中的还原酶系可以参与此类反应, 在黄酮分子上首先表现为C环上双键的重新饱和化, 如槲皮素可以被细枝真杆菌(*Eubacterium ramulus*)等代谢为二氢槲皮素^[39,56]。目前已有学者表征了可以介导此类反应的还原酶, Yang等^[39]在*Flavonifractor plautii* ATCC 49531菌中发现了一种黄酮还原酶, 由两个拥有N端 α - β - α 紧密结构域和C端延伸结构域的单体构成的同型二聚体。据报道, 该类黄酮还原酶功能的行使需要黄素单核苷酸(FMN)与烟酰胺腺嘌呤二核苷酸(NADH)等辅酶的参与, 同时, 该类酶系在人类肠道菌群以及富含黄酮的环境中的其他微生物含量较高, 表明了肠道菌对黄酮的还原反应广泛存在^[39]。

黄酮分子的还原反应一般作为肠道菌降解黄酮的

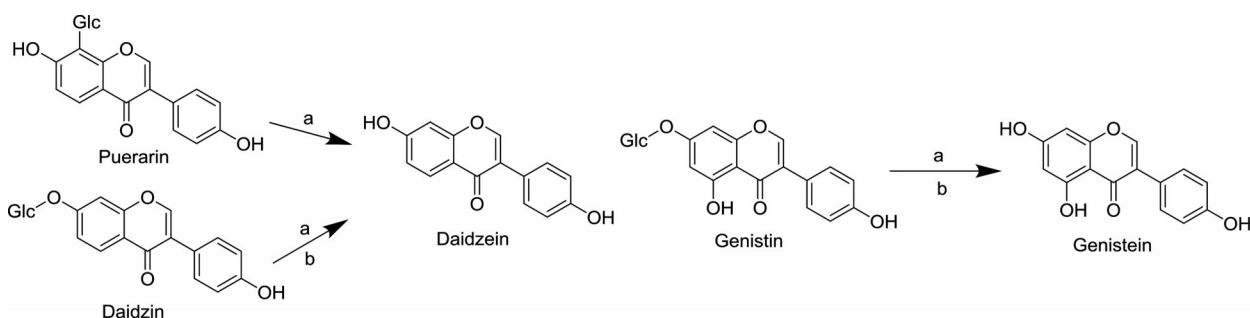


Figure 2 Examples of deglycosylation pathways of flavonoids by gut microbiota (strain CG19-1 (a) and *Eubacterium ramulus* (b))^[47]

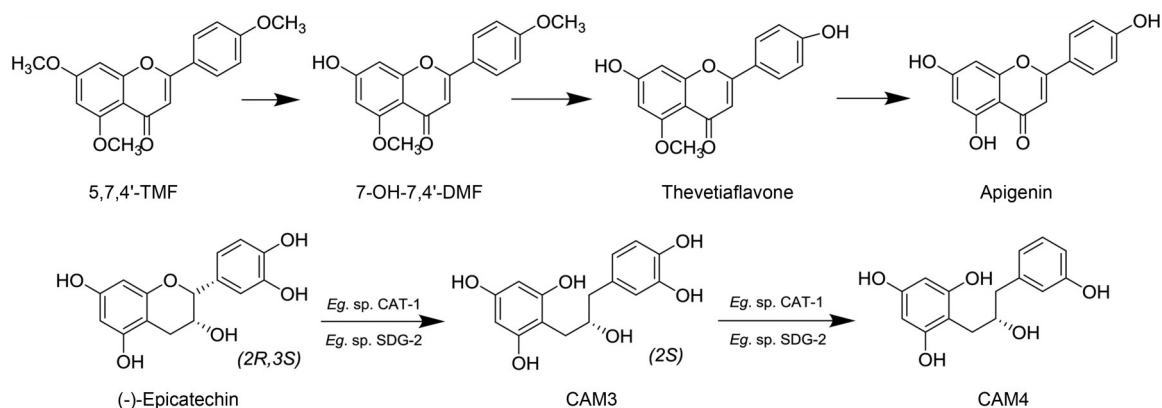


Figure 3 Metabolic pathways of demethylation (above) and dehydroxylation (below) of flavonoids^[55]. (above) Demethylation of 5,7,4'-trimethoxyflavone (5,7,4'-TMF) by *Blautia sp. MRG-PMF1*. 7-OH-7,4'-dimethoxyflavone, 7-OH-7,4'-DMF. (below) Dehydroxylation of (-)-epicatechin by *Eggerthella sp. SDG-2* and *Strain CAT-1*

启动反应, 黄酮分子经过 C2-C3 双键还原后一般不稳定, 肠道菌中的一些酶类, 如还原酶复合物当中的其他酶, 会进一步将黄酮分子的中心 C 杂环进行分解^[39]。不同类型的黄酮分子在还原反应与环裂变反应中存在一定差异^[37], 如黄酮醇类物质在 C2-C3 位置的双键被肠道菌还原后, C 环发生的环裂变后往往在氧原子与 C3 重新环合为五元环, 再进行后续分解反应, 如前所述二氢槲皮素由槲皮素生成后, 经 B 环环裂变反应又环合成高朦朧木素 (alphitonin) 的中间体^[37]。而黄酮类物质则在 C2-C3 还原后直接在 O 原子与 C2 位置发生分解反应, 如芹菜素在还原生成柚皮素, 此后则分解成称为 phioletin 的中间体^[37]。

而裂变后的中间产物将被进一步转化, 黄酮分子的 B 环部分一般会转化为羟苯基脂肪酸类物质, 如黄酮醇类物质 B 环最终生成苯乙酸类物质, 而黄酮类物质则生成苯丙酸类物质, 异黄酮类物质生成 2-甲基苯

乙酸类物质^[37]。A 环部分一般先生成多酚类物质, 而某些黄酮生成的多酚类物质本身存在烯醇互变现象, 如槲皮素生成的间苯三酚, 烯醇互变后的间苯三酚芳香性大大降低, 其在 NAD(P)H 的辅助下被某些肠道菌进一步分解, 最终生成短链脂肪酸, 后者可进一步用于菌体 ATP 的合成^[39,57,58], 图 4 展示了黄酮类物质被肠道菌还原反应及环裂变反应的反应路径。

3 黄酮类化合物对肠道菌的调节

研究表明, 一些肠道菌本身富含宿主所不存在的酶系, 可以介导独特的生物转化反应, 如短链脂肪酸、次级胆汁酸等物质的生成均离不开肠道微生物的参与, 而这些物质对于宿主本身健康生理状态的维持至关重要^[59-62]。在黄酮类物质与肠道菌群的相互作用过程中, 除了自身被肠道菌代谢以外, 黄酮类物质也可以通过调节特定肠道菌中菌属的相对丰度, 或者影响特定酶系的活性, 来调节肠道菌群自身代谢活动。

