肠道菌介导的药物毒性及机制研究进展

胡家淳, 叶孟亮, 宋建业, 蒋建东*, 王 琰*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室, 北京 100050)

摘要: 药物毒性及机制研究是药物在临床安全使用的重要内容, 备受关注。肠道菌群对药物的代谢转化、药效及作用机制具有重大意义, 可作为代谢器官在物质信息传递、生物转化等方面发挥重要作用。然而, 越来越多的研究发现, 肠道菌与某些药物毒性密切相关。一方面, 药物会在肠道菌的作用下转化成毒性代谢产物诱发药物的直接毒性; 另一方面, 肠道菌群会在药物的作用下改变组成和功能, 导致内源性代谢通路的紊乱, 进而使肠屏障受损而影响其他器官产生药物的间接毒性。本文总结了近年来由肠道菌引发的药物毒性的相关实例, 探讨了肠道菌特征代谢酶可能是口服药物毒性产生的重要原因, 并对未来肠道菌与药物毒性及机制研究进行了展望, 为药物在临床的合理使用及新药的安全性评价提供了新见解。

关键词: 肠道菌; 药物毒性; 药物代谢; 毒理机制; 新药研发

中图分类号: R917 **文献标识码**: A **文章编号**: 0513-4870(2023)12-3549-08

Research progress of drug toxicity mechanism based on the gut microbiota

HU Jia-chun, YE Meng-liang, SONG Jian-ye, JIANG Jian-dong*, WANG Yan*

(*State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*)

Abstract: The exploration of drug toxicity and mechanisms is a vital component in ensuring the safe use of drugs in clinical practice, as this topic has attracted widespread concern. The intestinal flora holds great significance for drug metabolism, efficacy and mechanism, and is an instrumental metabolic organ that facilitates material information transfer and biotransformation. However, an increasing number of studies have shown that intestinal bacteria are closely related to the toxicity of specific drugs. On the one hand, drugs are transformed into toxic metabolites under the influence of intestinal bacteria, thus inducing direct drug toxicity. On the other hand, the composition and function of the intestinal flora are altered under drug influence, resulting in disruption of endogenous metabolic pathways. Consequently, this disruption compromises the intestinal barrier and affects other organs, leading to indirect drug toxicity. This review meticulously compiles recent examples of drug toxicity attributed to intestinal bacteria, explores in depth the contention that metabolic enzymes of gut microbiota may be of great influence on oral drug toxicity, and outlines prospective avenues for future research on gut microbiota and drug toxicity and mechanisms. This not only provides novel perspectives for the judicious clinical utilization of drugs but also offers insights for the safety assessment of innovative pharmaceuticals.

Key words: gut microbiota; drug toxicity; drug metabolism; toxicity mechanism; drug development

收稿日期: 2023-10-24; 修回日期: 2023-11-22.

基金项目: 国家重点研发计划 (2022YFA0806400); 中国医学科学院医学与健康科技创新工程项目 (2021-I2M-1-007, 2022-I2M-2-002, 2021-I2M-1-027, 2021-I2M-1-028); 国家自然科学基金资助项目 (81973290, 82173888); 北京市创新药物非临床药物代谢及药代/药效研究重点实验室 (Z141102004414062).

*通讯作者 E-mail: jiang.jdong@163.com; wangyan@imm.ac.cn

DOI: 10.16438/j.0513-4870.2023-1198

许多临床常用药物是在使用过程中被发现具有不良反应[1-3], 如化药中的对乙酰氨基酚、庆大霉素, 中药中的何首乌、雷公藤等, 因此, 需要对这些药物开展毒性及其机制的研究使其在临床合理使用, 规避风险。随着生命科学的不断发展, 药物毒性研究的内容也得到了扩充与完善, 人们对于药物毒性机制的认识也更加全面与深刻。有研究发现不同的给药方式会造成药物毒性的差异, 而对于一些治疗窗狭窄的药物而言, 微小的生物利用度变化也会引起药物的毒性反应[4-8]。同一种药物对于不同的个体其毒性大小也不相同。这对于过去传统的药物毒性产生机制的认知提出了新的挑战, 亟待解决。

