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Review 综 述

肠道微生物群与药物相互作用的研究进展

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摘　要：药物的代谢是机体对药物处置过程的关键步骤，而肠道作为机体中重要的微生态系统，其在药物代谢方面的作用至关重要。肠道微生物群能够对各种药物等外源化合物进行生物转化、积累，并改变这些物质的活性和毒性，从而影响宿主机体对它们的反应。肠道微生物群与药物之间的相互作用相当复杂，亟待更多更加深入、全面的发掘和研究。近年来，随着人们对肠道微生物群代谢及其与药物互作关系，肠道菌-宿主共代谢认知的不断深化，越来越多的研究表明肠道微生物在药代动力学中扮演重要角色。本文通过调研、整理、归纳和总结国内外相关文献资料，对机体肠道微生物的分类、功能，几种常用药物对肠道微生物的影响以及肠道菌群对药物的代谢作用效果与几个主要的机制进行了梳理和综述，并讨论了微生物和药物之间的双向互作。有利于增进对微生物群影响药物疗效及其代谢途径和机制的了解，提高调控肠道微生物改善治疗的可能性，为指导临床合理用药、精准用药、个体化治疗、药物的评价和新药研发等提供科学参考。

关键词：肠道微生物群；药物；代谢；相互作用

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Advances in gut microbiota-drug interactions

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Abstract: Drug metabolism is a key step in the disposal of drugs, and the role of the gut as an important micro-ecosystem in the body is crucial in drug metabolism. The gut microbiota is capable of transforming and accumulating exogenous compounds (e.g., drugs) and modifying the activity and toxicity of these compounds, thereby influencing the host responses to the compounds. The interactions between gut microbiota and drugs are complex and need to be studied in detail. In recent years, the understanding of the metabolism of gut microbiota, gut microbiota-drug interactions, and the co-metabolism between gut microbiota and host are deepening, and increasing studies have shown that gut microorganisms play a crucial role in pharmacokinetics. By reviewing the relevant papers at home and abroad, we summarized the classification and functions of gut microorganisms, the effects of some commonly used drugs on gut microorganisms, and the metabolic effects and mechanisms of gut microbiota on drugs. In addition, we discussed the interactions between gut microbiota and drugs. The review helps to improve our understanding of the influences of gut microbiota on drug efficacy and the pathways and mechanisms of drug metabolism by gut microbiota, increase the possibility of modulating gut microbiota to improve treatment, and provide a reference for the rational and precise use of drugs, individualized treatment, and drug evaluation and development.
Keywords: gut microbiota; drug; metabolism; interaction

肠道微生物群是由细菌、噬菌体、病毒、古细菌、真菌和原生动物等数量丰富的物种形成的复杂多样的生态系统。该系统的细胞总数约为宿主自身的 10 倍，可达 10^{13} 个，所涵盖的编码基因甚至超过宿主的 150 倍之多[1-3]。作为消化道微生态环境的主要组成部分和关键要素，肠道细菌种类繁多，远端密度大于近端，结肠中就有约 400 多种[4]。从门的分类水平上来看，厚壁菌门、拟杆菌门，放线菌门和变形菌门数量最多(90%以上)，为肠道优势菌群，而其他菌群如螺旋体门、蓝细菌门、疣微菌门和梭杆菌门的含量较低[5-6]。这些细菌门类在肠道内形成一个稳定的生态系统，对宿主健康至关重要。

从肠道菌群对宿主机体的影响来看，可以将其分为有益共生菌、致病菌和条件致病菌 3 类。益生菌如双歧杆菌、嗜酸乳杆菌可以起到保护生物屏障、维持菌群平衡及微生态环境稳定、调节免疫反应的作用，现已广泛应用于临床预防和治疗相关疾病。近年来，一种重要的肠道微生

物嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)受到人们的高度关注，其在治疗多种疾病方面显示出巨大潜力，有望被开发成为下一代益生菌[7-8]。致病菌，如金黄色葡萄球菌、沙门氏菌和志贺氏菌入侵机体大量繁殖可引发疾病。而条件致病菌如大肠杆菌、肠球菌等正常情况下在肠道内一般不致病，一旦出现肠道菌群失调、机体免疫损伤或转移到其他器官或组织中聚集，就可能引起疾病[9-10]。

1 肠道微生物

1.1 肠道微生物的功能作用

肠道微生物影响肠道机械、化学、免疫和生物屏障的形成和稳定，在机体内发挥着关键的作用，它们几乎与宿主的各个系统和各个层面都有联系(表 1)。肠道微生物不仅具有代谢消化食物，合成营养物质(如维生素等)，调节脂质代谢、脂肪储存和刺激血管生成等关键功能[17-18]，还可以保护宿主免受病原体侵害，即定植抵抗。例如，肠道内定植的菌群在正常条件下会抑制艰难梭菌的增殖，当长期或大量使用抗生素时，肠道微生态环境失衡，有益菌群瓦解，艰难梭菌大量繁殖产生毒素就会引发严重的感染性疾病。肠道微生物重要代谢产物如多种短链脂肪酸(short-chain fatty acids, SCFAs)不仅为肠道环境提供营养、稳定 pH，还通过多种途径影响免疫细胞的功能和分化从而调节免疫反应。另有研究表明丁酸盐可以通过调节生物钟相关基因 RAR-related orphan receptor (RORα)的表达水平来控制 B 细胞的数量和功能[19]。肠道菌群失调与炎症、糖尿病和肿瘤等多种疾病的发生发展有关[1,20]，甚至在 *EphB6* 缺失小鼠的自闭症样社会行为调节中起着关键作用[21]。近年来随着微生物-肠-脑轴、心-肠轴和肺-肠轴等各种肠道-器官轴理论的提出和相关研究的深入开展，人们对肠道微生物与机体多器官系统相互作用联系产生了新的认知。

