

姜黄素体内吸收代谢及与肠道菌群互作研究进展

王浩楠¹, 邱哲瀚¹, 田文妮¹, 肖杰^{1,2*}

(¹华南农业大学食品学院 广州 510642

²广东省功能食品活性物重点实验室 广州 510642)

摘要 姜黄素是一种二苯基庚烷类化合物,因多样而显著的健康效应而被广泛关注。然而,姜黄素经口服消化吸收后生物利用度极低,其健康效应产生的物质基础和过程机制一直备受争议。本文综述姜黄素在机体内吸收转运及代谢过程的研究进展。姜黄素经由上消化道吸收并参与代谢时主要发生还原和结合反应,生成四氢姜黄素、六氢姜黄素、姜黄素葡萄糖苷酸、硫酸化姜黄素等特征代谢物。近年来,姜黄素在下消化道的代谢途径成为研究的热点。姜黄素不仅可被肠道菌群代谢为高活性代谢产物(如阿魏酸、四氢姜黄素、去甲氧基姜黄素、双去甲氧基姜黄素等),也可调节肠道菌群结构,维持菌群稳态。姜黄素的吸收和代谢过程及其与肠道菌群之间的相互作用,是揭示姜黄素健康效应和低生物利用度之间矛盾的关键。

关键词 姜黄素; 代谢转化; 肠道菌群; 生物利用度; 健康效应

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1 姜黄素类化合物

姜黄素类化合物在桦木科、巴西豆科、马尾树科、蒟蒻薯科等多科植物中均有发现,主要从姜黄根茎(含量为 2%~6%)中提取^[1]。自古以来,中国和印度利用姜黄素进行着色以及香料制作,印度亦用其进行改善消化、消除蠕虫、缓解肠胃胀气、清洁肝脏^[2]等。传统中药则将姜黄素用于行气破淤、活血止痛。在现代工业中,姜黄素被用于着色剂、酸碱指示剂、功能性食品以及膳食补充剂等领域。市场研究公司 SPINS 数据显示^[3],仅 2019 年,含姜黄提取物的冷热谷物产品分别增长 928% 和 620%,市场销售总额近 135 万美元。除谷物产品,在饮料产品、零食产品、乳制品中都可见姜黄提取物的身影。2020 年美国植物委员会报告显示^[4],姜黄提取物销售情况位列第 4,产品主要解决免疫健康、关节健康、消化健康等方面存在的问题。姜黄素具有的健康效应引起人们的关注并带动姜黄产业的发展,解析其健康效应产生的物质基础和过程机制并最大化其健康效应,是姜黄素类化合物研究中非常重要的科学问题。

1.1 类别与结构

姜黄素类化合物具有一条庚烷长链和双苯环

的基础结构,在此基础上,根据姜黄素类化合物庚烷母体长链上含氧取代基的种类和数目以及是否成环进一步分为单氧代型、双氧代型、三氧代型、吡喃取代型、呋喃取代型、大环醚型、二聚体型等 7 个类型(图 1)。一般而言,姜黄素类化合物是指姜黄素【1,7-双(4-羟基-3-甲氧基苯基)-1,6-庚二烯-3,5-二酮】、去甲氧基姜黄素【4-羟基肉桂酰基-(4-羟基-3-甲氧基肉桂酰基)甲烷】和双去甲氧基姜黄素【双-(4-羟基肉桂酰)甲烷】的混合物(图 1)。它们具有相同的庚烷长链和双苯环结构,区别在于苯环上的甲氧基数目不同。其中,姜黄素含两个甲氧基,去甲氧基姜黄素含一个甲氧基,双去甲氧基姜黄素不含甲氧基,在它们的长链上存在着酮-烯醇式互变结构,以晶体形式和无定形分子形式存在时均为烯醇式结构,特殊情况下可向酮结构转变^[5-6]。天然来源的典型姜黄素类化合物组成为 52%~63%姜黄素、19%~27%去甲氧基姜黄素、18%~28%双去甲氧基姜黄素^[7]。以姜黄素为例,分子结构以 β -二酮结构中心对称,降低了分子极性,母体链中存在多个双键结构,这是使它成为一种高效抗氧化剂的前提,而两端的对位酚羟基也可增加其活性^[8-10]。此外,姜黄素是一种天然的荧光标记物,在醇溶液和二甲基甲酰胺(DMF)作为潜在氢键供体时,荧光范围在 536~560 nm 范围^[11-12],而在极性溶液中其荧光光谱在 408~540 nm 范围^[13]。

