微生物学通报
Microbiology China
tongbao@im.ac.cn

Sep. 20, 2014, 41(9): 1872−1881

DOI: 10.13344/j.microbiol.china.130795

专论与综述

人肠道菌对天然产物代谢及转化的研究进展

赵磊　陈剑　任冰如　李维林*

(江苏省中国科学院植物研究所 江苏省抗糖尿病药物筛选服务中心　江苏 南京　210014)

摘　要：天然产物的人肠道菌代谢及转化研究已引起各国学者的重视，并作为热点课题进行了大量研究工作。本文对近二十年来各国学者关于黄酮类、萜类、苯丙素类、生物碱类、甾体类及其他天然产物的人肠道菌代谢及转化研究工作进行了综述，总结了各类天然产物在人肠道菌作用下的代谢路径及转化规律，以期为该领域的进一步深入研究提供参考。

关键词：人肠道菌，天然产物，代谢，转化

Advances in study on metabolism and biotransformation of natural products by human intestinal bacteria

ZHAO Lei　CHEN Jian　REN Bing-Ru　LI Wei-Lin*

(*Jiangsu Provincial Service Center for Antidiabetic Drugs Screening*, *Institute of Botany*, *Jiangsu Province and the Chinese Academy of Sciences*, *Nanjing*, *Jiangsu* 210014, *China*)

Abstract: The study on metabolism and biotransformation of natural products by human intestinal bacteria is receiving more and more attention. To gain insight and to trigger additional research in this field, we provide in this an overview of selected natural products bio-transformed or metabolized by human intestinal bacteria through the reported literatures in recent 20 years. The mechanism as well as pathway of metabolism or bio-transformation by human intestinal bacteria was discussed, according to the categories of natural products such as flavonoids, terpenoids, phenylpropanoids, alkaloids, steroids and the others. We also address the needs in further studies on metabolism and conversion action of natural products by human intestinal bacteria.

Keywords: Human intestinal bacteria, Natural products, Metabolism, Biotransformation

人体肠道内寄居着大量的微生物，构成了肠道复杂的微生态系统。栖息在人肠道中的细菌可达10^{14}个[1]，这使得人肠道成为地球上生物密度最高的微生境之一[2]。通过对人体肠道细菌的核糖体RNA基因进行比较分析，目前已发现395个种，分属8大门类：厚壁菌门、拟杆菌门、变形菌门、梭杆菌门、疣微菌门、蓝菌门、螺旋体门和放线菌门[3-4]。其中99%以上为厌氧菌，包括梭状芽孢杆菌和类杆菌的厚壁菌门最为丰富和多样，拟杆菌门也占有明显优势[3-4]。

基金项目：国家自然科学基金青年基金项目(No. 21102058)；江苏省科技基础设施建设计划—科技公共服务平台项目(No. BM2011117)；江苏省自然科学基金项目(No. BK20141387)

***通讯作者：**Tel：86-25-84438336；✉：lwlcnbg@mail.cnbg.net

收稿日期：2013-11-20；**接受日期：**2014-01-15；**优先数字出版日期**(www.cnki.net)：2014-02-20

口服药物在人体内不可避免地要与肠道细菌接触，参与肠肝循环的药物(包括静注、肌注或皮下注射的药物)，当其代谢物随胆汁分泌到肠道中时，也可能被肠道细菌代谢[5]。研究发现，人肠道菌的代谢活性与药物的释放、疗效及毒副作用存在着极为密切的关系[6]。考虑到人肠道菌代谢对药物性能或毒性潜在的严重影响，Sousa 等[5]认为人肠道微生物的作用评估应成为药物开发过程的组成部分。此外，人肠道微生物种类多、含酶丰富，利用肠道菌可进行多种生物转化反应，具有反应条件温和、选择性高、反应类型多样、对环境友好等优势[7]，可通过人肠道菌对天然产物进行生物转化，增加其分子结构的多样性和新颖性，进而为新药开发提供更具价值的先导化合物。

然而，由于天然产物的多样性，人肠道菌代谢活动的复杂性，以及其他因素的限制，天然产物人肠道菌的代谢及转化研究目前仍处于积累阶段。本文在大量文献检索的基础上，根据天然产物类别的不同，首次对近 20 年来各国学者关于人肠道菌代谢及转化天然产物的研究工作做一总结，以期为该领域的进一步深入研究提供参考。

1 黄酮类化合物

黄酮类化合物在药物及日常饮食中均广泛存在，是目前天然产物人肠道菌代谢及转化研究较多的一类化合物，结合黄酮、二氢黄酮、黄酮醇、黄烷-3-醇、异黄酮、二氢异黄酮等结构类型，人肠道菌对该类化合物的代谢及转化见表 1。以黄酮苷形式存在的黄酮类化合物，可首先被肠道菌去糖基化产生苷元，大多可进一步发生环裂解、脱羟基、还原、去甲基化、异构化等多种反应，其中环裂解反应普遍存在，且多发生在 C 环，生成 C_6-C_3 或 C_6-C_2 型的酚酸。