1.2 影响肠道微生物的内外因素

肠道微生态系统在个体之间存在巨大的异质性，只有少数的肠道微生物成员在大多数个体中是相似的[22]。一项研究发现，从欧洲收集到的 3 000 份粪便样本中只有 17 种细菌被确定为主要优势微生物，而大多数细菌则都是稀有的[23]。Zhernakova 等对来自荷兰的 1 135 份粪便样本进行分析研究，总共确定了 639 个肠道微生物物种，而其中 469 个(约占 73%)仅存在于不到 10 个个体之中[24]。这种高度的个体间差异可能是导致肠道微生物群代谢功能变化的原因。这些差异的存在表明肠道菌群基因组成分和结构易随其他内外因素的调节而发生改变。

表 1 肠道微生物群在疾病治疗中的潜在作用

Table 1 Potential role of gut microbiota in disease treatment

Diseases	Potential role of gut microbiota in disease treatment	References
Colitis associated colon cancer	Inhibiting NF-κB pathway and promoting apoptosis	[11]
Melanoma tumors	Activating dendritic cell and promoting optimal antitumor T cell responses	[12]
Colitis	Increasing the levels of beneficial metabolites, inhibiting NF-κB pathway and alleviating tissue damage	[13]
Acute pancreatitis	Inducing higher levels of NAD (nicotinamide adenine dinucleotide)-associated metabolites	[14]
Non-alcoholic fatty liver disease	Modulating bile acids and SCFAs metabolism	[15]
Perinatal depression	Influencing maternal mental health through the gut-brain axis	[16]

常见的内在因素包括遗传、性别、年龄、生理病理状态、感染和免疫情况等。宿主遗传学影响肠道微生物物种的丰度，许多研究证明了遗传因素在塑造肠道微生物群结构方面发挥关键作用[25]。年龄对微生物群的组成也有很大影响。取正常人的粪便样品进行测序，发现菌群 α 多样性随着年龄的增长而增加，青少年肠道中梭菌和双歧杆菌属的丰度明显更高，而健康成年人则以厚壁菌门和拟杆菌门为主，α 多样性的减少与代谢和炎症疾病以及老年人认知能力下降有关[26-27]。此外机体的一些生理病理状况、感染和免疫状态同样会引起肠道微生物群的变化。因此，肠道微生物群的改变可能为许多疾病的预测和预防提供参考。有研究发现，大肠癌患者和健康人之间的肠道微生物的组成存在差异，患者的微生物组中富含某些类群(如梭杆菌属、拟杆菌属、弯曲杆菌属等)或个别微生物丰度降低(如产丁酸盐的罗斯氏菌等)。此外，有证据表明，肠道微生物群的变化发生在结直肠癌发生的早期阶段，可用于识别有结直肠腺瘤(大肠癌的前兆病变)风险的个体[28-29]。还有一些代谢性疾病例如糖尿病、肥胖等，其发病率与患者个体在肠道菌方面存在的差异也有关联[30-31]。Borsom 等通过对阿尔茨海默病模型小鼠的肠道菌群进行纵向分析，发现在疾病早期肠道菌群组成的变化可以预测该病病理的发展[32]。急性猪流行性腹泻病毒感染会改变肠道微生物群的分布，也影响了仔猪肠道微生物群的氨基酸代谢、辅酶运输等生物学功能[33]。因此，更好地了解肠道微生物群的个体化性质和多样性，有助于解释疾病的易感性。微生物群的变化不仅可以被用作疾病早期检测的生物标志物，还可以为疾病的精准预防和治疗提供科学的参考。

此外，饮食、环境、药物和手术治疗、生活方式等外在因素也对肠道菌群存在影响。饮食在调节肠道微生物群方面发挥着至关重要的作用。Asnicar 等对英国和美国的共 1 098 人进行了分析，深入探究了肠道菌群特征与心血管和饮食习惯之间的关系，发现肠道菌群与食物类型、饮食模式等有显著关联，健康植物性食物更易塑造菌群的组成[34]。蓝莓、甜椒等富含多酚的水果蔬菜有助于增加双歧杆菌、乳杆菌等肠道有益菌的数量[35]。生活环境也会影响个人肠道微生物群落的组成。Valles-Colomer 等对 9 700 多组人类粪便和口腔宏基因组数据分析发现，正常菌群具有母婴、家庭和人群内部的传播模式，同居者之间存在一定程度的肠道和口腔菌群的菌株共享[36]。Yang 等的研究发现，长期接触镍的职业人员其肠道菌群中降尿酸菌(如乳酸杆菌、毛螺菌科和布劳特氏菌属)丰度降低，而致病菌(如志贺菌属)丰度增加[37]。同时，土壤、大气和水源等的污染也将干预个体肠道微生物的组成。药物对肠道微生物群有着深刻、持续的影响，了解这些影响将有助于调整抗生素治疗和益生菌的使用，以尽量减少一些对肠道共生菌的“附带损害”[38]。一项针对 40 种代表性肠道细菌菌株的研究发现，在所用的涵盖多种治疗类别的上市非抗生素药物中(大于 1 000 种)，有 24%的药物至少抑制了 1 种菌株的生长，这表明不仅是抗生素，许多非抗生素类药物也可能改变肠道微生物的组成和结构，从而影响药物代谢、药效和药物毒性，促进细菌耐药性的产生[39]。