肠道菌是近些年医学领域的研究热点, 越来越多的证据表明肠道菌也为药物在体内的代谢转化及药效分子机制等的研究开辟了新途径。人类肠道微生物组是一个非常复杂又极其重要的微生态系统, 介导了宿主与其环境的相互作用[9,10]。一个健康的成年人的肠道内大约有10^{13}～10^{14}个细菌寄居, 主要定居于小肠末端和结肠部位, 微生物菌群表达的基因数量更是人体细胞的100倍之多, 因此, 人类肠道微生物组被认为是人类的第二套基因组[9,10]。寄生于人体肠道中的微生物具有十分强大的营养、物质代谢、免疫调节与神经调节作用, 能够与宿主自身功能相互补充, 影响着人类的健康与疾病的发生发展。

肠道菌群作为人体重要的代谢性器官, 对外源性物质的生物转化具有重要作用, 而这种转化与药物的药理学意义息息相关[11-13]。肠道微生物组与药物之间的作用是复杂且双向的: 肠道微生物组的组成和功能可能受到药物的影响, 反过来肠道菌也会通过表达代谢酶催化药物结构的改变; 还会与免疫系统互作, 间接地影响机体对药物的敏感度[14,15]。而在这种相互作用的过程中, 不仅会改变药物的活性, 也有可能导致药物毒性的激活, 产生不良反应, 轻者可见腹痛腹泻, 重者可造成实质器官损伤, 甚至是休克, 乃至死亡[16-18]。因此, 研究肠道菌群在药物毒性激活中的角色具有重要的科学意义。

1 肠道菌代谢酶生成毒性代谢产物引起毒性

1.1 药物 糖苷水解酶 (glycoside hydrolyases, GH) 是肠道菌群中革兰阳性厚壁菌门产生的一类重要代谢酶[19], 可催化多种糖苷类物质及内源性激素发生水解反应, 释放苷元, 产生各种生物学效应, 其中, 反应中可能产生毒性物质, 即可引起药物毒性[20,21]。糖苷类成分在中药中分布广泛, 经口服后其是肠道菌表达GH的重要底物。苦杏仁苷主要存在于苦杏、苦扁桃等果仁和叶子中, 具有止咳平喘的作用, 但苦杏仁苷在临床使用中产生了严重的毒性甚至死亡, 主要原因在于苦杏仁苷口服后会在肠道菌GH的作用下水解产生氢氰酸, 氰离子能够与细胞色素氧化酶结合, 影响正常呼吸, 使机体因组织缺氧陷入窒息状态[22,23]。洋地黄毒苷在临床上主要用于慢性心功能不全, 能选择性地直接作用于心脏。洋地黄毒苷在植物毛花洋地黄中多以其前体形式毛花一级苷A存在, 毛花一级苷A能被肠道菌GH水解失去1分子葡萄糖后, 再去乙酰基生成洋地黄毒苷, 后者在体内蓄积产生毒性[24,25]。京尼平苷是常用中药栀子中环烯醚萜苷类主要成分之一, 具有抗炎、抗氧化和抗癌等活性, 京尼平苷在体内可被肠道菌群的GH水解成京尼平 (genipin, GP)[26]。Khanal等[27]研究发现, GP可能通过调节Bcl-2和caspase-3的活性而诱导细胞凋亡, 且GP诱导的毒性与ROS的产生有关。苏铁素是热带植物苏铁种子所含的糖苷类毒素, 有报道指出中药白土苓中也有检出苏铁素的存在, 而其致癌性是由于所含的氧化偶氮类苷—苏铁苷经肠道菌的GH水解后产生的苏铁素。苏铁素长期或一次喂饲或灌肠, 可使大鼠发生乳癌、肝癌、肾癌、肠癌, 使小鼠发生肺腺癌, 也能使豚鼠发生肿瘤[28-30]。伊立替康是一种抗肿瘤的静脉制剂, 主要用于治疗晚期大肠癌, 接受伊立替康治疗的患者约40%都曾经历严重的腹泻[31]。伊立替康通常会以一种非活性的形式注射到患者体内, 在肝脏中代谢生成活性形式SN-38, SN-38再由UGT1A1葡萄糖醛酸化后生成SN-38G, SN-38G被排入肠道中, 肠道菌表达的GH会重新将其水解产生SN-38而损伤肠道内壁组织产生迟发性腹泻[32], 伊立替康是肠道菌代谢酶介导的发生肝肠循环的典型例证药物。