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第一作者: 王浩楠,男,硕士生

通信作者: 肖杰 E-mail: xiaojieacademic@163.com

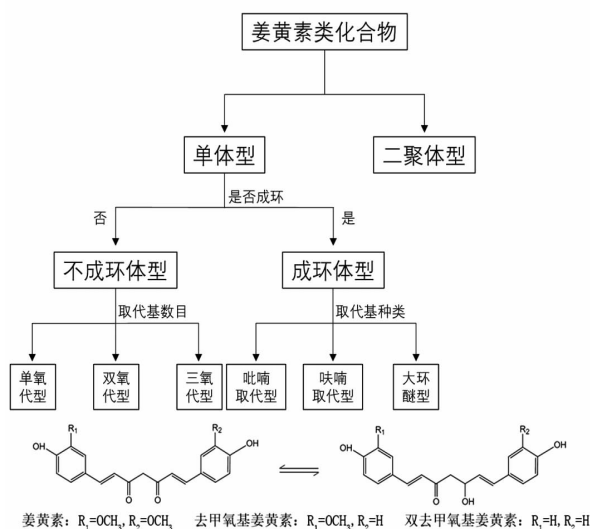


图1 姜黄素类化合物分类及其3种常见姜黄素类化合物的化学结构

Fig.1 Classification of curcuminoids and chemical structures of three kinds of major components of curcuminoids

1.2 姜黄素的稳定性及生物利用度

姜黄素难溶于水(小于 50 $\mu\text{mol/L}$)^[14],其水溶液在中性至碱性条件下不稳定,主要分解产物为阿魏酰甲烷(4-羟基-3-甲氧基肉桂酰甲烷)、阿魏酸(4-羟基-3-甲氧基肉桂酸)和香草醛(3-甲氧基-4-羟基苯甲醛)^[15]。姜黄素是一种光敏性物质,在 24 h 强光照射条件下姜黄素无水乙醇溶液被完全降解,其溶液由黄色转变为无色^[16]。经口摄入后在胃液及小肠液溶解度低,其小肠透过性低^[17],可被肠腔游离的还原酶、上皮细胞和肝脏代谢(I相和II相)并排除^[18],最终导致其生物利用度极低。Perkins 等^[19]进行小鼠体内实验,高效液相色谱法测定口服 100 mg/kg 姜黄素后,小鼠血浆中仅有 0.22 $\mu\text{g/mL}$ 姜黄素;Yang 等^[20]结合 LC-MS/MS 方法测定口服 500 mg/kg 姜黄素的大鼠血浆中姜黄素浓度,血药质量浓度仅达 0.06 $\mu\text{g/mL}$ 。

针对上述姜黄素存在的稳定性差以及口服生物利用度低的问题,研究人员尝试了多种稳态递送体系对其进行包埋和递送^[21-23]。前期研究^[24]以高粱醇溶蛋白-羧甲基壳聚糖纳米颗粒对姜黄素进行包埋递送,改善了姜黄素在胃肠道的溶解度和细胞摄取效率。利用粉碎淀粉颗粒稳定的 Pick-

ering 乳液递送姜黄素^[25],试验显示包封姜黄素的生物可及性比游离姜黄素高 22.1%。Karade 等^[26]制备抗坏血酸和姜黄素共递送的结肠定向微球,以抗坏血酸为 pH 值调节剂可使姜黄素在结肠碱性环境中保持稳定,最终结肠释放的姜黄素生物利用度提高 7 倍。

1.3 姜黄素的健康效应

姜黄素作为一种被广泛关注的活性物,临床耐受可达 12 g/d 而无不良反应^[27-28],是一种具备高效保健潜力的功能食品配料,常作为递送体系研究的模式物。姜黄素在体外和体内表现出多种生物学活性,如抗癌^[29-31]、抗炎^[29,32-33]、抗氧化^[34-36]、抗 HIV^[37]、抗动脉粥样硬化^[38-39]、抗糖尿病^[40-41]、心血管疾病^[42]、降脂保肝^[43-45],保护神经等。近年来,其对阿尔茨海默症等神经退行性疾病的预防作用受到人们的关注^[46-48]。