生活方式如运动、吸烟、熬夜、饮酒和压力等也会影响肠道微生物群的组成和结构。一些研究表明，运动丰富了肠道微生物群的多样性，并与蛋白质摄入和肌酸激酶水平呈正相关，能够减少发病率[40]。在治疗与菌群失调相关的疾病，如肥胖症和其他一些胃肠道疾病时，可

以将运动作为一种治疗支持。在戒烟的健康个体的粪便微生物群中也观察到了明显的变化，包括厚壁菌门和放线菌门的相对丰度增加，拟杆菌门和变形菌门的减少[41]。压力和睡眠之间存在着双向关系，压力会影响肠道通透性、炎症和免疫激活，引发肠道微生物群组成的改变，这些变化可能会导致睡眠障碍[42]。

肠道微生物群组成和功能的改变对人类健康有直接影响，并在一些疾病的发生中发挥重要作用。重新平衡这些内外因素的影响对治疗疾病有效，因此对肠道微生物群和宿主之间关系的持续研究是至关重要的。

2 影响肠道微生物的常用药物

2.1 抗生素

肠道微生物群在许多病理生理过程中扮演着关键的角色，越来越多的研究表明，一些临床药物的疗效也取决于肠道共生菌的作用，抗生素是对抗致病菌的宝贵武器，然而，其改变微生物群的组成和功能，对肠道共生菌产生附带损害，也会给机体带来长期的有害影响[43]，这与本课题组前期进行的多种抗生素(如喹赛多、替米考星和土拉霉素等)对人体肠道菌群微生物毒理学评价的结果相似[44-46]。抗生素对肠道菌群的影响主要表现在多样性和一些特定类群代表性的急剧下降，抗生素耐药基因上调以及抗生素耐药菌株的出现，特别是多重耐药性病原体引起了人们对普遍的、不恰当的抗生素使用的关注。不同种类的抗生素对不同肠道细菌的影响仍然缺乏系统性研究。Maier 等分析了 144 种抗生素对 38 种代表性人肠道细菌的影响，发现不同抗生素有不同的抑制谱。喹诺酮类药物对肠道共生菌的抑菌谱随药物的换代升级而扩大，β-内酰胺类药物的影响则具有种系特异性，作为广谱抑菌性蛋白合成抑制剂的大环内酯类和四环素类药物，在广泛抑制共生菌的同时，也杀死了一些菌种，从而明显地影响了肠道菌群的组成。规避抗生素对肠道微生物群的不利影响，减少抗生素对共生细菌“误伤”且不影响其对致病菌效力的方法值得深究[47]。肠道共生菌携带的大量抗生素耐药基因很可能是致病细菌获得耐药性的重要来源。Thanh 等发现索氏志贺氏菌很可能从肠道共生大肠杆菌中获得多重耐药性，而且抗生素的使用可能会影响它们之间的质粒转移，进一步促进耐药基因的转移[48]。Kienesberger 等的研究发现，抗生素的使用导致克雷伯氏菌产生的一种 DNA 烷基化肠毒素(tilimycin, TM)在肠腔中积累，改变了微生物群的分类组成，同时有可能通过损伤 DNA 来诱导基因突变，促使肠道共生条件性致病菌产生抗生素耐药性，导致新耐药性的出现[49]。除了耐药基因，抗生素处理还显著影响了小鼠肠道菌群代谢基因的表达。Cabral 等的研究发现阿莫西林提高了拟杆菌的相对丰度，相反大多数其他门类菌群的丰度却被广泛削减，这种变化与肠道环境的改变(葡萄糖浓度大幅降低)有关，阿莫西林上调了多形拟杆菌中与多糖利用有关基因的表达，提高了其对多糖的利用率[50]。Shi 等的研究表明抗抑郁药物度洛西汀和氯霉素有很强的协同作用，联合使用时增加了大肠杆菌的氯霉素抗性突变频率(2.45−9.01 倍)，并可能加强其传播，产生的突变体对 12 种抗生素的抗性增强，并对 8 种抗生素产生耐药性。这是因为 2 种药物的联合使用上调了细菌的外排泵相关基因的表达和氧化应激反应，活性氧诱导的外排泵调节基因 *marR* 突变促进了外排泵 AcrAB-TolC 和 MlaFEDB 的活化[51]。