大肠杆菌表达的嘌呤核苷磷酸化酶 (purine nucleoside phosphorylase, PNP) 能够催化嘌呤核苷分解形成核糖-1-磷酸和相应的嘌呤碱基[33,34]。临床上常用的抗病毒药物如溴夫定, 属于核苷类似物, 通过与病毒DNA聚合酶的作用, 抑制病毒复制[35-37]。溴夫定能够通过肠道菌来源的PNP酶转化成具有肝毒性的溴苯尿嘧啶, 并且在无菌小鼠中溴苯尿嘧啶的全身暴露量减少, 后续实验也证明循环中的溴苯尿嘧啶约80%是由肠道菌产生的, 揭示了肠道微生物组对血清溴苯尿嘧啶水平的贡献[38]。

除了水解反应之外, 还原反应也是肠道菌对药物进行结构修饰的一种重要方式, 例如硝基还原反应。肠道菌表达的硝基还原酶 (nitroreductase, NR) 是完成该项反应的重要代谢酶[39]。NR可催化多种外源硝基芳香族、醌类和黄素类化合物的还原反应[40]。甲硝唑是硝基咪唑类抗菌药, 在所有硝基咪唑类药物中, 它的临床不良

反应最为明显[41,42]。甲硝唑的毒性来源于肠道菌NR代谢后的活性中间体, 该中间体能够与DNA相互作用, 因此, 具有一定的致突变风险; 同时, 动物水平的研究也发现甲硝唑对小鼠的致突变作用呈现肠道菌依赖的特征[43]。苯二氮䓬类药物硝西泮具有镇静催眠和抗惊厥作用, 其7位上的硝基能在肠道菌NR的作用下被还原成氨基, 该代谢产物会产生致畸作用, 而在伪无菌大鼠模型中硝西泮的畸形作用被显著减小了[44-46]。

1.2 食物 除药物以外, 食物也能被肠道微生物转化, 生成毒性代谢物。例如鱼、牛肉和鸡蛋中富含的胆碱能够在肠道菌表达的胆碱-TMA裂解酶的作用下转化为三甲胺 (TMA), TMA在肠道中被吸收, 经门静脉进入肝脏后被黄素单加氧酶 (flavin-containing monooxygenases, FMOs) 氧化生成三甲胺-*N*-氧化物 (TMAO)[47]。越来越多的证据表明, TMAO是心血管疾病的重要危险因素, 能够加速动脉粥样硬化的进程[48-51]。膳食–肠道微生物–肝脏共同组成了TMAO的生物合成途径。TMA-TMAO通路是饮食、肠道微生物群、心血管疾病之间的一种新的交叉, 也为心血管疾病的治疗提供了可行的靶点[52]。