首先,姜黄素显示出突出的体内抗氧化健康效应。活性氧(ROS)和其它自由基是机体正常代谢的副产物,可传导细胞信号和维持体内稳态。一旦体内 ROS 水平急剧上升则可造成细胞损伤^[49]。姜黄素可以在这种氧化应激过程中对机体起到保护作用,其健康效应归功于其抗氧化能力,包括清除自由基、过氧化氢和金属螯合等^[50]。Hejazi 等^[51]通过双盲试验评估姜黄素的抗氧化能力,患者以 3 g/d 的剂量口服,试验结果显示超氧化物歧化酶(SOD)活性下降且血浆总抗氧化能力(TAC)增加。抗炎作用是姜黄素另一明确的、受到广泛研究的健康效应。研究表明,姜黄素能够抑制炎症相关的信号通路,包括核因子 κB (NF- κB)、环氧合酶(COX)和脂氧合酶通路,从而降低促炎细胞因子水平和减少体内产生的前列腺素^[52]。Desai 等^[53]评估结肠靶向微丸递送姜黄素和环孢菌素对肠道炎症的干预效果,药效学研究结果表明,其在乙酸诱导的结肠炎症模型中有治疗效果且与环孢菌素显示出协同作用。错误折叠的淀粉样蛋白在体内累积是突触损伤和神经元沟通受损的主要原因之一,最终可发展成神经退行性疾病^[54]。除上述抗炎机制,姜黄素可以透过血脑屏障(BBB)^[55],抑制淀粉样蛋白的聚集和减轻其神经毒性作用^[56]。此外,姜黄素可提高神经元生长因子(如 NGF、BDNF、GDNF)的表达水平,这对减少突触损伤和神经元

死亡具有重要作用^[57]。Maiti 等^[58]通过固体脂质纳米粒递送姜黄素发现其通过激活分子伴侣（如 HSP70、HSP90、HSP60 和 HSP40 等蛋白）起到神经保护作用。

姜黄素显著的、多样的健康效应被广泛报道，而这与其在物理稳定性差、上消化道生物利用度及药代动力学特征存在巨大反差，姜黄素健康效应的发挥机制是长期以来困扰科学家的重要科学问题。解析姜黄素的体内吸收代谢途径是解决上述科学问题的关键所在。

2 姜黄素的吸收代谢过程研究进展

2.1 姜黄素体内代谢转化过程

以回肠-盲肠为分界点，口腔、胃、十二指肠、空肠和回肠通常被统称为上消化道，盲肠、结肠、直肠被称为下消化道。姜黄素在体内的吸收代谢及分布情况一直以来被广泛研究，研究对象包括小鼠、大鼠以及人体（如表 1 所示）。从表 1 结果可

知，只有痕量姜黄素可以被上皮细胞吸收，并在肝脏和血浆中分布，而绝大多数无法吸收的姜黄素最终随着消化进程的推进进入结肠。研究表明，诸如儿茶素^[59-61]、大豆异黄酮^[62-65]、姜黄素等多种化合物由于体内代谢位点的不同，会发生不同的代谢反应并产生不同的代谢产物。姜黄素经口摄入后在上消化道被还原酶代谢发生还原反应，同时部分被吸收进入小肠上皮细胞，在上皮细胞作用下发生结合反应。虽然部分姜黄素可避免小肠首过效应进入肝脏，但仍会在肝脏处发生代谢生成极性更大的代谢产物并排出体外。由于姜黄素水溶性低和小肠透过性差，绝大部分姜黄素未经小肠消化直接进入结肠部位，经过结肠微生物及其相应酶系的羟基化、乙酰化、甲基化、还原、去甲氧基等作用，母体姜黄素被进一步代谢降解，其代谢产物可经过肠壁吸收进入体循环或随粪便排出体外（图 2）。

表 1 姜黄素在体内的吸收分布研究(体内试验)

Table 1 Absorption and distribution of curcumin (derived from *in vivo* experiments)