需要指明的是，直接用人肠道菌群代谢药物所得的产物多于使用其粗酶提取物，这可能与某些酶为细胞结合性酶有关。该现象在人肠道菌转化实验中较为常见，如 Kim 等[8-9]将分离自中药黄芩根中的一种黄酮类化合物黄芩苷分别与人粪便菌群粗酶和人新鲜粪便液体外厌氧共培养，均可得到黄芩苷的去糖基化产物黄芩黄素，然而人新鲜粪便液可进一步通过环裂解、脱羟基等反应将黄芩黄素代谢为 3,4-二羟基苯甲酸、焦没食子酚和苯乙酸。槲皮素广泛分布于植物中，研究发现人肠道内厌氧菌细枝真杆菌(*Eubacterium ramulus*)在槲皮素或其环裂解中间体间苯酚中不能生长，但槲皮素与葡萄糖作为共基质存在时，该菌可裂解槲皮素的环系统[13-14]。人肠道菌和大鼠肠道菌在对天然产物的代谢及转化作用上也存在一定差异，Meselhy 等[18]分别采用人粪便菌液和大鼠粪便菌液对大多数药用植物中主要的抗氧化活性成分(–)-表儿茶精，(–)-表没食子儿茶精和它们的 3-*O*-没食子酸酯类成分的代谢作用进行了比较研究，结果发现，(–)-表儿茶精，(–)-表没食子儿茶精和它们的 3-*O*-没食子酸酯类成分可被人粪便菌液广泛代谢，而 3-*O*-没食子酸酯类成分却抵制大鼠粪便菌液的代谢。此外，培养、驯化、分离特异性的能水解 C-苷键的肠道菌，将对新药开发起到非常有意义的推动作用[6]，如豆科植物主要的异黄酮类化合物葛根素，具有潜在的保健作用，是一类很难被酸水解的 C-糖苷，Jin 等[21]联合使用从人新鲜粪便中分离出的单一新种 PUE 和 DZE，提高了 C-糖苷的转化和代谢效果，使葛根素产生新的活性物质雌马酚，这一成分的产生，不仅给葛根素带来新的药理活性，也为利用肠道菌代谢开发葛根素提供了一种有益的途径。

2 萜类化合物

萜类化合物在天然药物中广泛分布，人肠道菌对该类化合物的代谢及转化研究，目前主要集中于单萜类、二萜类和三萜类化合物(表 2)，其中对三萜皂苷研究较多。人肠道菌对三萜皂苷的代谢及转化作用以去糖基化反应为主，对苷元报道相对较少。

值得注意的是，人肠道菌可利用代谢过程中产生的氨基酸，把一些天然产物中的含氧化合物代谢为独特的含氮化合物，产生全新活性，这是肠道菌

表 1 人肠道菌对黄酮类化合物的代谢及转化
Table 1 Metabolism and biotransformation of flavonoids by human intestinal bacteria

类别 Category	底物 Substrate	肠道菌 Intestinal bacteria	终产物 End products	文献 Ref.
黄酮类 Flavones	Baicalin	Crude enzymes of human fecal microflora	Baicalein	[8]
		Human fecal microflora	Pyrogallol; Phenylacetic acid; 3,4-Dihydroxybenzoic acid	[9]
	Abrusin-2″-*O*-apioside	Human fecal microflora	3-Phenylpropionic acid	[10]
二氢黄酮类 Flavanones	Poncirin	Crude enzymes of human fecal microflora	Ponciretin	[8]
		Human fecal microflora	2,4-Dihydroxyacetophenone; Pyrogallol; 4-Hydroxybenzoic acid; Phloroglucinol	[9]
	Hesperidin	Crude enzymes of human fecal microflora	Hesperetin	[8]
		Human fecal microflora	2,4-Dihydroxyphenylacetic acid; Phloroglucinol; Resorcinol	[9]
	Naringin	Human fecal microflora	2,4,6-Trihydroxybenzoic acid; 4-Hydroxybenzoic acid; 4-Hydroxyphenylacetic acid; Phloroglucinol	[9]
黄酮醇类 Flavonols	Kaempferol-3-*O*-glucoside	*Bifidobacterium* species	Kaempferol	[11]
	Kaempferitrin	Human fecal microflora	*p*-Hydroxybenzoic acid	[12]
	Isoquercitrin	*Eubacterium ramulus*	3,4-Dihydroxyphenylacetic acid	[13-14]
	Rutin	Human fecal microflora	4-Hydroxybenzoic acid; 3,4-Dihydroxybenzoic acid; 3,4-Dihydroxyphenylacetic acid	[9]
			3-Hydroxyphenylacetic acid	[15]
	Icariin	Human fecal microflora	Icaritin; Isoicaritin	[16]
黄烷-3-醇类 Flavan-3-ols	(+)-Catechin (2*R*, 3*S*)/ (+)-Epicatechin (2*S*, 3*S*)	*Eubacterium* sp. Strain SDG-2	(2*R*)-1-(3′,4′-Dihydroxyphenyl)-3-(2",4",6"-trihydroxyphenyl)-propan-2-ol	[17]
	(−)-Catechin (2*S*, 3*R*)/ (−)-Epicatechin (2*R*, 3*R*)	*Eubacterium* sp. Strain SDG-2	(2*S*)-1-(3′-Hydroxyphenyl)-3-(2",4",6"-trihydroxyphenyl)-propan-2-ol	[17]
	(−)-Epigallocatechin (2*R*, 3*R*)/ (−)-Gallocatechin (2*S*, 3*R*)	*Eubacterium* sp. Strain SDG-2	(2*S*)-1-(3′,5′-Dihydroxyphenyl)-3-(2",4",6"-trihydroxyphenyl)-propan-2-ol	[17]
	(−)-Epicatechin-3-*O*-gallate	Human fecal microflora	Pyrogallol; 5-(3′-Methoxyphenyl) valeric acid; 1-(3′,4′-Dihydroxyphenyl)-3-(2",4",6"-trihydroxyphenyl)-propan-2-ol; 1-(3'-Hydroxyphenyl)-3-(2",4",6"-trihydroxyphenyl)-propan-2-ol; 2",3"-Dihydroxyphenoxyl (3′,4′-dihydroxyphenyl) propionate; (3′-Hydroxyphenyl) propionic acid	[18]
	Catechin	Human fecal microflora	2,4,6-Trihydroxybenzoic acid; Phloroglucinol; 4-Methoxysalicylic acid; 4-Hydroxybenzoic acid	[9]
异黄酮类 Isoflavones	Daidzin	*Bifidobacterium* species, *Escherichia coli* HGH21	Daidzein	[11,19-20]
		Strain HGH6	Dihydrodaidzein	[20]
		Human fecal microflora	2,4-Dihydroxyacetophenone; 4-Hydroxybenzoic acid; Resorcinol; 4-Hydroxyphenylacetic acid; 2,4-Dihydroxybenzoic acid	[9]
	Genistin	*Bifidobacterium* species, *Escherichia coli* HGH21	Genistein	[11,20]