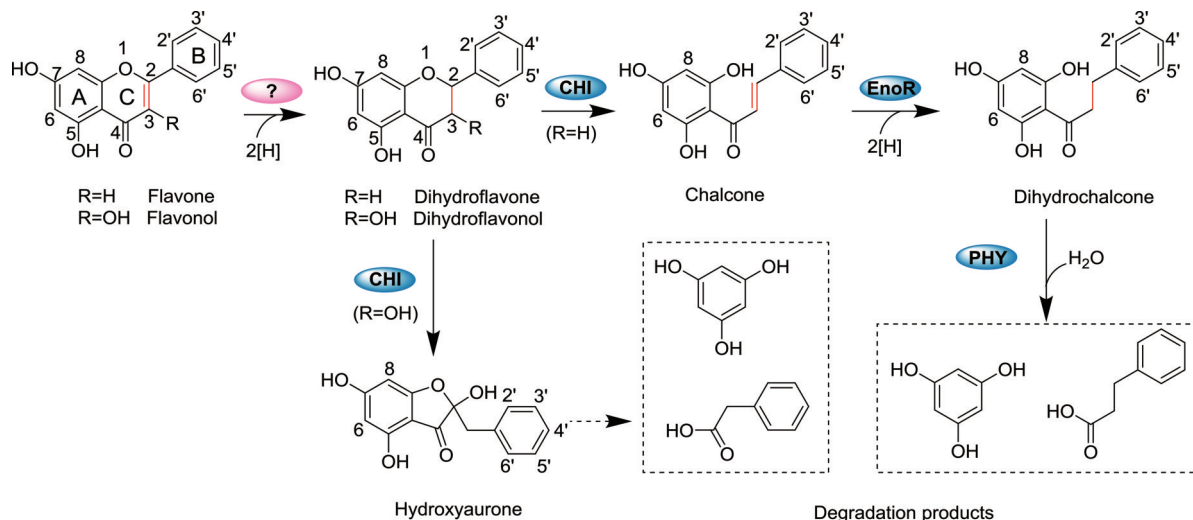


Figure 4 Metabolic pathway of flavones and flavonols by gut microbiota^[39]. CHI: Chalcone isomerase; EnoR: Enoate reductase; PHY: Phloretin hydrolase

3.1 对菌群构成的调节 由于肠道菌利用黄酮分子作为碳源的能力不同,同时,肠道菌自身对于某些黄酮类物质的抑菌和杀菌作用的抵抗也有差异,因此,黄酮类化合物能够对人体肠道菌群的构成进行调节^[41]。花青素类黄酮对菌群调节能力较强,临床研究表明一些花青素能够上调益生菌的丰度,如双歧杆菌属(*Bifidobacterium* spp.)、乳杆菌属(*Lactobacillus* spp.)等^[63,64];同时,花青素能够下调一些致病菌的丰度,如溶组织梭菌(*Clostridium histolyticum*)、金葡菌(*Staphylococcus aureus*)等^[65]。目前对于黄酮调节人体肠道菌群的研究还集中在黄酮类膳食的调节作用,而黄酮类药物或候选物的研究仍然较少,Etxeberria等^[66]考察了高脂饮食和高碳水饮食大鼠模型中槲皮素对肠道菌组成的影响,研究发现槲皮素能够在门水平下调厚壁菌门/拟杆菌门的比率(ratio of F/B),同时下调与肥胖相关的菌属,如韦荣球菌科(*Erysipelotrichaceae*)、芽孢杆菌属(*Bacillus* spp.)、圆柱状真杆菌(*Eubacterium cylindroides*)等。而Shanthi等^[67]利用体外实验证实柚皮素可以促进鼠李糖乳杆菌(*Lactobacillus rhamnosus*)、大肠杆菌(*Escherichia coli*)、金葡菌的生长,相较于革兰阴性菌,革兰阳性菌如金葡菌对于柚皮素的刺激更为敏感。Clavel等^[68]分析了服用异黄酮类2个月的绝经妇女体内肠道菌的组成后发现,球形梭菌(*Clostridium coccoides*)与直肠真杆菌(*Eubacterium rectale*)的丰度明显上升。通过黄酮分子与肠道菌群的相互作用,肠道菌群的优势菌属受到调节而发生了改变,因此,有必要建立黄酮与肠道菌互作的数据库,以进一步了解肠型与黄酮类物质的相互关系,从而有利于口服黄酮类药物的开发。

3.2 刺激肠道菌产生短链脂肪酸 短链脂肪酸是指具有主链含6个碳以内的饱和脂肪酸^[69]。肠道菌可通过分解胃肠道中的碳水化合物、支链氨基酸、脂肪等物质而产生短链脂肪酸。由于肠道菌中富含宿主所没有的代谢酶,如丙酰辅酶A转移酶、丙醛脱氢酶等,因此,机体中短链脂肪酸成分主要由肠道菌介导生成^[70,71]。目前,短链脂肪酸已经成为肠道菌群代谢物中研究较为广泛的一类。黄酮类化合物影响肠道菌产生短链脂肪酸的途径主要有三类:①直接促进或抑制特定肠道菌的生长,一些黄酮分子本身可以破坏菌膜完整性或抑制酶的活性从而抑制菌体的活性,此外某些黄酮分子可直接作为益生元促进某些菌体的生长或提高相关酶系的活性^[34,72];②间接促进或抑制某些菌属的生长,如某些黄酮通过竞争性排斥、诱导宿主免疫反应来抑制病原菌的定殖^[60];③黄酮本身作为碳源提供短链脂肪酸的前体,肠道菌可以将黄酮作为唯一碳源^[41],黄酮苷的糖基部分被肠道菌最终代谢为短链脂肪酸;另

一方面,肠道菌对黄酮C环进行裂环反应后,A环部分被代谢为多酚类化合物,后者会进一步被转化为短链脂肪酸^[56]。

Mao等^[73]利用肠道菌体外温孵体系筛选了黄芩素、槲皮素、淫羊藿苷、木犀草素、柚皮苷等几种黄酮类物质对肠道菌短链脂肪酸生成的影响,结果表明除黄芩苷外,其他5种物质均能刺激肠道菌温孵体系产生短链脂肪酸,尤其是乙酸和丁酸的生成。有报道认为黄酮苷元诱导肠道菌产生短链脂肪酸的能力强于对应的黄酮苷,这可能是由于黄酮苷元在小肠部位抑制了 α -胰淀粉酶的作用,从而增加了淀粉类物质在大肠部位的排泄,进而增加了大肠中肠道菌群代谢短链脂肪酸的原料^[74]。Tomonori等^[74]比较了口服橙皮苷元与对应苷后大鼠肠道内容物短链脂肪酸的含量,结果表明橙皮苷元与橙皮苷均能增加短链脂肪酸的生成,而苷元表现出了更强的刺激作用。黄酮类刺激肠道菌产生的短链脂肪酸可以作为肠道细胞的能量来源,同时丁酸可以刺激肠道细胞水钠吸收并调节结肠功能的运动性,此外,丁酸可以诱导细胞分化,从而在体外诱导癌细胞凋亡,阻止癌症发展^[73]。