对象	给药方法	剂量	上消化道吸收分布量				下消化道	参考文献
			小肠	肝脏/胆汁	血浆	尿液	粪便	
小鼠	口服	100			0.22 μg/mL			[19]
	腹腔注射	mg/kg	200 nmol/g	73 nmol/g	25 nmol/g			
小鼠	腹腔注射	100 mg/kg	117 μg/g	26.9 μg/g	2.25 μg/mL			[66]
大鼠	口服	2.4 mg/kg				6%	90%	[67]
	腹腔注射			80%		11%	73%	
	静脉注射			85%				
大鼠	口服	1 g/kg		<0.01%	<5 ng/mL		65%~85%	[68]
大鼠	口服	500 mg/kg			0.06 μg/mL			[20]
大鼠	口服	1 g/kg				很少	75%	[69], [70]
大鼠	口服	400 mg		<20 μg/tissue	<5 μg/mL	/	40%	[71]
大鼠	口服	340 mg/kg	1.4 mg/g	3 671.8 ng/g	16.1 ng/mL			[72], [73]
大鼠	静脉注射	10 mg/kg			0.36 μg/mL			[74]
人	口服	4~8 g/d			1.3 μg/mL	/		[27]
人	口服	180 mg/d				/		[75]
人	口服	3.6 g/d			11 nmol/L			[76]
人	口服	10/12 g			50 ng/mL			[28]
人	口服	4 g/d						[77]
人	口服	3.6 g/d			3 nmol/L			[78]
人	口服	2 g/kg			0.006 μg/mL			[74]

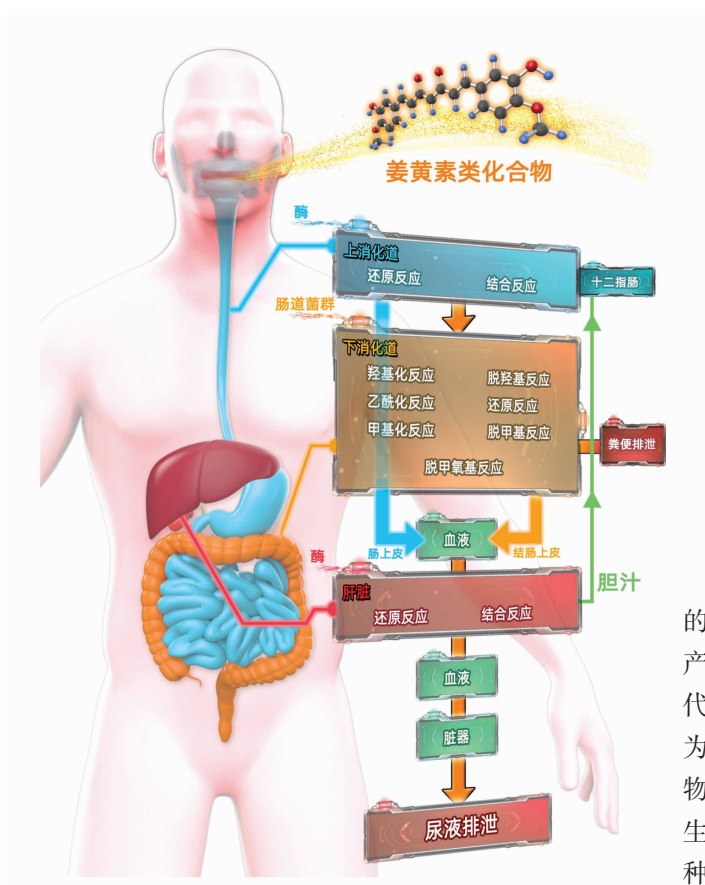


图2 姜黄素体内吸收代谢过程示意图
Fig.2 Adsorption and metabolic pathways of curcumin *in vivo*

2.2 姜黄素在上消化道的代谢转化

姜黄素在上消化道主要发生氧化反应,还原反应和结合反应(图3)。氧化反应生成双环戊二酮衍生物,其有两种产生途径:一种是姜黄素发生自氧化,另一种是通过脂肪氧化酶(LOX)和COX的催化作用产生,母链上羟基的氢脱去并发生环化和氧合,从而产生醌甲基和庚二酮链中的离域自由基,随后醌甲基继续发生水合和重排反应,最终姜黄素转化成双环戊二酮衍生物。虽然在体内有两种途径可以产生双环戊二酮衍生物,但是酶催化氧化产生的速率更快,在LOX和COX含量高的细胞里,双环戊二酮衍生物的含量通常高于其它代谢产物^[10,79]。