(待续)

(续表)

		Strain HGH6	Dihydrogenistein	[20]
	Genistein	Strain DZE	5-Hydroxyequol	[21]
	Formononetin	*Eubacterium limosum* (ATCC 8486)	Daidzein	[22]
	Glycitein	*Eubacterium limosum* (ATCC 8486)	6,7,4′-Trihydroxyisoflavone	[22]
	Glycitin	*Bifidobacterium* species	Glycitein	[11]
	Puerarin	Strain PUE & DZE	(3*S*)-Equol	[21]
		Crude enzymes of human fecal microflora	Daidzein	[8]
		Human fecal microflora	2,4-Dihydroxyacetophenone; 4-Hydroxybenzoic acid; 4-Hydroxyphenylacetic acid; Resorcinol; 2,4-Dihydroxybenzoic acid	[9]
	Tectoridin	*Bacteriodes spercoris* HJ-15	Tectorigenin	[25]
	Kakkalide	Human fecal microflora	Irisolidone	[28]
二氢异黄酮类 Isoflavanones	Dihydrodaidzein	*Eggerthella* Strain Julong 732	(3*S*)-Equol	[29]
	Biochanin a	*Eubacterium limosum* (ATCC 8486)	Genistein	[22]
其他 Others	Taxifolin	*Eubacterium* sp. Strain SDG-2	*α*,2′,3,4,4′,6′-Hexahydroxydihydrochalcone	[17]
	Xanthohumol	Human fecal microflora	8-Prenylnaringenin	[30]

代谢相比一般化学合成反应所具有的突出特点[6]，如从中药玄参干燥根中分离出的一个主要环烯醚萜类化合物哈巴苷，通过去糖基化、酯解、*O*→*N*、氧化、脱羟基等反应可被转化为 3 个生物碱类代谢物，揭示了哈巴苷发挥药理活性的潜在药效基础[32]。此外，人肠道菌组成不同，对萜类化合物的代谢能力也有差异，如 Abdel-Hafez 等[33]对 25 株人肠道内单菌株转化中药巴豆中一个活性成分大戟醇的作用进行筛选研究，其中只有 9 株表现出转化能力。

3 苯丙素类化合物

苯丙素类天然产物主要包括苯丙酸类、香豆素类及木脂素类三大类化合物，人肠道菌对该三类化合物的代谢及转化研究均有报道(表 3)。目前研究主要集中在若干代谢特异性菌株上，这些菌株可选择性代谢多种木脂素类化合物，该类化合物主要为植物雌激素类前体化合物，可被代谢为肠内醇、肠内酯等一些重要的活性物质。紫花前胡苷为中药羌活根及根茎中主要的香豆素成分之一，Zhang 等[44]研究发现紫花前胡苷可完全被人粪便菌群转化为紫花前胡苷元，而所有被使用的人肠道单菌株也可转化紫花前胡苷为紫花前胡苷元，但大多转化率较低，表明人肠道菌在天然产物转化过程中存在协同作用。

4 生物碱类化合物

人肠道菌对生物碱类化合物的代谢及转化见表 4，与其他天然产物相比，该类化合物的人肠道菌代谢及转化研究报道相对较少，值得进一步探究。有趣的是将存在于川乌、草乌、附子等药用植物中的主要有毒成分乌头碱与人肠道菌在厌氧条件下温孵培养，可得到甲酰乌头胺的 C_8 位羟基与脂肪酸结合成酯的混合物，这些脂肪酸可能来源于所使用的细菌[51]，乌头碱成酯后更易于进入心肌发挥作用，这可能是其强心作用的基础[7]。此外，

表 2 人肠道菌对萜类化合物的代谢及转化
Table 2 Metabolism and biotransformation of terpenoids by human intestinal bacteria