3.3 调节肠道菌产生次级胆汁酸 机体中的胆固醇在肝脏中首先通过细胞色素酶发生羟基化,而后通过一系列反应生成胆汁酸,合成的胆汁酸通过胆汁分泌入十二指肠^[75]。根据代谢胆固醇时的羟化位置不同,生成的初级胆汁酸一般有两种,即胆酸(CA)和鹅去氧胆酸(CDCA),初级胆汁酸还可以结合甘氨酸或牛磺酸等物质生成结合型的初级胆汁酸^[76]。肠道中的一些菌属含有胆盐水解酶(BSH),如厚壁菌门、拟杆菌门以及放线菌门(*Actinobacteria*)中均含有该酶系的基因,BSH负责对结合胆汁酸的水解,从而生成游离胆汁酸^[77]。肠道菌中的另一种酶系,7-脱羟基化酶可进一步将初级胆汁酸7位上的羟基消除,生成次级胆汁酸,由CA脱羟基后生成脱氧胆酸(DCA),而CDCA脱羟基后生成石胆酸(LCA),不同物种的胆汁酸的组成有所差异^[78]。厚壁菌门中的多数菌属都含有7-脱羟基化酶,此类酶的编码基因可被胆汁酸诱导^[79]。黄酮类物质可通过调节含有以上酶系菌属的相对丰度和代谢活性调节次级胆汁酸的生成,同时,有观点认为黄酮对次级胆汁酸的影响可能存在物种间差异。Han等^[80]通过给大鼠饲喂儿茶素、芦丁、槲皮素等黄酮类化合物后检测粪便中的胆汁酸,发现次级胆汁酸的含量明显下降。某些次级胆汁酸,如LCA和DCA被认为对正常结肠细胞具有细胞毒性,导致结肠上皮细胞代偿性增殖增加,从而导致结肠癌风险增加,因此儿茶素、芦丁、槲皮素的摄入有降低机体患结肠癌的潜能^[80]。而人口

服儿茶素后,球形梭菌属 (*Clostridium coccooides*) 的丰度升高,而球形梭菌属中7-脱羟基化酶的活性很高,可将初级胆汁酸代谢为次级胆汁酸^[81,82]。而 Yamakoshi 等^[83]比较了服用含有原花青素的葡萄籽提取物后的成年人粪便中的肠道菌群组成,结果表明双歧杆菌属的丰度大大提高,而双歧杆菌属的细菌中拥有 BSH, 可以负责水解结合型胆汁酸^[84]。

4 基于肠道菌的黄酮类化合物的药理学效应

黄酮类物质在人体胃肠道内经历了肠道菌群的广泛代谢,其原形分子在机体循环中的比例往往不高,因此,除关注黄酮类分子本身的药理活性以外,肠道菌群的代谢产物也应该引起重视。目前,肠道菌参与下的黄酮类物质的药理活性主要集中于代谢性疾病,如肥胖、糖代谢紊乱、炎症、中枢神经系统疾病、心血管系统等^[85-90]。下面将重点阐述黄酮类成分与肠道菌交互调节及多种药理活性的研究进展。

4.1 肥胖和糖尿病 黄酮类物质对肥胖与糖尿病症状的改善已经被多项研究证实,目前认为,黄酮类物质对糖尿病和肥胖的治疗需要肠道菌群的参与^[85,88]。Esposito 等^[91]研究了黑加仑花青苷对肥胖小鼠的治疗效果,与服用联合抗生素的伪无菌组相比,8周时花青苷治疗组小鼠的粪便中的花青苷含量提高了16~25倍,同时,拥有完整肠道菌的花青苷治疗组显示出抵抗高脂饮食的体重增加和葡萄糖代谢改善,提示花青苷的肠道菌代谢产物,如苷元或其他小分子多酚酸类物质在改善肥胖中起到了主要作用。有文献显示黄酮在肠道菌转化下的代谢产物可以通过抑制脂质生成^[92]、减少炎症反应^[93]、维持能量代谢稳态^[94]及改善胰岛素抵抗^[95]等调节机体糖尿病及肥胖状态。黄酮类物质及代谢产物还可以通过调节与糖脂代谢密切相关的菌群的丰度实现肥胖和糖尿病的治疗,如粪杆菌属、乳酸菌属、拟杆菌属等可以参与机体糖脂代谢^[96]。

4.2 抑郁与神经炎症 肠道菌对黄酮的水解作用可将黄酮苷类水解为黄酮苷元,产生了与原药不同的活性。如芦丁的水解产物通过肠道菌的水解生成槲皮素,通过体循环进入脑部,以槲皮素-3-*O*-葡萄糖醛酸的形式在脑中积累,后者可以改善脑部神经炎症^[87,97]。锦葵素-3'-*O*-葡萄糖苷以及代谢物3,4-二羟基苯丙酸能通过调节大鼠神经元可塑性及外周炎症,同时,锦葵素-3'-*O*-葡萄糖苷能够增加调节突触可塑性相关基因序列的组蛋白乙酰化,3,4-二羟基苯丙酸还能抑制白介素-6相应基因中富含 CpG 序列 DNA 的甲基化,显著提高对应激性抑郁的认知适应能力^[98]。

4.3 神经退行性疾病 据报道,一些黄酮类物质在肠道菌群的代谢物,尤其是多酚类代谢物可能参与到中

枢神经退行性疾病的进程。Ho 等^[90]建立了拥有不同肠型的两种悉生小鼠模型,黄酮类饮食处理后的动物体内产生了不同的多酚酸类代谢物,其中,3-羟基苯丙酸、3-羟基苯甲酸以及3,4-二羟基苯甲酸被证实可以抑制 α -突触核蛋白的错误折叠,同时抑制炎症,揭示了黄酮类饮食及化合物在治疗帕金森综合征方面的前景^[99,100]。另一项研究中,Wang 等^[101]也研究了花青素类化合物在治疗阿尔茨海默症方面的作用,每天给大鼠模型饲喂 25 mg·kg⁻¹的葡萄籽提取物后,在脑部发现了微生物降解产物3-羟基苯甲酸与3-羟基苯丙酸以 μ mol 级别聚集,有文献^[102]报道了该两种物质可在体外干扰 β -淀粉样蛋白的组装,因此它们可以对阿尔茨海默症产生积极作用。