还原反应是姜黄素在上消化道中发生的更为普遍的反应,还原酶存在时姜黄素即可能被还原。由于存在多个双键,姜黄素能根据发生氧化双键

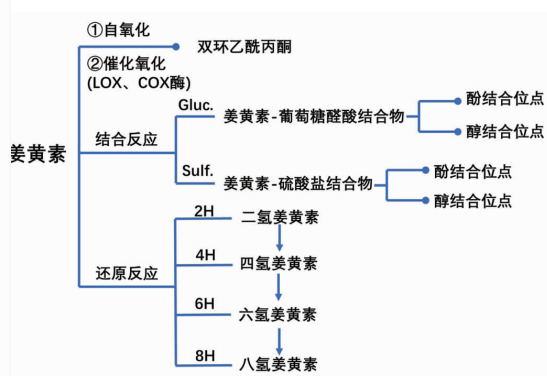


图3 姜黄素在上消化道的代谢转化途径

Fig.3 Metabolic transformation pathways of curcumin in the upper gastrointestinal tract

的个数分别被氧化为二氢、四氢、六氢和八氢代谢产物,以姜黄素为例,四氢姜黄素和六氢姜黄素的代谢水平较高,血浆中以四氢姜黄素的形式存在为主^[80]。值得注意的是,肠道内姜黄素及其还原产物在进入肠道上皮细胞和到达肝脏之后很容易发生结合反应,主要分为葡萄糖醛酸化和硫酸化两种,可分别发生或者共同发生。以葡萄糖醛酸化为例,在 β -葡萄糖醛酸苷酶的作用下姜黄素主链羟基上或是苯环上的氢被葡萄糖醛酸取代,增加化合物的极性便于溶解和排出体外。多项研究显示^[81-83],六氢姜黄素-葡萄糖醛酸结合物是姜黄素在体液、器官和细胞中的主要代谢物。

3 姜黄素与肠道菌群的互作过程

长期以来研究人员普遍认为上消化道是消化代谢的主要场所,下消化道主要负责水分、电解质的重吸收和排泄,然而针对提高姜黄素上消化道吸收所作出的尝试并未取得重大成效。近年来,学界开始意识到姜黄素极有可能在分布水平较高的下消化道发挥作用^[69],包括代谢成具有更高活性的代谢物^[84]和调节肠道菌群区系,从而直接或间接影响其在体内表现出的健康效应。

3.1 姜黄素在下消化道的代谢转化

相较于上消化道代谢产物的种类,姜黄素经下消化道肠道菌群代谢所产生的代谢产物更为丰富。其主要反应包括甲基化、去甲基化、羟基化、去羟基化、还原和去甲氧基化等反应途径,基本代谢

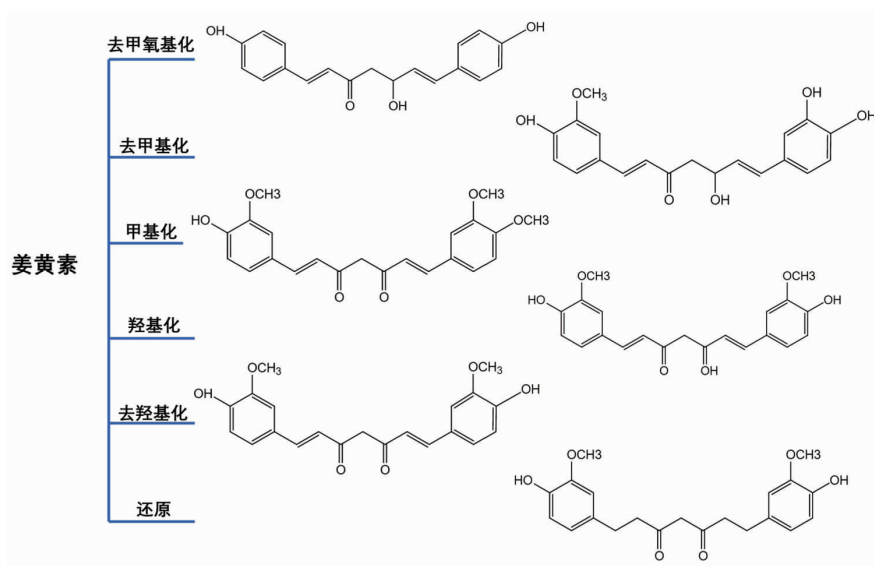


图 4 姜黄素在下消化道的代谢途径

Fig.4 Metabolic transformation pathways of curcumin in the lower gastrointestinal tract