类别 Category	底物 Substrate	肠道菌 Intestinal bacteria	终产物 End products	文献 Ref.
单萜类 Monoterpenoids	Geniposide	*Bifidobacterium longum* HY8001, *Bacteroides fragilis*, Human fecal microflora, Crude enzymes of human fecal microflora and 4 other selected bacteria	Genipin	[8,31]
	Harpagoside	*Bacteroides fragilis ss vulgatus*, *Veillonella parvula ss parvula* ATCC 10790, *Lactobacillus* species, et al.	Aucubinine b	[32]
二萜类 Diterpenoids	Phorbol	Human fecal microflora	4*β*,9*α*,20-Trihydroxy-13,15-seco-1,6,15-tigliatriene-3,13-dione; 4*β*,9*α*,20-Trihydroxy-14(13→12)-abeo-12*αH*-1,6-tigliadiene-3,13-dione; Isophorbol; Deoxyphorbol; 4*β*,9*α*,20-Trihydroxy-15,16,17-trinor-1,6-tigliadiene-3,13-dione	[33]
三萜类 Triterpenoids	Ginsenoside Rb1	Crude enzymes of human fecal microflora, Human fecal microflora, *Eubacterium* sp. A-44	Compound K	[8,34, 36]
	Ginsenoside Rc	Human fecal microflora	Compound K	[35]
	Ginsenoside Rb2	Human fecal microflora	Compound K	[34]
	Notoginsenoside R1	Human fecal microflora	Protopanaxatriol	[37]
	Ginsenoside Re	Crude enzymes of human fecal microflora	Ginsenoside Rh1	[8]
	Mogroside III	Human fecal microflora	Aglycone mogrol	[38]
	Glycyrrhizin	Crude enzymes of human fecal microflora, Human fecal microflora	18*β*-Glycyrrhetinic acid	[8,39]
	Escins-Ia	Crude enzymes of human fecal microflora, *Lactobacillus brevis* II-46	Protoaescigenin	[40]
	Kalopanaxsaponin B/H	Human fecal microflora	Hederagenin	[41]
	Chiisanoside	Human fecal microflora, *Bacteroides* JY-6	Chiisanogenin	[42]

人肠道菌含有丰富的硝基、亚硝基还原酶，进入人体的含有氮、硝基或亚硝基的生物碱类成分往往在肠道菌的作用下发生各类还原反应，如马兜铃科植物中普遍存在的一种特殊类型的生物碱马兜铃酸和马兜铃酸 I，可被人肠道内菌还原为对应的内酰胺化合物马兜铃内酰胺和马兜铃内酰胺 I[53]。

5 甾体类化合物

甾体类化合物的人肠道菌代谢及转化研究报道的也较少(表 5)，已有的报道显示，人肠道菌对甾体类化合物的转化作用主要发生在取代基上，而甾核较为稳定，抵制肠道菌的代谢。

6 其他类化合物

人肠道菌对其他类化合物的代谢及转化研究也有报道，见表 6。值得注意的是，对矿物药丹砂(HgS)的人肠道菌代谢研究表明丹砂的解毒机制为生成了可溶性汞的多硫化物，而非甲基汞[56]。

7 结论与展望

研究天然产物的人肠道菌代谢及转化过程，可发现人肠道菌是天然药物活化、抑制或产生毒性的

直接原因，也是前体药物活化的必要手段，同时影响天然药物的稳定性和生物利用度。如人参皂苷Rb1，作为中药人参中主要的原人参二醇型皂苷之一，本身不能被肠道吸收而经粪便排出，通过肠道菌的逐步去糖基化作用，渗透性提升，发挥药理作用[36-37]；蟾蜍中主要成分华蟾毒精和羟基华蟾毒精由肠道菌代谢为对应的脱乙酰基产物后几乎丧失了对肿瘤细胞生长的抑制作用[55]；马兜铃酸和马兜铃酸 I 被肠道菌还原为对应的内酰胺化合物后，产生很强的毒性，可引起肝癌和肾病[53]。

表 3 人肠道菌对苯丙素类化合物的代谢及转化

Table 3 Metabolism and biotransformation of phenylpropanoids by human intestinal bacteria