4.4 心血管疾病 不少黄酮类化合物及其酚酸类代谢物也通过多种通路对心血管疾病产生疗效。3-羟基苯丙酮酸是原花青素的一种肠道菌群裂环代谢物,其可以通过 NF- κ B 通路降低氧化低密度脂蛋白导致的细胞氧化应激,同时体外实验证实其通过调节细胞脂质代谢从而抑制巨噬细胞向泡沫细胞的转化^[103],对动脉粥样硬化的治疗有一定前景。而 Zhang 等^[104]报道了大豆苷元的一种代谢产物雌马酚 (equol),其可以降低高脂饮食的 ApoE 敲除小鼠模型血浆中甘油三酯、总胆固醇、低密度脂蛋白结合胆固醇,同时升高高密度脂蛋白胆固醇,减少了心动脉斑块。同时,雌马酚还可以通过下调白介素 12/白介素 18 诱导的自然杀伤细胞激活,抑制干扰素- γ 的生成以及减少氧化应激等途径缓解动脉粥样硬化^[105,106]。此外,花青素的代谢物原儿茶酸能够降低单核细胞的黏附和聚集,同时抑制单核细胞在主动脉夹层的浸润和抑制炎症从而对动脉粥样硬化的治疗产生积极作用^[91,107,108]。体外实验表明原花青苷的代谢物3-羟基苯丙酸可以通过刺激胰岛素相关通路调节一氧化氮合酶的表达,从而促进高糖环境下内皮细胞 NO 的产生,有助于机体血压的调节^[109]。Iveta 等^[110]在原发高血压大鼠模型中也证实了3-羟基苯丙酸的血管舒张和降血压作用,同时表明了3-羟基苯丙酸在体内的作用是 NO 依赖的。

4.5 其他 黄酮类物质与肠道菌群的相互作用产生的代谢物也可以用于感染性疾病的治疗,如梭状芽孢杆菌 (*Clostridium orbiscindens*) 能够代谢原花青苷成为4-羟基苯丙酸,后者可通过增强 I 型干扰素信号传导从而改善肺部免疫病理学状态,因此可以用于流感的治疗与预防^[111,112]。黄芩苷也被报道了具有抗流感作用,但其发挥作用需要肠道菌将其转化为黄芩素^[113]。柑橘和苹果多酚对患者的系统性红斑狼疮的症状有改善作用,进一步研究发现其中的黄烷酮类物质可提高

乳酸菌属水平,而二氢黄酮醇类可以升高双歧杆菌属水平,其中二氢黄酮醇一部分可由肠道菌转化而来,两种菌属均可调节机体的免疫机能,从而纠正系统性红斑狼疮的症状^[114]。

5 思考与展望

天然药物的研究是药物研发的重要来源,而黄酮类化合物已被报道具有疗效广泛,简单易得的优势,但也存在生物利用度较差,作用机制不明确的特点。近年来,黄酮类物质与肠道微生物的相互作用研究表明,黄酮类物质能被肠道微生物广泛代谢,而缺少肠道菌调节的黄酮类物质其药物活性往往会发生显著改变,说明肠道菌群在黄酮类物质的药理活性方面起到了关键作用。图5总结了肠道菌与黄酮类化合物间的相互作用及潜在药理学意义。

肠道菌可将黄酮类物质的糖配基作为唯一碳源用于自身生长,而一部分游离出的苷元被动吸收进入循环产生疗效,另一部分则可被肠道菌中的代谢酶进一步转化生成多酚酸类物质,后者可能发挥了黄酮类物质本身所不具有的药理作用;此外,黄酮类物质通过直接或间接作用调节肠道菌群的相对丰度和活性改变肠道微环境的生理状态。由此可见,仅仅考虑黄酮分子本身的药理活性已经不能满足现有黄酮类药物研发的需求。有学者提出应当将药物及代谢产物等组成的化学成分,与靶标分子、信号传导分子和肠道菌等组成的生物成分,共同视为药物复合物系统,其激活的生物途径与诱导的分子末端信号网络,即药效云,综合介导了

多靶标药物的多效性^[115],这为黄酮类物质的活性物质基础和生物利用度研究提出了新的思路。

目前,黄酮类化合物与肠道菌的相互作用的研究仍然处于起步阶段,需要更多的实验和理论来补充到现有成果当中。阐明似乎相反的药物特性对研究黄酮类化合物药物研发有积极意义,比如有体外实验表明黄酮类物质能够降低T淋巴细胞的增殖,但在实验性自身免疫病脑脊髓炎小鼠模型中却显示黄酮类物质会延迟症状的恢复^[116],这种矛盾的结果可能是由于肠道菌群起到了关键作用。而已有体外实验表明槲皮素与甲氧雌二醇联用可以增强对人前列腺肿瘤细胞的生长抑制作用^[117],肠道菌群是否参与黄酮类对癌症的治疗值得进一步探索。此外,口服香青兰的黄酮提取物能够改善 β -淀粉样蛋白诱导的小鼠阿尔茨海默症症状,而黄酮类成分通过肠-脑轴通路的作用机制值得学者深入探讨^[118]。而对黄酮类单体,尤其是药物候选物与肠道菌的互作研究依然较少,作为植物中含量巨大的物质,人们往往关注黄酮类物质的膳食补充对健康的损益。同时,肠道菌群作为人体的隐形器官,受到了多种因素影响,从而导致肠道菌群在不同物种、同一物种不同个体之间的巨大差异。这样,一方面肠道菌可以作为个性化治疗的关键靶标,而另一方面也增加了对黄酮类药物与肠道菌群相互作用研究的难度。人体肠道中肠道菌的数量约为人体细胞数量的10倍,其丰富的微生物基因库对研究黄酮类代谢物生成机制提出了富有意义的挑战。