2.2 质子泵抑制剂

质子泵抑制剂(proton-pump inhibitors, PPIs)作为清除幽门螺旋杆菌、治疗胃酸相关疾病的

一线药物，主要是通过直接抑制质子泵(H^+/K^+腺苷三磷酸酶)从而抑制胃酸分泌，发挥其抗酸作用[52]。因其具有较高的有效性和安全性，越来越多的患者开始接受 PPIs 治疗，部分药物被过度用于处方医疗[53]，人们对该药物的潜在副作用也越来越关注。有研究对 PPIs 与多重耐药微生物(multidrug-resistant microorganisms, MDROs)定殖风险的关系进行系统分析，并对数据库进行荟萃分析，发现使用 PPI 会使多重耐药细菌定殖的概率增加 70%，然而，该研究并没有排除生活方式等其他相关因素的影响，仍然存在局限性[54]。Willems 等对 2 239 例住院患者进行调查试验，该研究的结果证明了使用 PPI 是超广谱 β-内酰胺酶或碳青霉烯酶肠杆菌感染的独立风险因素[55]。Lin 等在 240 名艰难梭菌感染(*Clostridioides difficile* infection, CDI)患者中发现，PPI 的使用与患者的高死亡率有关，这种关联可能是由 PPI 诱导的肠道菌群失调所介导的，PPI 的使用与普氏菌及瘤胃球菌的相对丰度呈负相关，与粪副拟杆菌及艰难梭菌的相对丰度呈正相关，这表明长期使用 PPI 可能会加速 CDI 的复发[56]。Hojo 等发现反流性食管炎患者在接受 PPI 治疗后的第 4 周和第 8 周，粪便中乳杆菌种(加氏乳杆菌亚种、发酵乳杆菌、罗伊氏乳杆菌亚种和瘤胃乳杆菌亚种)和链球菌种相对丰度显著增加[57]。Reveles 等评估了 24 名平均年龄为 71.4 岁的健康老年人使用 PPI 对肠道菌群的影响，发现 PPI 的使用会降低肠道菌群的 α 多样性，降低了放线菌门、毛螺菌科和双歧杆菌科的丰度，增加了链球菌科的丰度，并显著改变了 β 多样性[58]，这与 Imhann 等和 Jackson 等的研究结果一致[59-60]。尽管人们普遍认为 PPIs 是安全的，但是大约 13%的使用者会出现低镁血症。Gommers 等通过动物实验发现奥美拉唑诱发了肠道微生物组成的转变，其研究结果意味着奥美拉唑治疗扰乱了肠道内部环境，并可能对结肠中的 Mg^{2+}吸收构成风险，低肠道微生物群多样性和膳食中镁离子吸收降低与 PPI 引起的低镁血症的发生有关[61]。

2.3 二甲双胍

二甲双胍是源于草药山羊豆的一种双胍类药物，自 20 世纪 50 年代以来一直被用于治疗糖尿病，因其强大的降糖作用、良好的安全性以及相对较低的价格已成为全世界最广泛的 2 型糖尿病(type 2 diabetes mellitus, T2D)处方药[62]。人们普遍认为二甲双胍对 T2D 患者的降糖作用主要是通过抑制肝脏的糖代谢来实现的，但是截至目前，二甲双胍的具体降糖机制仍然存在很大争议，围绕其作用机制的共识依旧难以达成[63]。有研究已经描述了二甲双胍降糖作用的肠道机制，以及在部分病人身上出现的胃肠道副作用，例如腹泻、恶心、呕吐、胀气、腹痛和食欲不振等[64]。Forslund 等的研究发现，二甲双胍处理后个体的肠道埃希氏菌数量显著增加，丁酸和丙酸产生潜力显著增强，这些短链脂肪酸在结肠产生后通过互补机制触发了肠道糖异生(intestinal gluconeogenesis, IGN)，IGN 的增加对葡萄糖和能量稳态有益，减少了肝脏糖异生，这表明了二甲双胍的药效在一定程度上是由微生物介导的[65]。Sun 等通过分析我国 T2D 患者样本，结合体外和动物实验，阐释了二甲双胍改善高血糖等代谢障碍的另一条途径：二甲双胍治疗后肠道菌群组成大幅重塑，脆弱拟杆菌的叶酸和蛋氨酸代谢受到破坏，该菌的丰度及其胆盐水解酶的活性降低，增加了 T2D 患者肠道中甘氨熊去氧胆酸和牛磺熊去氧胆酸的表达，进而拮抗了肠道法尼酯 X 受体信号，改善了血糖稳态[66]。Mueller 等的研究发现二甲双胍治疗改变了菌群的 62 个功能通路，包括一条产乙酸途径和三条糖代谢途径[67]。Bauer

等的研究证明二甲双胍使乳杆菌属的丰度增加，改变了小肠上部的微生物群，并改善了葡萄糖协同转运蛋白-1 感知的葡萄糖调节途径[68]。二甲双胍除了是 T2D 的一线治疗药物之外，人们也注意到它的抗衰老作用[69-70]。Cabreiro 等通过对秀丽隐杆线虫的研究发现了二甲双胍延缓衰老的一个潜在机制，即改变微生物的叶酸和蛋氨酸代谢[71]。使用二甲双胍将改变微生物组，这种作用是影响二甲双胍的抗高血糖治疗效果、胃肠道副作用以及可能的抗衰老作用的重要因素[72]。目前，二甲双胍调节微生物组的确切机制在很大程度上仍是未知的。