类别 Category	底物 Substrate	肠道菌 Intestinal bacteria	终产物 End products	文献 Ref.
苯丙酸类 Phenylpropionic acids	Caffeic acid	*Eubacterium* sp. strain SDG-2	Dihydrocaffeic acid; *m*-Hydroxyphenylpropionic acid	[17]
香豆素类 Coumarins	Aesculin	Human fecal microflora	Aesculetin	[43]
	Nodakenin	Human fecal microflora	Nodakenetin	[44]
木脂素类 Lignans	(−)-Secoisolariciresinol	*Ruminococcus* sp. END-1	(−)-Dihydroxyenterolactone	[45]
		Strain END-2 & ARC-1	(−)-Enterodiol	[47]
	(+)-Secoisolariciresinol	Strain END-2 & ARC-1	(+)-Enterolactone	[47]
		Ruminococcus sp. END-1, *Eubacterium* sp. ARC-2	(+)-Dihydroxyenterodiol	[45,48]
	(−)-Arctigenin	*Ruminococcus* sp. END-1 & *Eggerthella* sp. SDG-2	(−)-Enterolactone	[45]
		Ruminococcus sp. END-1, *Eubacterium* sp. ARC-2	(−)-Dihydroxyenterolactone	[45,48]
	(−)-Enterodiol	Cell-free extracts of *Ruminococcus* sp. END-1	(−)-Enterolactone	[45]
	(−)-Dihydroxyenterodiol	*Ruminococcus* sp. END-1	(−)-Dihydroxyenterolactone	[45]
		Strain ARC-1	(−)-Enterodiol	[46]
	(+)-Dihydroxyenterodiol	*Eggerthella* sp. SDG-2	(+)-Enterodiol	[46]
	(−)-Hydroxyenterodiol	*Ruminococcus* sp. END-1	(−)-4''-Hydroxyenterolactone; (−)-4'-Hydroxyenterolactone	[45]
	(+)-Secoisolariciresinol-diglucoside	*Ruminococcus* sp. END-1	(+)-Dihydroxyenterodiol	[45]
		Ruminococcus sp. END-1 & *Eggerthella* sp. SDG-2	(+)-Enterodiol	[45]
	Pinoresinol-diglucoside	*Ruminococcus* sp. END-1	(+)-Desdimethylpinoresinol	[45]
		Ruminococcus sp. END-1 & *Eggerthella* sp. SDG-2, Human fecal microflora	(−)-Enterolactone	[45,50]
	(+)-Dihydroxyenterolactone	Strain ARC-1	(+)-Enterolactone	[46]
	(−)-Dihydroxyenterolactone	*Eggerthella* sp. SDG-2	(−)-Enterolactone	[46]
	(−)-Secoisolariciresinol-4''-*O*-methyl ether	*Eubacterium* sp. ARC-2	(−)-Dihydroxyenterodiol	[48]
	Arctiin	Human fecal microflora	(−)-Enterolactone	[49]

表 4 人肠道菌对生物碱类化合物的代谢及转化
Table 4 Metabolism and biotransformation of alkaloids by human intestinal bacteria

底物 Substrate	肠道菌 Intestinal bacteria	终产物 End products	文献 Ref.
Aconitine	*Bacteroides fragilis*, *Klebsiella pneumonia*, *Clostridium butyricum*	Lipoaconitines	[51]
Strychnine *N*-oxide	*Lactobacillus acidophilus* ATCC 4356, *L. xylosus* ATCC l55775, *Veillonella parvula ss. parvula* ATCC 10790, et al.	16-Hydroxystrychnine; Strychnine	[52]
Brucine *N*-oxide	*Bifidobacterium longum* IV-55, *Lactobacillus acidophilus* ATCC 4356, *L. xylosus* ATCC 155775, et al.	16-Hydroxyhrucine; Brucine	[52]
Aristolochic acid	Human fecal microflora	Aristololactam	[53]
Aristolochic acid I	Human fecal microflora	Aristololactam I	[53]

表 5 人肠道菌对甾体类化合物的代谢及转化
Table 5 Metabolism and biotransformation of steroidal compounds by human intestinal bacteria

底物 Substrate	肠道菌 Intestinal bacteria	终产物 End products	文献 Ref.
Cholic acid	*Bacteroides intestinalis* AM-1	7-Oxo-deoxycholic acid	[54]
Chenodeoxycholic acid	*Bacteroides intestinalis* AM-1	7-Oxo-lithocholic acid	[54]
Cinobufagin	*Escherichia coli* O-127, *Bacteroides fragilis ss. vulgatus*, *Lactobacillus brevis* II-46, et al.	Deacetylcinobufagin	[55]
Cinobufotalin	*Escherichia coli* O-127, *Bacteroides fragilis ss. vulgatus*, *Lactobacillus brevis* II-46, et al.	Deacetylcinobufotalin	[55]

表 6 人肠道菌对其他类化合物的代谢及转化
Table 6 Metabolism and biotransformation of other compounds by human intestinal bacteria

底物 Substrate	肠道菌 Intestinal bacteria	终产物 End products	文献 Ref.
Cinnabar (HgS)	Human fecal microflora	Mercuric polysulfides	[56]
α-Linolenic acid	*Bifidobacterium* species	Conjugated *α*-linolenic acid	[57]
Crocin	Crude enzymes of human fecal microflora	Crocetin	[8]
Rhaponticin	Human fecal microflora	Rhapontigenin	[58]
Chrysophanol-8-*O*-glucopyranoside	Human fecal microflora	Chrysophanol	[58]
Mangiferin	*Bacteroides* sp. MANG	Norathyriol	[59]
Amygdalin	Crude enzymes of human fecal microflora	Benzaldehyde	[8]
Synergyl	Human fecal microflora	Short-chain fatty acid (SCFA)	[60]

人肠道菌对天然产物的代谢及转化反应几乎包括了所有的有机化学反应类型，如水解[8]、氧化(环裂解)[17]、还原[21]、脱羟基[46]、去甲基[22]、异构化[57]、羟基化[52]、去酰基化[55]等，其中以水解、氧化、还原、脱羟基、去甲基化反应较为常见。与有机化学反应相比，这些反应常具有专一性和选择性[10,45-50]，其反应的实质是肠道菌所产生的多种代谢酶(胞内或胞外酶)的酶促作用，这些酶主要有水