产物如图 4 所示。值得注意的是,不同反应之间可以相互叠加,从而产生一些含量水平较低、结构更为复杂的次级代谢产物。例如,去甲基姜黄素和双去甲氧基姜黄素可以在人类结肠代谢产物中发现^[85],它们可提高 β -淀粉样蛋白降解酶的活性,减少 β -淀粉样蛋白在海马体和大脑皮层中蓄积,而母体姜黄素则不能。姜黄素的两个苯环上各有一个甲氧基,当 $-\text{OCH}_3$ 被替代成 $-\text{H}$ 属于去甲氧基化,当甲氧基上的 $-\text{CH}_3$ 被肠道菌群代谢转换为 $-\text{H}$,则为去甲基化过程;与去甲基化不同的是,有研究显示^[86-87]甲基化反应可以发生在姜黄素母链的醇羟基上,也可以发生在苯环上的酚羟基上,存在较多可能。羟基化是发生在姜黄素母链上的代谢途径,肠道菌群在母链的碳原子上引入一个氧原子,从而形成一个羟基或者进一步生成羰基,而去羟基化则是更倾向于脱去母链上的羟基。因为还原酶在体内大量存在,结肠也不例外,所以姜黄素及其代谢产物在进入结肠后也可以继续发生还原反应。

肠道菌群对姜黄素的生物转化研究主要应用人类粪便浆液以及单一细菌菌株两类试验模型。虽然两种模型的分析方法相近,但通过人类粪便浆液模型所产生的代谢产物种类更为丰富,足见菌群多样性对代谢产物种类和水平的影响。姜黄素的肠道菌群代谢产物种类繁多(表 2),以阿魏

酸、四氢姜黄素、八氢姜黄素、去甲氧基姜黄素、双去甲氧基姜黄素等为主。已有研究证明这些代谢产物具有比姜黄素更高的生物活性,并可以通过不同途径影响姜黄素的炎症治疗和保护神经效果^[88-91]。

3.2 姜黄素对肠道菌群的调节作用

姜黄素进入结肠后不仅会受到肠道菌群影响,同时也可以影响肠道菌群结构,这种结构上的调整可间接影响姜黄素健康效应的发挥^[92]。肠道菌群结构表现为菌群的丰富度、多样性及表达水平。保持肠道有益菌群水平处于优势有助于人体健康,而致病菌一旦过度繁殖会导致机体产生系统性疾病,尽管生物失调和疾病之间的直接因果关系尚不明确,但它们之间相互影响的关系越来越被学界认可^[93-94]。研究表明,姜黄素的摄入往往会调节结肠内肠道菌群的丰富度和多样性^[92,95]。Shen 等^[92]探究了口服姜黄素对 C57BL/6 小鼠肠道微生物区系的调节作用,普雷沃氏菌科、理研菌科和类杆菌科等代表性菌属的表达水平显著下降。Sun 等^[96]研究了姜黄素与 APP/PS1 双转基因小鼠肠道微生物区系的相互作用,与对照组相比,姜黄素处理组类杆菌科、普雷沃氏菌科和乳杆菌科的丰度显著下降,而理研菌的丰度显著提升。Sreng 等^[97]发现姜黄素处理影响到不同的菌属,显著增加类杆菌科而减少了理研菌科的丰度。尽管不同

表2 肠道菌群对姜黄素类化合物的代谢研究
Table 2 Studies on the metabolism of curcumins by gut microbiota