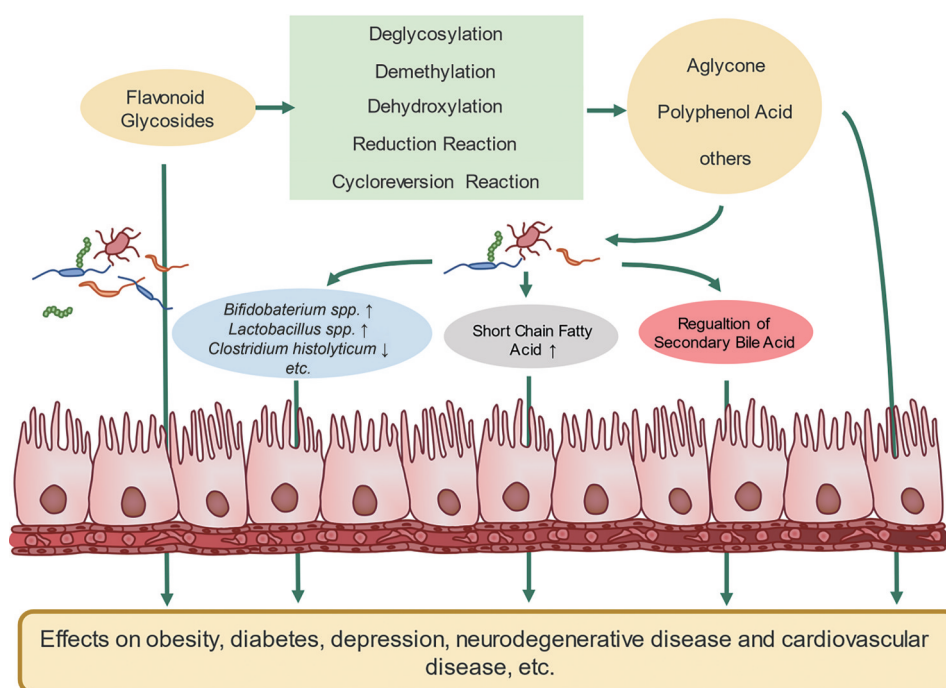


Figure 5 The interaction between flavonoids and gut microbiota

同时,关于黄酮类成分与肠道菌的相互研究的主要技术方法还处于探索阶段,如体外肠道菌培养体系的建立,目前尚无建立与肠道上皮及其上层黏液层直接接触的稳定的肠道共生微生物复杂群落的方法,因此,迫切需要能够维持人类有氧和厌氧菌群与人类活组织接触的实验模型,以分析生理相关的人类宿主-黄酮类成分-微生物组动态的相互作用。16S rRNA高通量测序技术目前已被用于微生物基因组的研究,以帮助学者了解黄酮类成分对宿主肠道菌群结构的调节。而新一代全基因组测序在黄酮与肠道菌群研究中还处于起步阶段,这似乎与全基因组的巨大潜力相矛盾,值得进一步研究。代谢组学可以有效解决黄酮类成分对人类健康影响的复杂性,将代谢组学与微生物组研究相结合,是未来黄酮类成分与肠道菌研究的趋势,探索一套理想的解决方案需要很长的路要走。此外,对于含量少、灵敏度低的黄酮小分子代谢物,如何建立完善的分析技术体系和后续的药效评价方法,是解释口服黄酮类药物药效物质基础和分子机制的关键科学问题。质谱成像技术已经用于分析整块生物组织的化学组成及其分子质量的空间分布研究,使用质谱成像技术可以检测细菌生物膜发酵过程中产生的增强的代谢产物信号,质谱成像技术可以用作可视化肠道菌群与黄酮类成分的代谢研究的强大工具。

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References

- [1] Fraga CG, Croft KD, Kennedy DO, et al. The effects of polyphenols and other bioactives on human health [J]. *Food Funct*, 2019, 10: 514-528.
- [2] Wiciński M, Gębalski J, Mazurek E, et al. The influence of polyphenol compounds on human gastrointestinal tract microbiota [J]. *Nutrients*, 2020, 12: 350.
- [3] Pei R, Liu X, Bolling B. Flavonoids and gut health [J]. *Curr Opin Biotechnol*, 2020, 61: 153-159.
- [4] Ciumărnean L, Milaciu MV, Runcan O, et al. The effects of flavonoids in cardiovascular diseases [J]. *Molecules*, 2020, 25: 4320.
- [5] Guo XF, Ruan Y, Li ZH, et al. Flavonoid subclasses and type 2 diabetes mellitus risk: a meta-analysis of prospective cohort studies [J]. *Crit Rev Food Sci Nutr*, 2019, 59: 2850-2862.
- [6] Lee YM, Yoon Y, Yoon H, et al. Dietary anthocyanins against obesity and inflammation [J]. *Nutrients*, 2017, 9: 1089.
- [7] de Angelis M, Garruti G, Minervini F, et al. The food-gut human axis: the effects of diet on gut microbiota and metabolome [J]. *Curr Med Chem*, 2019, 26: 3567-3583.
- [8] Oteiza PI, Fraga CG, Mills DA, et al. Flavonoids and the gastrointestinal tract: local and systemic effects [J]. *Mol Aspects Med*, 2018, 61: 41-49.
- [9] Vitale DC, Piazza C, Melilli B, et al. Isoflavones: estrogenic activity, biological effect and bioavailability [J]. *Eur J Drug Metab Pharmacokinet*, 2013, 38: 15-25.
- [10] Silvina BL, Zhang WJ, Yang CS, et al. Metabolic conversion of dietary flavonoids alters their anti-inflammatory and antioxidant properties [J]. *Free Radic Biol Med*, 2011, 51: 454-463.
- [11] Marin L, Miguez EM, Villar CJ, et al. Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties [J]. *Biomed Res Int*, 2015, 2015: 905215.
- [12] Duda-Chodak A, Tarko T, Satora P, et al. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review [J]. *Eur J Nutr*, 2015, 54: 325-341.
- [13] Illiano P, Brambilla R, Parolini C. The mutual interplay of gut microbiota, diet and human disease [J]. *FEBS J*, 2020, 287: 833-855.
- [14] Gupta A, Saha S, Khanna S. Therapies to modulate gut microbiota: past, present and future [J]. *World J Gastroenterol*, 2020, 26: 777-788.
- [15] Chen HT, Huang HL, Li YQ, et al. Therapeutic advances in non-alcoholic fatty liver disease: a microbiota-centered view [J]. *World J Gastroenterol*, 2020, 26: 1901-1911.
- [16] Li H, He J, Jia W. The influence of gut microbiota on drug metabolism and toxicity [J]. *Expert Opin Drug Metab Toxicol*, 2016, 12: 31-40.
- [17] Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity [J]. *Transl Res*, 2017, 179: 204-222.
- [18] Yu JB, Zhao ZX, Peng R, et al. Gut microbiota-based pharmacokinetics and the antidepressant mechanism of paeoniflorin [J]. *Front Pharmacol*, 2019, 10: 268.
- [19] Zhao ZX, Fu J, Ma SR, et al. Gut-brain axis metabolic pathway regulates antidepressant efficacy of albiflorin [J]. *Theranostics*, 2018, 8: 5945-5959.
- [20] Zhang J, Zhang J, Wang R. Gut microbiota modulates drug pharmacokinetics [J]. *Drug Metab Rev*, 2018, 50: 357-368.
- [21] Huttenhower C, Gevers D, Knight R, et al. Structure, function and diversity of the healthy human microbiome [J]. *Nature*, 2012, 486: 207-214.
- [22] Methe BA, Nelson KE, Pop M, et al. A framework for human microbiome research [J]. *Nature*, 2012, 486: 215-221.
- [23] Pan LB, Han P, Ma SR, et al. Abnormal metabolism of gut microbiota reveals the possible molecular mechanism of nephropathy induced by hyperuricemia [J]. *Acta Pharm Sin B*, 2020, 10: 249-261.