解酶、氧化还原酶、裂解酶、转移酶等，其中各种水解酶尤为丰富[6]。进一步对人肠道菌代谢及转化天然产物的反应进行研究，可能促进人肠道菌新种和新酶的发现。

由于天然产物的多样性，人肠道菌代谢活动的复杂性，以及其他因素的限制，天然产物的人肠道菌代谢及转化研究尚存在一系列亟待解决或值得深入探讨的问题：现已建立的供人肠道菌代谢研究的模型与人体内肠道菌代谢相比，仍存在一定差异，因此建立良好的肠道菌群转化模型还需进一步实践和探索；目前对不同类型天然产物的代谢及转化研究仍处于积累阶段，缺少系统的研究；对有转化能力、尤其具有转化特异性菌株的筛选和鉴定目前还处于起步阶段，多种特异菌的联合使用也鲜有报道；人肠道菌群组成的个体差异(如个体细菌组成的多样性，有转化能力细菌数目的个体差异，正常或患病时肠道菌的差异)，可以反映在其对天然产物的代谢及转化上，能否利用此进行疾病诊断，以便“对症下药”值得探究；分子生物学等新技术在天然产物的人肠道菌代谢及转化研究中的应用目前主要局限于对肠道菌进行归属鉴定或用于比较肠道菌群落组成差异等方面，值得进一步开拓。

总之，人肠道菌在天然产物代谢及转化研究中的重要性已引起各国学者的重视，相信随着研究的深入，人肠道菌在天然产物药效基础、药物毒效关系、新药发现、药物吸收机制、药物转运机制等方面的应用将更加广阔。

参 考 文 献

[1] Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine[J]. Cell, 2006, 124(4): 837-848.

[2] Whitman WB, Coleman DC, Wiebe WJ. Prokaryotes: The unseen majority[J]. Proceedings of the National Academy of Sciences of the United States of America, 1998, 95(12): 6578-6583.

[3] Wang M, Ahrne S, Jeppsson B, et al. Comparison of bacterial diversity along the human intestinal tract by direct cloning and sequencing of 16S rRNA genes[J]. FEMS Microbiology Ecology, 2005, 54(2): 219-231.

[4] Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora[J]. Science, 2005, 308(5728): 1635-1638.

[5] Sousa T, Paterson R, Moore V, et al. The gastrointestinal microbiota as a site for the biotransformation of drugs[J]. International Journal of Pharmaceutics, 2008, 363(1/2): 1-25.

[6] 张景红. 微生物在药物研究中的应用[M]. 北京: 化学工业出版社, 2011: 133,136,167,181,182-183.

[7] 杨秀伟, 郝美荣, 服部征雄(日). 中药成分代谢分析[M]. 北京: 中国医药科技出版社, 2003: 41,681.

[8] Kim YS, Kim JJ, Cho KH, et al. Biotransformation of ginsenoside Rb1, crocin, amygdalin, geniposide, puerarin, ginsenoside Re, hesperidin, poncirin, glycyrrhizin, and baicalin by human fecal microflora and its relation to cytotoxicity against tumor cells[J]. Journal of Microbiology and Biotechnology, 2008, 18(6): 1109-1114.

[9] Kim DH, Jung EA, Sohng IS, et al. Intestinal bacterial metabolism of flavonoids and its relation to some biological activities[J]. Archives of Pharmacal Research, 1998, 21(1): 17-23.

[10] Li Y, Meselhy MR, Wang LQ, et al. Biotransformation of a C-glycosylflavone, abrusin 2"-O-beta-D-apioside, by human intestinal bacteria[J]. Chemical & Pharmaceutical Bulletin, 2000, 48(8): 1239-1241.

[11] Marotti I, Bonetti A, Biavati B, et al. Biotransformation of common bean (*Phaseolus vulgaris* L.) flavonoid glycosides by bifidobacterium species from human intestinal origin[J]. Journal of Agricultural and Food Chemistry, 2007, 55(10): 3913-3919.

[12] 杨秀伟, 张建业, 徐嵬, 等. 山柰苷的人肠内细菌生物转化研究[J]. 药学学报, 2005, 40(8): 717-721.

[13] Schneider H, Simmering R, Hartmann L, et al. Degradation of quercetin-3-glucoside in gnotobiotic rats associated with human intestinal bacteria[J]. Journal of Applied Microbiology, 2000, 89(6): 1027-1037.

[14] Schneider H, Schwiertz A, Collins MD, et al. Anaerobic transformation of quercetin-3-glucoside by bacteria from the human intestinal tract[J]. Archives of Microbiology, 1999, 171(2): 81-91.

[15] Aura AM, O'leary KA, Williamson G, et al. Quercetin derivatives are deconjugated and converted to hydroxyphenylacetic acids but not methylated by human fecal flora *in vitro*[J]. Journal of Agricultural and Food Chemistry, 2002, 50(6): 1725-1730.

[16] 刘铁汉, 王毅, 王本祥, 等. 淫羊藿苷的肠菌代谢研究 I: 肠内细菌对淫羊藿苷的代谢转化[J]. 中草药, 2000, 31(11): 834-837.

[17] Wang LQ, Meselhy MR, Li Y, et al. The heterocyclic ring fission and dehydroxylation of catechins and related compounds by *Eubacterium* sp. strain SDG-2, a human

intestinal bacterium[J]. Chemical & Pharmaceutical Bulletin, 2001, 49(12): 1640-1643.

[18] Meselhy MR, Nakamura N, Hattori M. Biotransformation of (-)-epicatechin 3-O-gallate by human intestinal bacteria[J]. Chemical & Pharmaceutical Bulletin, 1997, 45(5): 888-893.