模型	原型物	菌群代谢产物	分析方法
人类粪便浆液	姜黄素、去甲氧基姜黄素、双去甲氧基姜黄素	四氢姜黄素、二氢阿魏酸、1-(4-羟基-3-甲氧基苯基)-2-丙醇	超高压液相色谱(UH-PLC)线性离子阱质谱
	姜黄素	23种去甲基化、还原、羟基化和乙酰化、或这些的组合的产物	超高效液相色谱结合四极杆飞行时间质谱(UPLC-Q-TOF MS)
细菌菌株	布劳特氏菌属 MRG-PMF1	姜黄素、去甲氧基姜黄素、双去甲氧基姜黄素	去甲基姜黄素、双去甲基姜黄素
	费格森埃希菌和 大肠杆菌	姜黄素、去甲氧基姜黄素、双去甲氧基姜黄素	二氢姜黄素、四氢姜黄素、阿魏酸、姜黄素-L-半胱氨酸
	巨大芽孢杆菌 DCMB-002	姜黄素	7种去甲基化、还原、羟基化和去甲氧基化代谢产物
			高效液相色谱-四极杆飞行时间串联质谱

试验对肠道菌群相同菌属的影响可能不同,但姜黄素能显著影响的菌群种类已经逐渐清晰,这种影响与姜黄素健康效应之间的关系有望被理清。其次,口服姜黄素可提高产短链脂肪酸有益菌群水平,而短链脂肪酸对心血管疾病、代谢疾病、神经退行性疾病和免疫疾病^[98-99]等领域都具有重要贡献。Li等^[100]对姜黄素给药后结肠内的乙酸、丙酸、丁酸、异丁酸、戊酸、异戊酸和己酸进行定量分析,除丁酸外基本回到正常表达水平,丙酸表达水平甚至超过对照组。

姜黄素在下消化道所引起的变化让研究人员不得不重新审视姜黄素发挥健康效应的作用途径。低生物利用度和广泛的健康效应之间的矛盾可能需要通过姜黄素与肠道菌群区系之间的相互作用进行阐释,高活性的姜黄素代谢物直接引起机体的健康效应,而肠道菌群结构的调节影响有益、有害代谢产物和疾病相关因子的产生,从而间接促进健康效应的发挥。

4 结论

姜黄素的诸多健康效应如抗炎、抗氧化、抗神经退行性疾病等都已经证实。令人不解的是,姜黄素在体内由于溶解性差和透过性差导致有效浓度低下,这与其广泛的健康效应相违背,以至于学界对其发挥功效的物质基础和作用途径存在较大

争议。一直以来对姜黄素的研究都集中于上消化道的功能作用,从而忽略了下消化道可能存在的代谢和吸收。随着肠道菌群被视为人体的“第二大脑”,包括姜黄素在内的植物化学活性物质是否可通过结肠发挥健康效应逐渐得到重视。目前姜黄素的口服递送增效体系的设计目标旨在增强上消化道的吸收从而提高生物利用度,然而这对姜黄素的功效发挥不一定是有利的。在下消化道与肠道菌群相互作用更可能是其发挥健康效应的基础,通过结肠靶向递送体系规避上消化道吸收的同时提高下消化道的释放,是探究姜黄素健康效应作用机制的有效手段。

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Research Progresses on the Absorption, Metabolism *in Vivo* and Gut Microbiota Intervention of Curcumin

Wang Haonan¹, Qiu Zhehan¹, Tian Wenni¹, Xiao Jie^{1,2*}

¹College of Food Science, South China Agricultural University, Guangzhou 510642

²Guangdong Provincial Key Laboratory of Nutraceuticals and Functional Foods, Guangzhou 510642)

Abstract Curcumin is a kind of diphenylheptane compound, which has been widely studied because of its evidenced

health benefiting effects. However, due to the poor bioavailability of curcumin after digestion and absorption, the mechanisms underlying its bioefficacy have been controversial. This paper reviewed the research progress on the absorption, transportation and metabolism of curcumin *in vivo*. Curcumin mainly experiences the reduction and conjugation reactions when absorbed through the upper gastrointestinal tract and participates in metabolic pathways where characteristic metabolites such as tetrahydrocurcumin, hexahydrocurcumin, curcumin glucuronide, sulfated curcumin are produced. Its metabolic process in the lower gastrointestinal tract has become the research hotspot in recent years. Curcumin can not only be metabolized into highly active metabolites by gut microbiota, but can also regulate the profile of gut microbiota and maintain the homeostasis of gut microbiota. The absorption and metabolism of curcumin and its bidirectional interaction with the gut microbiota are critical in unveiling the contradiction between the health effect of curcumin and its low bioavailability.

Keywords curcumin; metabolic transformation; gut microbiota; bioavailability; health effect