- [24] Peng R, Ma SR, Fu J, et al. Transforming of triptolide into characteristic metabolites by the gut microbiota [J]. *Molecules*, 2020, 25: 606.
- [25] Wang Y, Tong Q, Ma SR, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota [J]. *Signal Transduct Target Ther*, 2021, 6: 77.
- [26] Liu YT, Hao HP, Xie HG, et al. Extensive intestinal first-pass elimination and predominant hepatic distribution of berberine explain its low plasma levels in rats [J]. *Drug Metab Dispos*, 2010, 38: 1779-1784.
- [27] Tan XS, Ma JY, Feng R, et al. Tissue distribution of berberine and its metabolites after oral administration in rats [J]. *PLoS One*, 2013, 8: e77969.
- [28] Wang Y, Jiang JD. A new research mode of drug PK-PD mediated by the gut microbiota: insights into the pharmacokinetics of berberine [J]. *Acta Pharm Sin (药学报)*, 2018, 53: 659-666.
- [29] Li J, Zhang Y, Fan A, et al. Pharmacokinetics and bioavailability study of ginsenoside Rk1 in rat by liquid chromatography/electrospray ionization tandem mass spectrometry [J]. *Biomed Chromatogr*, 2019, 33:e4580.
- [30] Hawke RL, Schrieber SJ, Soule TA, et al. Silymarin ascending multiple oral dosing phase I study in noncirrhotic patients with chronic hepatitis C [J]. *J Clin Pharmacol*, 2010, 50: 434-449.
- [31] Deng LJ, Qi M, Li N, et al. Natural products and their derivatives: promising modulators of tumor immunotherapy [J]. *J Leukoc Biol*, 2020, 108: 493-508.
- [32] Ma X, Jiang Y, Zhang W, et al. Natural products for the prevention and treatment of cholestasis: a review [J]. *Phytother Res*, 2020, 34: 1291-1309.
- [33] Wang D, Hiebl V, Xu T, et al. Impact of natural products on the cholesterol transporter ABCA1 [J]. *J Ethnopharmacol*, 2020, 249: 112444.
- [34] Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019 [J]. *J Nat Prod*, 2020, 83: 770-803.
- [35] Bang SH, Hyun YJ, Shim J, et al. Metabolism of rutin and poncirin by human intestinal microbiota and cloning of their metabolizing α -L-rhamnosidase from *Bifidobacterium dentium* [J]. *J Microbiol Biotechnol*, 2015, 25: 18-25.
- [36] Riva A, Kolimár D, Spittler A, et al. Conversion of rutin, a prevalent dietary flavonol, by the human gut microbiota [J]. *Front Microbiol*, 2020, 11: 585428.
- [37] Braune A, Blaut M. Bacterial species involved in the conversion of dietary flavonoids in the human gut [J]. *Gut Microbes*, 2016; 7: 216-234.
- [38] Paraiso IL, Plagmann LS, Yang L, et al. Reductive metabolism of xanthohumol and 8-prenylnaringenin by the intestinal bacterium *Eubacterium ramulus* [J]. *Mol Nutr Food Res*, 2019, 63: e1800923.
- [39] Yang G, Hong S, Yang P, et al. Discovery of an ene-reductase for initiating flavone and flavonol catabolism in gut bacteria [J]. *Nat Commun*, 2021, 12: 790.
- [40] Ruan JQ, Li S, Li YP, et al. The presystemic interplay between gut microbiota and orally administered calycosin-7-O- β -D-glucoside [J]. *Drug Metab Dispos*, 2015, 43: 1601-1611.
- [41] Hidalgo M, Oruna-Concha MJ, Kolida S, et al. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth [J]. *J Agric Food Chem*, 2012, 60: 3882-3890.
- [42] Day AJ, Gee JM, Dupont MS, et al. Absorption of quercetin-3-glucoside and quercetin-4'-glucoside in the rat small intestine: the role of lactase phlorizin hydrolase and the sodium-dependent glucose transporter [J]. *Biochem Pharmacol*, 2003, 65: 1199-1206.
- [43] Day AJ, Cañada FJ, Díaz JC, et al. Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase [J]. *FEBS Lett*, 2000, 468: 166-170.
- [44] Day AJ, Dupont MS, Ridley S, et al. Deglycosylation of flavonoid and isoflavonoid glycosides by human small intestine and liver beta-glucosidase activity [J]. *FEBS Lett*, 1998, 436: 71-75.
- [45] Erlund I, Kosonen T, Alftan G, et al. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers [J]. *Eur J Clin Pharmacol*, 2000, 56: 545-553.
- [46] Jin JS, Nishihata T, Kakiuchi N, et al. Biotransformation of C-glucosylisoflavone puerarin to estrogenic (3S)-equol in co-culture of two human intestinal bacteria [J]. *Biol Pharm Bull*, 2008, 31: 1621-1625.
- [47] Braune A, Blaut M. Deglycosylation of puerarin and other aromatic C-glucosides by a newly isolated human intestinal bacterium [J]. *Environ Microbiol*, 2011, 13: 482-494.
- [48] Michlmayr H, Kneifel W. β -Glucosidase activities of lactic acid bacteria: mechanisms, impact on fermented food and human health [J]. *FEMS Microbiol Lett*, 2014, 352: 1-10.
- [49] Braune A, Engst W, Blaut M. Identification and functional expression of genes encoding flavonoid O- and C-glycosidases in intestinal bacteria [J]. *Environ Microbiol*, 2016, 18: 2117-2129.
- [50] Wei B, Wang YK, Qiu WH, et al. Discovery and mechanism of intestinal bacteria in enzymatic cleavage of C-C glycosidic bonds [J]. *Appl Microbiol Biotechnol*, 2020, 104: 1883-1890.
- [51] Kim M, Lee J, Han J. Deglycosylation of isoflavone C-glycosides by newly isolated human intestinal bacteria [J]. *J Sci Food Agric*, 2015, 95: 1925-1231.
- [52] Braune A, Blaut M. Intestinal bacterium *Eubacterium cellulosolvens* deglycosylates flavonoid C- and O-glucosides [J]. *Appl Environ Microbiol*, 2012, 78: 8151-8153.
- [53] Schoefer L, Mohan R, Braune A, et al. Anaerobic C-ring cleavage of genistein and daidzein by *Eubacterium ramulus* [J]. *FEMS Microbiol Lett*, 2002, 208: 197-202.
- [54] Cao H, Chen X, Jassbi AR, et al. Microbial biotransformation of bioactive flavonoids [J]. *Biotechnol Adv*, 2015, 33: 214-223.