2.4 其他药物

其他的许多常用药物也会影响肠道菌群。有证据表明，临床上使用的抗抑郁药具有抗菌作用，特别是对革兰氏阳性菌。选择性 5-羟色胺再摄取抑制剂类、三环类抗抑郁药物等会改变微生物的多样性和组成，药物和菌群之间相互作用可以改变细菌代谢和药物活性和疗效，这可能是它们有抗抑郁效果的部分原因[73-75]。

Deng 等的研究发现，恩格列净增加了血浆代谢物如鞘磷脂的水平，但降低了甘氨鹅脱氧胆酸、顺乌头酸和尿酸的水平，同时，恩格列净上调了短链脂肪酸产生菌如罗斯氏菌属等的水平，降低了埃希氏菌、志贺氏菌属等有害菌的丰度。这些结果表明恩格列净可能是 T2D 合并心血管疾病患者的首选治疗方法，其对心血管的保护作用可能与肠道微生物群和血浆代谢物的变化有关[76]。

除此之外，口服中药在体内不可避免会与肠道细菌接触。传统中药通过调节肠道微生物群在治疗代谢性疾病方面已经显示出了相当可观的效果，例如可以增加益生菌(黏蛋白降解菌)的丰度以调节肠道的完整性和屏障功能；增加短链脂肪酸产生菌以改善宿主的代谢和炎症；减少诱发代谢性内毒素血症和炎症的致病性脂多糖产生菌的丰度[77-79]。近期有研究发现五味子粗多糖及其纯化多糖可以逆转阿尔茨海默病大鼠的肠道菌群失调情况，尤其是纯化多糖 SCP2 显著增加了大鼠粪便中短链脂肪酸的含量，阐明了五味子纯化多糖治疗阿尔茨海默病的潜在机制，为肠道菌群在阿尔茨海默病发病机制中的作用提供了新的见解[80]。Li 等通过抗生素处理以及粪菌移植证明了雷公藤红素的治疗效果是菌群依赖性的，它可能通过调节肠道菌群及其代谢产物来调节免疫，最终缓解结肠炎[81]。大麦叶能够改善结肠炎模型小鼠的炎症和肠道菌群失调情况，促进肠道菌群(如乳杆菌)衍生物肌苷的富集，肌苷可通过 PPARγ 通路作用于肠道上皮细胞，进而对结肠起到保护作用[82]。

3 肠道微生物对药物的影响

3.1 肠道微生物对药物代谢的作用效果

肠道微生物可以通过酶或者一些其他的途径重塑药物结构、改变其药代动力学特性、生物利用度、生物活性或毒性从而影响个体对药物的反应，对原药的激活至关重要，同时也可能会导致药效消失或出现不良反应(表 2)。

肠道菌群可以增强药物疗效。Routy 等发现，患者对免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)的临床反应与 *A. muciniphila* 的相对丰度有关，抗生素抑制了 ICIs 对晚期癌症患者的临床治疗效果。通过口服或者是粪菌移植的方式增加肠道微生物群中 *A. muciniphila* 的数量，可改善程序性死亡受体 1 (programmed cell death protein 1, PD-1)单抗的抗肿瘤作用[97]。一项研究显示了阿尔茨海默病转基因小鼠中由肠道微生物群诱导的姜黄素的生物转化过程，该研究共鉴定出 8 种代谢物，其中许多已被证明具有神经保护作用，表明由肠道微生物群转

表 2　肠道菌代谢药物的效果及其主要产物

Table 2　Effect of metabolism of drugs by intestinal bacteria and their main products

Results of metabolic drugs	Drugs	Main species/Genus	Metabolic enzymes	Reaction	Metabolic products	References
Activation	Prontosil	/	Azo reductase	Reduction reaction	Sulfanilamide	[83]
	Sulfasalazine	/	Azo reductase	Reduction reaction	5-ASA, sulfapyridine	[84]
	Glycyrrhizin	*Eubacterium*	β-glucosidase	Hydrolysis reaction	18 β-glycyrrhetic acid	[85-87]
	Protopanxadiol-type ginsenosides	*Bifidobacterium*, *Provotella oris*, *Bacteroides*	β-glucosidase	Hydrolysis reaction	Compound K, ginsenoside Rh2	[88]
Reactivation	Irinotecan	*Escherichia coli*, *Clostridium perfringens*, *Bacteroides fragilis*	β-glucuronidase	Hydrolysis reaction	SN-38G	[89]
Deactivation	Aspirin	/	Carboxylesterase	Hydrolysis reaction	Salicylic acid	[90]
	Acarbose	*Turicibacter sanguinis*	Acarbose kinase	Phosphorylation reaction	Phosphorylates acarbose	[91]
	Doxorubicin	*Raoultella planticola*	Molybdopterin-dependent enzyme	Hydrolysis reaction	7-deoxydoxorubicino, l7-deoxydoxorubicinolone	[92]
	5-aminosalicylic acid	*Bacteroides*	N-acetyltransferase	Functional group transfer	N-acetyl-5-aminosalicylic acid	[93]
Toxicogenesis	Brivudine	*Bacteroides thetaiotaomicron*, *Bacteroides ovatus*	Purine nucleoside phosphorylase	Phosphorylation reaction	BVU	[94]
	Nitrazepam	*Clostridium*, *Eubacterium*	Nitroreductases	Reduction reaction	7-aminonitrazepam	[95]
	5-flucytosine	*E. coli*	Cytosine deaminase	Functional group transfer	5-fluorouracil	[96]

/: Presents the data unknow.