[19] Raimondi S, Roncaglia L, De Lucia M, et al. Bioconversion of soy isoflavones daidzin and daidzein by *Bifidobacterium* strains[J]. Applied Microbiology and Biotechnology, 2009, 81(5): 943-950.

[20] Hur HG, Lay JO Jr, Beger RD, et al. Isolation of human intestinal bacteria metabolizing the natural isoflavone glycosides daidzin and genistin[J]. Archives of Microbiology, 2000, 174(6): 422-428.

[21] 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]. Biological & Pharmaceutical Bulletin, 2008, 31(8): 1621-1625.

[22] Hur H, Rafii F. Biotransformation of the isoflavonoids biochanin A, formononetin, and glycitein by *Eubacterium limosum*[J]. FEMS Microbiology Letters, 2000, 192(1): 21-25.

[23] Mitchell JH, Gardner PT, Mcphail DB, et al. Antioxidant efficacy of phytoestrogens in chemical and biological model systems[J]. Archives of Biochemistry and Biophysics, 1998, 360(1): 142-148.

[24] Setchell KDR, Brown NM, Lydeking-olsen E. The clinical importance of the metabolite equol-A clue to the effectiveness of soy and its isoflavones[J]. Journal of Nutrition, 2002, 132(12): 3577-3584.

[25] Kang KA, Lee KH, Chae S, et al. Cytoprotective effect of tectorigenin, a metabolite formed by transformation of tectoridin by intestinal microflora, on oxidative stress induced by hydrogen peroxide[J]. European Journal of Pharmacology, 2005, 519(1/2): 16-23.

[26] Bae EA, Han MJ, Lee KT, et al. Metabolism of 6''-O-xylosyltectoridin and tectoridin by human intestinal bacteria and their hypoglycemic and *in vitro* cytotoxic activities[J]. Biological & Pharmaceutical Bulletin, 1999, 22(12): 1314-1318.

[27] Park EK, Shin YW, Lee HU, et al. Passive cutaneous anaphylaxis-inhibitory action of tectorigenin, a metabolite of tectoridin by intestinal microflora[J]. Biological & Pharmaceutical Bulletin, 2004, 27(7): 1099-1102.

[28] Han YO, Han MJ, Park SH, et al. Protective effects of kakkalide from Flos puerariae on ethanol-induced lethality and hepatic injury are dependent on its biotransformation by human intestinal microflora[J]. Journal of Pharmacological Sciences, 2003, 93(3): 331-336.

[29] Kim M, Kim SI, Han J, et al. Stereospecific biotransformation of dihydrodaidzein into (3S)-equol by the human intestinal bacterium *Eggerthella* strain Julong 732[J]. Applied and Environmental Microbiology, 2009, 75(10): 3062-3068.

[30] Hanske L, Loh G, Sczesny S, et al. Recovery and metabolism of xanthohumol in germ-free and human microbiota-associated rats[J]. Molecular Nutrition & Food Research, 2010, 54(10): 1405-1413.

[31] Kang MJ, Khanal T, Kim HG, et al. Role of metabolism by human intestinal microflora in geniposide-induced toxicity in HepG2 cells[J]. Archives of Pharmacal Research, 2012, 35(4): 733-738.

[32] Yang XW, Zou CT, Hattori M. Harpagometabolins I and II, two new metabolites from harpagoside by human intestinal bacteria[J]. Chinese Chemical Letters, 2000, 11(9): 779-782.

[33] Abdel-hafez A AM, Nakamura N, Hattori M. Biotransformation of phorbol by human intestinal bacteria[J]. Chemical & Pharmaceutical Bulletin, 2002, 50(2): 160-164.

[34] Bae EA, Park SY, Kim DH. Constitutive beta-glucosidases hydrolyzing ginsenoside Rb1 and Rb2 from human intestinal bacteria[J]. Biological & Pharmaceutical Bulletin, 2000, 23(12): 1481-1485.

[35] Bae EA, Choo MK, Park EK, et al. Metabolism of ginsenoside R(c) by human intestinal bacteria and its related antiallergic activity[J]. Biological & Pharmaceutical Bulletin, 2002, 25(6): 743-747.

[36] Akao T, Kida H, Kanaoka M, et al. Intestinal bacterial hydrolysis is required for the appearance of compound K in rat plasma after oral administration of ginsenoside Rb1 from Panax ginseng[J]. The Journal of Pharmacy and Pharmacology, 1998, 50(10): 1155-1160.

[37] Ruan JQ, Leong WI, Yan R, et al. Characterization of metabolism and *in vitro* permeability study of notoginsenoside R1 from Radix notoginseng[J]. Journal of Agricultural and Food Chemistry, 2010, 58(9): 5770-5776.

[38] 杨秀伟, 张建业, 徐嵬. 罗汉果皂苷Ⅲ的人肠内细菌生物转化[J]. 北京大学学报: 医学版, 2007, 39(6): 657-662.

[39] Kim DH, Hong SW, Kim BT, et al. Biotransformation of glycyrrhizin by human intestinal bacteria and its relation to biological activities[J]. Archives of Pharmacal Research, 2000, 23(2): 172-177.

[40] 杨秀伟, 赵静, 崔景荣, 等. 七叶树皂苷-Ia 的人肠内细菌生物转化产物及其抗肿瘤活性研究[J]. 北京大学学报: 医学版, 2004, 36(1): 31-35.