- [55] Kim MH, Kim NY, Han JH. Metabolism of *Kaempferia parviflora* polymethoxyflavones by human intestinal *Bacterium bautia* sp. MRG-PMF1 [J]. J Agric Food Chem, 2014, 62: 12377-12383.
- [56] Braune A, Gütschow M, Blaut M. An NADH-dependent reductase from *Eubacterium ramulus* catalyzes the stereospecific heteroring cleavage of flavanones and flavanonols [J]. Appl Environ Microbiol, 2019, 85: e01233-e01219.
- [57] Brune A, Schink B. Phloroglucinol pathway in the strictly anaerobic *Pelobacter acidigallici*: fermentation of trihydroxybenzenes to acetate via triacetic acid [J]. Arch Microbiol, 1992, 157: 417-424.
- [58] Schoefer L, Mohan R, Schwirtz A, et al. Anaerobic degradation of flavonoids by *Clostridium orbiscindens* [J]. Appl Environ Microbiol, 2003, 69: 5849-5854.
- [59] Chambers KF, Day PE, Aboufarrag HT, et al. Polyphenol effects on cholesterol metabolism via bile acid biosynthesis, CYP7A1: a review [J]. Nutrients, 2019, 11: 2588
- [60] Feng W, Ao H, Peng C. Gut microbiota, short-chain fatty acids, and herbal medicines [J]. Front Pharmacol, 2018, 9: 1354.
- [61] Cardona F, Andres-Lacueva C, Tulipani S, et al. Benefits of polyphenols on gut microbiota and implications in human health [J]. J Nutr Biochem, 2013, 24: 1415-1422.
- [62] Wang Y, Tong Q, Shou JW, et al. Gut microbiota-mediated personalized treatment of hyperlipidemia using berberine [J]. Theranostics, 2017, 7: 2443-2451.
- [63] Boto-Ordóñez M, Urpi-Sarda M, Queipo-Ortuño MI, et al. High levels of Bifidobacteria are associated with increased levels of anthocyanin microbial metabolites: a randomized clinical trial [J]. Food Funct, 2014, 5: 1932-1938.
- [64] Queipo-Ortuño MI, Boto-Ordóñez M, Murri M, et al. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers [J]. Am J Clin Nutr, 2012, 95: 1323-1334.
- [65] Sun H, Zhang P, Zhu Y, et al. Antioxidant and prebiotic activity of five peonidin-based anthocyanins extracted from purple sweet potato (*Ipomoea batatas* (L.) Lam.) [J]. Sci Rep, 2018, 8: 5018.
- [66] Etxeberria U, Arias N, Boque N, et al. Reshaping faecal gut microbiota composition by the intake of trans-resveratrol and quercetin in high-fat sucrose diet-fed rats [J]. J Nutr Biochem, 2015, 26: 651-660.
- [67] Parkar SG, Stevenson DE, Skinner MA. The potential influence of fruit polyphenols on colonic microflora and human gut health [J]. Int J Food Microbiol, 2008, 124: 295-298.
- [68] Clavel T, Fallani M, Lepage P, et al. Isoflavones and functional foods alter the dominant intestinal microbiota in postmenopausal women [J]. J Nutr, 2005, 135: 2786-2792.
- [69] Cait A, Hughes MR, Antignano F, et al. Microbiome-driven allergic lung inflammation is ameliorated by short-chain fatty acids [J]. Mucosal Immunol, 2018, 11: 785-795.
- [70] Fernández J, Redondo-Blanco S, Gutiérrez-Del-Río I, et al. Colon microbiota fermentation of dietary prebiotics towards short-chain fatty acids and their roles as anti-inflammatory and antitumour agents: a review [J]. J Functional Foods, 2016, 25: 511-522.
- [71] Blachier F, Mariotti F, Huneau JF, et al. Effects of amino acid-derived luminal metabolites on the colonic epithelium and physiopathological consequences [J]. Amino Acids, 2007, 33: 547-562.
- [72] Dueñas M, Muñoz-González I, Cueva C, et al. A survey of modulation of gut microbiota by dietary polyphenols [J]. Biomed Res Int, 2015, 2015: 850902.
- [73] Mao S, Zhu W. Effects of six flavonoid compounds addition on short-chain fatty acids production and human fecal microbial community change during in vitro fermentation [J]. Afr J Microbiol Res, 2011, 5: 4484-4491.
- [74] Unno T, Hisada T, Takahashi S. Hesperetin modifies the composition of fecal microbiota and increases cecal levels of short-chain fatty acids in rats [J]. J Agric Food Chem, 2015, 63: 7952-7957.
- [75] Chiang JY. Bile acids: regulation of synthesis [J]. J Lipid Res, 2009, 50: 1955-1966.
- [76] Staley C, Weingarden AR, Khoruts A, et al. Interaction of gut microbiota with bile acid metabolism and its influence on disease states [J]. Appl Microbiol Biotechnol, 2017, 101: 47-64.
- [77] Odermatt A, Da Cunha T, Penno CA, et al. Hepatic reduction of the secondary bile acid 7-oxolithocholic acid is mediated by 11 β -hydroxysteroid dehydrogenase 1 [J]. Biochem J, 2011, 436: 621-629.
- [78] Hofmann AF. The continuing importance of bile acids in liver and intestinal disease [J]. Arch Intern Med, 1999, 159: 2647-2658.
- [79] Sayin SI, Wahlström A, Felin J, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist [J]. Cell Metab, 2013, 17: 225-235.
- [80] Han Y, Haraguchi T, Iwanaga S, et al. Consumption of some polyphenols reduces fecal deoxycholic acid and lithocholic acid, the secondary bile acids of risk factors of colon cancer [J]. J Agric Food Chem, 2009, 57: 8587-8590.
- [81] Tzounis X, Vulevic J, Kuhnle GG, et al. Flavanol monomer-induced changes to the human faecal microflora [J]. Br J Nutr, 2008, 99: 782-792.
- [82] Louis P, Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine [J]. FEMS Microbiol Lett, 2009, 294: 1-8.
- [83] Yamakoshi J, Tokutake S, Kikuchi M, et al. Effect of proanthocyanidin-rich extract from grape seeds on human fecal flora and fecal odor [J]. Microbial Ecol Health Dis, 2001, 13: 25-31.
- [84] Vendrame S, Guglielmetti S, Riso P, et al. Six-week consumption of a wild blueberry powder drink increases bifidobacteria in