化的姜黄素可能作为微生物群靶向治疗阿尔茨海默病的有效工具[98-99]。此外，另有研究表明姜黄素的代谢物显示出与姜黄素相似或更高的效力。例如，四氢姜黄素作为自由基淬灭剂比姜黄素更有优势，对神经退行性疾病有治疗作用。这些作用可能是由于其抑制某些细胞因子的释放，包括白细胞介素-6 (IL-6)和肿瘤坏死因子-α (TNF-α)，或抑制 NF-κB 的激活而产生的[100]。

一些前体药物能够被代谢激活从而发挥药效。例如，5-氨基水杨酸(5-ASA)的前药(奥沙拉嗪、柳氮磺吡啶)和磺胺类化合物的前药百浪多息[83-84]。甘草甜素是一种糖基化的皂苷，生物活性差，腹腔注射时对肝脏无保护活性。然而，它可以被肠道微生物群水解为更易吸收的 18β-甘草酸，这种化合物在腹腔注射时显示出肝保护活性[85-87]。

肠道菌群代谢也会使药物失活或降低其生物利用度。阿司匹林对结直肠癌的预防与它对环氧合酶-2 (cyclooxygenase-2, COX-2)的抑制作用有关，Zhao 等经研究发现肠道微生物球形赖氨酸芽孢杆菌(*Lysinibacillus sphaericus*)可以降解阿司匹林，降低其抑制 COX-2 和 β-连环蛋白(β-catenin)的水平，从而削弱了阿司匹林抑制小鼠肠道肿瘤形成的能力[90]。植生拉乌尔菌(*Raoultella planticola*)在厌氧环境中是一种潜在的可使抗癌药物阿霉素失活的菌株，其可将

阿霉素去糖基化，代谢产物为 7-脱氧阿霉素醇和 7-脱氧阿霉素醇非对映异构体[92]。Balaich 等发现并初步证实了口腔及肠道菌群广泛携带的 *Mak* 基因编码的阿卡波糖激酶可能使阿卡波糖磷酸化从而导致药物失活，降低其对糖尿病的治疗效果[91]。有研究表明肠道菌群可能通过腺嘌呤脱氨酶和嘌呤核苷磷酸化酶对甲氨蝶呤(methotrexate, MTX)进行生物转化，肠道菌群组成有差异的类风湿关节炎患者对 MTX 的治疗反应不同[101]。Shang 等的研究发现肠道微生物如鲍曼氏菌等所表达的 CYP51 可参与介导番荔枝酰胺衍生物 N-2-[(4-羟基苯基)-乙基]-2-(2,5-二甲氧基苯基)-3-(3-甲氧基-4-羟基苯基)-丙烯酰胺(N-2-[(4-hydroxy-phenyl)-ethyl]-2-(2,5-dimethoxy-phenyl)-3-(3-methoxy-4-hydroxy-phenyl)-acrylamide, FLZ)的转化，生成的主要产物 M1 被吸收进入血液，而肠道菌群失调会减少机体对 FLZ 的吸收，因此抑制了 FLZ 对帕金森的治疗效果[102]。粪肠球菌的酪氨酸脱羧酶已被证实参与左旋多巴的脱羧作用，从而降低了其生物利用度[103-104]。Mehta 等通过将肠道微生物群宏基因组学、宏转录组学和代谢组学等多组学相结合的方式发现了 2 个蛋白质超家族硫酶和酰基 CoA N-乙酰转移酶与 5-ASA 失活有关，这些肠道微生物乙酰转移酶可以乙酰化 5-ASA 以降低其在炎症性肠病中的临床疗效[105]，该研究为预测炎症性肠病的产生及其后续的个性化治疗提供了科学参考。

药物的无活性代谢产物可经肠道菌群代谢重新恢复药物活性，这也是菌群与肿瘤相关领域的研究热点。一项研究表明肠道内菌群基因编码的 β-葡萄糖醛酸酶可以使排泄至肠道的无活性伊立替康代谢产物恢复活性[89]。

一些药物经肠道微生物代谢后还会产生毒性。Zimmermann 等通过测定和比较普通和无菌小鼠血清中布里夫定及其肝毒性代谢产物(E)-5-(2-乙烯基溴)尿嘧啶(bromovinyluracil, BVU)的含量，表明肠道微生物促进了布里夫定的毒性作用，尤其是多形拟杆菌和卵形拟杆菌[94]。硝西泮的致畸性可能与肠道菌群对其的硝基还原作用有关[95]。

肠道微生物对粪便中未被吸收的残留药物的代谢也会对机体产生潜在的副作用，例如产孢子梭菌将左旋多巴脱氨转化为 3-(3,4-二羟基苯基)丙酸[3-(3,4-dihydroxyphenyl)propionic acid, DHPPA]，该产物对回肠运动有一定程度的抑制，引发便秘等胃肠道症状[106]。