[41] Kim DH, Yu KW, Bae EA, et al. Metabolism of kalopanaxsaponin B and H by human intestinal bacteria and antidiabetic activity of their metabolites[J]. Biological & Pharmaceutical Bulletin, 1998, 21(4): 360-365.

[42] Bae EA, Yook CS, Oh OJ, et al. Metabolism of chiisanoside from Acanthopanax divaricatus var. albeofructus by human intestinal bacteria and its relation to

some biological activities[J]. Biological & Pharmaceutical Bulletin, 2001, 24(5): 582-585.

[43] Ding WJ, Deng Y, Feng H, et al. Biotransformation of aesculin by human gut bacteria and identification of its metabolites in rat urine[J]. World Journal of Gastroenterology, 2009, 15(12): 1518-1523.

[44] Zhang P, Yang XW. Biotransformation of nodakenin and simultaneous quantification of nodakenin and its aglycone in incubated system of human intestinal bacteria by HPLC method[J]. Journal of Asian Natural Products Research, 2009, 11(4): 371-379.

[45] Jin JS, Hattori M. Further studies on a human intestinal bacterium *Ruminococcus* sp. END-1 for transformation of plant lignans to mammalian lignans[J]. Journal of Agricultural and Food Chemistry, 2009, 57(16): 7537-7542.

[46] Jin JS, Zhao YF, Nakamura N, et al. Enantioselective dehydroxylation of enterodiol and enterolactone precursors by human intestinal bacteria[J]. Biological & Pharmaceutical Bulletin, 2007, 30(11): 2113-2119.

[47] Jin JS, Hattori M. Human intestinal bacterium, strain END-2 is responsible for demethylation as well as lactonization during plant lignan metabolism[J]. Biological & Pharmaceutical Bulletin, 2010, 33(8): 1443-1447.

[48] Jin JS, Zhao YF, Nakamura N, et al. Isolation and characterization of a human intestinal bacterium, *Eubacterium* sp. ARC-2, capable of demethylating arctigenin, in the essential metabolic process to enterolactone[J]. Biological & Pharmaceutical Bulletin, 2007, 30(5): 904-911.

[49] Xie LH, Ahn EM, Akao T, et al. Transformation of arctiin to estrogenic and antiestrogenic substances by human intestinal bacteria[J]. Chemical & Pharmaceutical Bulletin, 2003, 51(4): 378-384.

[50] Xie LH, Akao T, Hamasaki K, et al. Biotransformation of pinoresinol diglucoside to mammalian lignans by human intestinal microflora, and isolation of *Enterococcus faecalis* strain PDG-1 responsible for the transformation of (+)-pinoresinol to (+)-lariciresinol[J]. Chemical & Pharmaceutical Bulletin, 2003, 51(5): 508-515.

[51] Kawata Y, Ma C, Meselhy M, et al. Conversion of aconitine to lipoaconitine by human intestinal bacteria and their antinociceptive effects in mice[J]. Journal of Traditional Medicines, 1999, 16: 15-23.

[52] Elmekkawy S, Meselhy MR, Kawata Y, et al. Metabolism of strychnine n-oxide and brucine n-oxide by human intestinal bacteria[J]. Planta Medica, 1993, 59(4): 347-350.

[53] Hattori M. Metabolism of drugs by human intestinal bacteria[J]. Methods in Kampo Pharmacology, 1997, 1: 15-22.

[54] Fukiya S, Arata M, Kawashima H, et al. Conversion of cholic acid and chenodeoxycholic acid into their 7-oxo derivatives by *Bacteroides intestinalis* AM-1 isolated from human feces[J]. FEMS Microbiology Letters, 2009, 293(2): 263-270.

[55] 杨秀伟, 邢增涛, 崔景荣, 等. 华蟾毒精和羟基华蟾毒精的人肠内细菌代谢研究[J]. 北京大学学报: 医学版, 2001, 33(3): 199-204.

[56] Zhou X, Wang L, Sun X, et al. Cinnabar is not converted into methylmercury by human intestinal bacteria[J]. Journal of Ethnopharmacology, 2011, 135(1): 110-115.

[57] Coakley M, Banni S, Johnson MC, et al. Inhibitory effect of conjugated alpha-linolenic acid from bifidobacteria of intestinal origin on SW480 cancer cells[J]. Lipids, 2009, 44(3): 249-256.

[58] Kim DH, Park EK, Bae EA, et al. Metabolism of rhaponticin and chrysophanol 8-o-beta-D-glucopyranoside from the rhizome of Rheum undulatum by human intestinal bacteria and their anti-allergic actions[J]. Biological & Pharmaceutical Bulletin, 2000, 23(7): 830-833.

[59] Sanugul K, Akao T, Li Y, et al. Isolation of a human intestinal bacterium that transforms mangiferin to norathyriol and inducibility of the enzyme that cleaves a C-glucosyl bond[J]. Biological & Pharmaceutical Bulletin, 2005, 28(9): 1672-1678.

[60] Sauer J, Richter KK, Pool-zobel BL. Products formed during fermentation of the prebiotic inulin with human gut flora enhance expression of biotransformation genes in human primary colon cells[J]. The British Journal of Nutrition, 2007, 97(5): 928-937.