- the human gut [J]. *J Agric Food Chem*, 2011, 59: 12815-12820.
- [85] Tomás-Barberán FA, Selma MV, Espín JC. Interactions of gut microbiota with dietary polyphenols and consequences to human health [J]. *Curr Opin Clin Nutr Metab Care*, 2016, 19: 471-476.
- [86] Man AWC, Zhou Y, Xia N, et al. Involvement of gut microbiota, microbial metabolites and interaction with polyphenol in host immunometabolism [J]. *Nutrients*, 2020, 12: 3054.
- [87] Westfall S, Pasinetti GM. The gut microbiota links dietary polyphenols with management of psychiatric mood disorders [J]. *Front Neurosci*, 2019, 13: 1196.
- [88] Ozdal T, Sela D A, Xiao J, et al. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility [J]. *Nutrients*, 2016, 8: 78.
- [89] Ma J, Zheng Y, Tang W, et al. Dietary polyphenols in lipid metabolism: a role of gut microbiome [J]. *Anim Nutr*, 2020, 6: 404-409.
- [90] Ho L, Zhao D, Ono K, et al. Heterogeneity in gut microbiota drive polyphenol metabolism that influences α -synuclein misfolding and toxicity [J]. *J Nutr Biochem*, 2019, 64: 170-181.
- [91] Esposito D, Damsud T, Wilson M, et al. Black currant anthocyanins attenuate weight gain and improve glucose metabolism in diet-induced obese mice with intact, but not disrupted, gut microbiome [J]. *J Agric Food Chem*, 2015, 63: 6172-6180.
- [92] Jamar G, Estadella D, Pisani LP. Contribution of anthocyanin-rich foods in obesity control through gut microbiota interactions [J]. *Biofactors*, 2017, 43: 507-516.
- [93] Peng Y, Yan Y, Wan P, et al. Gut microbiota modulation and anti-inflammatory properties of anthocyanins from the fruits of *Lycium ruthenicum* Murray in dextran sodium sulfate-induced colitis in mice [J]. *Free Radic Biol Med*, 2019, 136: 96-108.
- [94] Azzini E, Giacometti J, Russo GL. Antiobesity effects of anthocyanins in preclinical and clinical studies [J]. *Oxid Med Cell Longev*, 2017, 2017: 2740364.
- [95] Belwal T, Nabavi SF, Nabavi SM, et al. Dietary anthocyanins and insulin resistance: when food becomes a medicine [J]. *Nutrients*, 2017, 9: 1111.
- [96] Noratto GD, Garcia-Mazcorro JF, Markel M, et al. Carbohydrate-free peach (*Prunus persica*) and plum (*Prunus salicina*) juice affects fecal microbial ecology in an obese animal model [J]. *PLoS One*, 2014, 9: e101723.
- [97] Ho L, Ferruzzi MG, Janle EM, et al. Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease [J]. *FASEB J*, 2013, 27: 769-781.
- [98] Wang J, Hodes GE, Zhang H, et al. Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice [J]. *Nat Commun*, 2018, 9: 477.
- [99] Ono K, Tsuji M, Yamasaki TR, et al. Anti-aggregation effects of phenolic compounds on α -synuclein [J]. *Molecules*, 2020, 25: 2444.
- [100] Yamasaki TR, Ono K, Ho L, et al. Gut microbiome-modified polyphenolic compounds inhibit α -synuclein seeding and spreading in α -synucleinopathies [J]. *Front Neurosci*, 2020, 14: 398.
- [101] Wang D, Ho L, Faith J, et al. Role of intestinal microbiota in the generation of polyphenol-derived phenolic acid mediated attenuation of Alzheimer's disease β -amyloid oligomerization [J]. *Mol Nutr Food Res*, 2015, 59: 1025-1040.
- [102] Wang J, Ferruzzi MG, Ho L, et al. Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment [J]. *J Neurosci*, 2012, 32: 5144-5150.
- [103] Zhang YY, Li XL, Li TY, et al. 3-(4-Hydroxyphenyl) propionic acid, a major microbial metabolite of procyanidin A2, shows similar suppression of macrophage foam cell formation as its parent molecule [J]. *RSC Adv*, 2018, 8: 6242-6250.
- [104] Zhang T, Hu Q, Shi L, et al. Equol attenuates atherosclerosis in apolipoprotein e-deficient mice by inhibiting endoplasmic reticulum stress *via* activation of Nrf2 in endothelial cells [J]. *PLoS One*, 2016, 11: e0167020.
- [105] Yuan JP, Wang JH, Liu X. Metabolism of dietary soy isoflavones to equol by human intestinal microflora--implications for health [J]. *Mol Nutr Food Res*, 2007, 51: 765-781.
- [106] Kawabata K, Yoshioka Y, Terao J. Role of intestinal microbiota in the bioavailability and physiological functions of dietary polyphenols [J]. *Molecules*, 2019, 24: 370.
- [107] Wang Y, Zhou J, Fu S, et al. Preventive effects of protocatechuic acid on Lps-induced inflammatory response in human gingival fibroblasts *via* activating PPAR- γ [J]. *Inflammation*, 2015, 38: 1080-1084.
- [108] Xi Z, Hu X, Chen X, et al. Protocatechuic acid exerts protective effects *via* suppression of the P38/JNK- NF- κ B signalling pathway in an experimental mouse model of intracerebral haemorrhage [J]. *Eur J Pharmacol*, 2019, 854: 128-138.
- [109] Qian Y, Babu PVA, Symons JD, et al. Metabolites of flavonoid compounds preserve indices of endothelial cell nitric oxide bioavailability under glucotoxic conditions [J]. *Nutr Diabetes*, 2017, 7:e286.
- [110] Najmanova I, Pourova J, Vopršalova M, et al. Flavonoid metabolite 3-(3-hydroxyphenyl)propionic acid formed by human microflora decreases arterial blood pressure in rats [J]. *Mol Nutr Food Res*, 2016, 60: 981-991.
- [111] Steed AL, Christophi GP, Kaiko GE, et al. The microbial metabolite desaminotyrosine protects from influenza through type I interferon [J]. *Science*, 2017, 357: 498-502.
- [112] Saura-Calixto F, Perez-Jimenez J, Touriño S, et al. Proanthocyanidin metabolites associated with dietary fibre from *in vitro* colonic fermentation and proanthocyanidin metabolites in human plasma [J]. *Mol Nutr Food Res*, 2010, 54: 939-946.
- [113] Xu G, Dou J, Zhang L, et al. Inhibitory effects of baicalin on the influenza virus *in vivo* is determined by baicalin in the serum [J]. *Biol Pharm Bull*, 2010, 33: 238-243.

- [114] Cuervo A, Hevia A, López P, et al. Association of polyphenols from oranges and apples with specific intestinal microorganisms in systemic lupus erythematosus patients [J]. *Nutrients*, 2015, 7: 1301-1317.
- [115] Kong WJ, Vernieri C, Foiani M, et al. Berberine in the treatment of metabolism-related chronic diseases: a drug cloud (dCloud) effect to target multifactorial disorders [J]. *Pharmacol Ther*, 2020, 209: 107496.
- [116] Verbeek R, Van Tol EA, Van Noort JM. Oral flavonoids delay recovery from experimental autoimmune encephalomyelitis in SJL mice [J]. *Biochem Pharmacol*, 2005, 70: 220-228.
- [117] Wang G, Song L, Wang H, et al. Quercetin synergizes with 2-methoxyestradiol inhibiting cell growth and inducing apoptosis in human prostate cancer cells [J]. *Oncol Rep*, 2013, 30: 357-363.
- [118] Liu QS, Jiang HL, Wang Y, et al. Total flavonoid extract from *Dracocephalum moldavica* L. attenuates β -amyloid-induced toxicity through anti-amyloidogenesis and neurotrophic pathways [J]. *Life Sci*, 2018, 193: 214-225.