3.2 肠道微生物对药物的代谢机制

目前，肠道菌群调节药物治疗效果的一个主要机制是菌群对药物的生物转化，通过肠道微生物酶的作用，引起一系列还原反应、水解反应、官能团转移、裂解反应等代谢转化反应的发生(图 1)。Tian 等在人类肠道中发现了一种能够降解阿卡波糖的细菌 *Klebsiella grimontii* TD1，该细菌通过分泌一种葡糖苷酶 Apg 可以将阿卡波糖降解为小分子，使其失去活性。这种酶广泛分布在人类肠道微生物中，尤其是克雷伯氏菌[107]。大肠杆菌、粪肠球菌、金黄色葡萄球菌和产气荚膜梭菌等表达的偶氮还原酶能够将偶氮键裂解还原，代谢激活偶氮类前药柳氮磺胺吡啶等药物[83-96,101-108]。肠道微生物产生的硝基还原酶能够将硝基基团还原成氨基，这对含有特殊官能团的苯二氮卓类药物(如硝西泮、氯硝西泮和溴西泮等)的代谢至关重要[109]。β-葡萄糖醛酸酶主要来自厚壁菌门(60%)和拟杆菌门(21%)，这些优势菌群在药物代谢和毒性、肠道癌变以及宿主-菌群相互作用等方面至关重要[110]。β-葡萄糖醛酸酶可将化疗药物盐酸伊立替康的非活性代谢产物解偶联为具有药理活性的 7-乙基-10-羟基喜树碱(SN-38)，从而导致严重的胃肠毒性[111]。

此外，肠道微生物还能够通过影响代谢酶的活性来间接地影响药物代谢[112] (图 1)。越来越多的证据显示，肠道微生物群的缺失对几种代谢酶和运输工具有很大影响[113-114]。一项针对健康志愿者的研究发现，使用改良的“鸡尾酒”探针药物法，选取咖啡因、奥美拉唑和咪达唑仑作为药物探针分别对细胞色素氧化酶(CYP1A2、CYP2C19 和 CYP3A4)的活性进行检测，在服用头孢丙烯后，3 种药物表型参数发生改变，反映了 CYP1A2、CYP2C19 和 CYP3A4 的活性下降。对受试者肠道微生物群落进行分析，结果显示菌群 α 多样性降低，表明 α 多样性的丧失与药物及其代谢物的形成之间存在相关性[115]。使用抗生素治疗会改变肠道微生物的组成，导致相关代谢酶的活性降低，这表明健康和多样性的菌群结构可能是药物代谢酶发挥最佳功能所必需的[115]。CYP3A 是最重要的 CYP450 同源异构体之一，在肝脏和胃肠道高度表达，能够代谢约 50%的临床药物，它与 P 糖蛋白一起影响着口服药物的生物利用度。Selwyn 等通过对比试验发现无菌化明显降低了小鼠体内 CYP3A 基因的表达水平，而无菌小鼠的常规化处理使

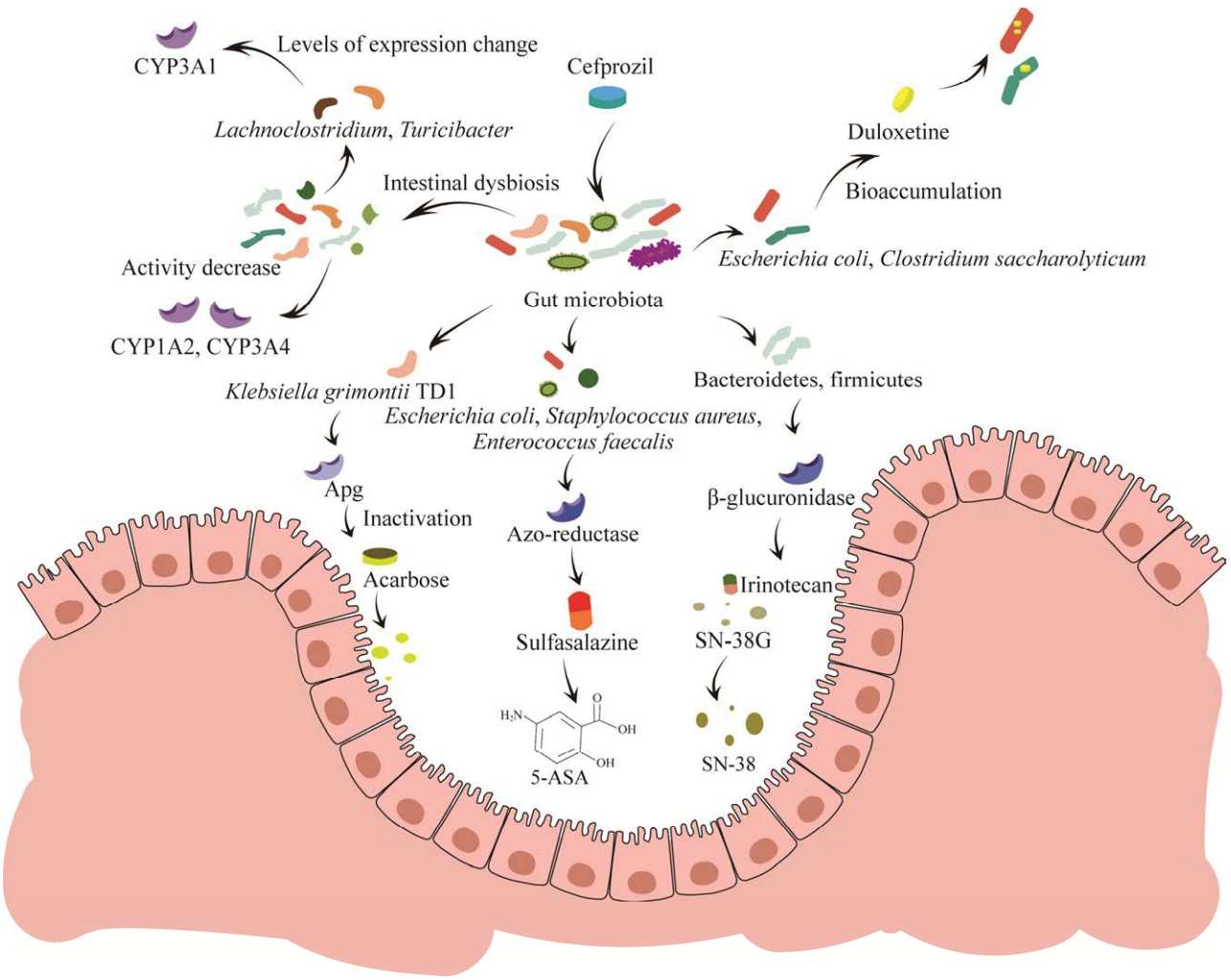

图 1　肠道微生物对药物的作用机制

Figure 1　Mechanism of action of gut microbiota on drugs.

CYP3A 的部分基因表达量恢复正常[116]。Hu 等通过体内外试验证明了 CYP3A1 和转运蛋白在结肠中的表达与某些肠道微生物，如 *Lachnoclostridium*、*Turicibacter* 等的相对丰度有关[117]。

Klünemann 等的研究还揭示了一种新的机制，即肠道细菌将药物积累在自身体内，这样一方面直接减少了药物在体内的生物利用度；另一方面通过改变细菌代谢间接地影响了菌群的组成(图 1)。该研究调查了多种具有代表性的肠道细菌对 15 种结构不同的药物的作用，结果显示有近 30 种细菌与药物的互作方式未曾报道过，且超过一半可以归因于生物积累。这项研究表明细菌将药物储存在细胞内而不进行化学修饰，且在大多数情况下细菌的生长不会受到影响，这一发现挑战了细菌与药物相互作用的主要模式是生物转化的观点[118]。例如，唾液链球菌、解糖梭菌和大肠杆菌可以对抗抑郁药物度洛西汀进行生物积累，该药物在具有生物累积功能菌种的存在下作用于秀丽隐杆线虫时，其抑制运动性的效果被削弱，而在非生物累积菌株存在的情况下，度洛西汀会抑制线虫的运动。这项研究结果表明微生物的生物累积可以影响药物对宿主的作用，肠道细菌的生物积累可能是改变细菌代谢和药物有效性的一种普遍机制[119]。这一定程度上可以解释一些其他研究的结果，例如显示药物被消耗而没有检测到药物的代谢产物[120]。这一发现拓展了人们对细菌与药物相互作用的认知，为进一步阐明菌群对药物疗效和副作用的影响带来了全新的启示。

4 展望

肠道微生物群是一个代谢非常活跃的系统，它与包括肝脏在内的体内经典药物代谢途径共同影响着药物的安全性和有效性，并且也可能是诱导调节药物药理和毒理作用的良好靶点。

目前，功能基因组学、比较基因组学、转录组测序等多种科学技术手段被广泛用于菌群研究，并将菌群代谢与基因紧密联系起来[121-123]，将研究机制具体精确到生物体、基因和酶相联系的水平。Zhou 等介绍了一个基因组的数据分析工具 METABOLIC，其可以基于微生物基因组或宏基因组来分析单个微生物或者菌群的代谢功能网络，结果以各种可视化的形式呈现[124]。稳定同位素探测、荧光原位杂交以及基质辅助激光解吸电离飞行时间质谱等培养组学的方法也可用于检测代谢特定化合物的细胞，这些方法与单细胞基因组学相结合可能有助于探究与难培养肠道菌群有关的活动[125-127]。在药物与肠道微生物互作的研究方面，个体差异仍然是主要的影响因素，破译肠道微生物对药物的转化，还需要将临床研究与模型系统相结合，将肠道菌群纳入生理药代动力学模型。由于肠道微生物组成复杂，在多种条件下测试数种药物和代谢产物存在技术挑战，目前仍然缺乏关于肠道菌群代谢药物的系统性研究。最新的研究提出了一种微生物组衍生代谢筛选的定量试验方案，为药物微生物组的研究提供了新手段，或将进一步推动药物微生物组的发展[120]。

当前，有关微生物群驱动的药物修饰数据库仍未完全挖掘，需要进一步开发和利用。将肠道微生物转化药物的知识进一步整合到药物开发、临床试验设计和实践中，解析易被微生物代谢的官能团，规避这些结构特征，或将其纳入原药，以便在胃肠道内实现选择性激活。此外，深入研究参与有害代谢活动的肠道微生物酶可能是未来新药研发的方向。总之，药物微生物学的研究正在兴起，深入了解微生物群代谢药物或改善(例如抗癌治疗)疗效的作用机制，将为调节肠道微生物群以及宿主健康并提

高临床疗效开辟新的道路，有助于促进临床合理用药和精准治疗。

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