另外, 膳食蛋白质中含有的芳香族氨基酸色氨酸和酪氨酸也会在肠道微生物的作用下产生吲哚酚和对甲酚, 两者吸收进入循环后在肝脏被硫酸化生成硫酸对甲酚 (*p*-cresyl sulfate, PCS) 和硫酸吲哚酚 (indoxyl sulfate, IS), 并经肾脏有机阴离子转运体转运进入肾脏[53,54]。有研究表明, 慢性肾病患者血浆中PCS和IS的水平与健康人相比, 分别升高了54倍和17倍, 两者在循环中极易与白蛋白结合, 无法通过血液透析的方式有效清除, 而蓄积在体内的PCS和IS能够激活炎症及纤维化相关的信号通路, 加速肾病的进程[55-57]。表1总结了上述肠道菌特征酶介导的典型化合物毒性产生的代谢过程及反应类型。

2 肠道菌结构改变影响内源性代谢通路产生毒性

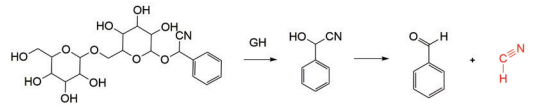
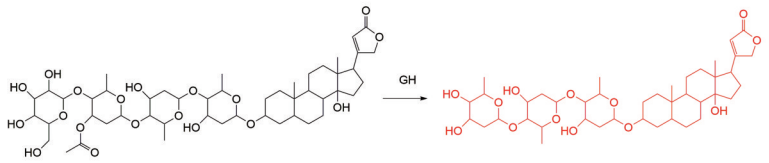
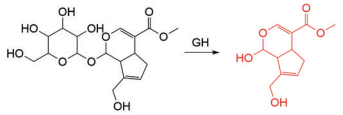
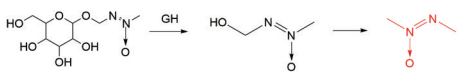
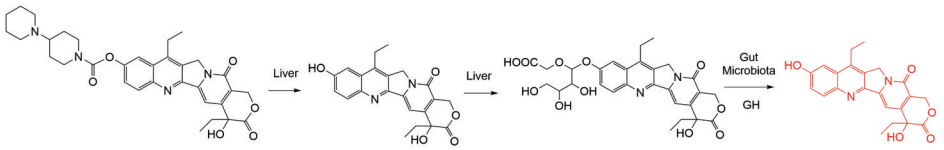
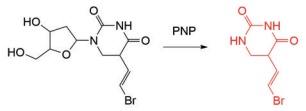
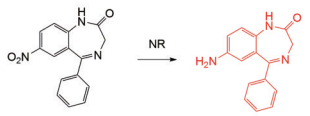
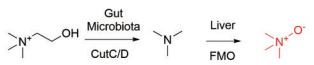
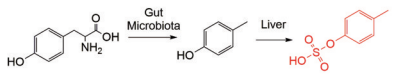
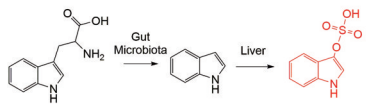
2.1 药物 有些药物虽然不会被肠道菌表达的酶代谢转化, 但会影响部分肠道菌群的生长, 进而影响肠道菌产生的内源性代谢产物, 导致下游的代谢通路出现紊乱。抗生素就是其中之一, 抗生素不仅会抑制人体内的致病菌, 还会抑制一些有益菌, 导致菌群结构的失调, 进而产生不良反应[58]。比如阿莫西林和克林霉素抑制梭杆菌属[59]、头孢菌素和克林霉素抑制阿克曼菌属[60], 菌落数都显示显著性较少 ($P < 0.001$)。流行病学调查发现, 抗生素相关性腹泻的发病率高达30%[61]。这是由于结肠上皮细胞正常生理代谢所需的能量由肠道菌群发酵产生的大量短链脂肪酸提供。这一过程关乎肠道屏障的稳态。抗生素引起的肠道菌群锐减, 严重影响肠道内多糖的发酵及短链脂肪酸的合成, 导致肠道物理屏障被破坏; 同时过多未经发酵的多糖无法被人体吸收, 长期在肠道滞留会导致渗透性腹泻[62]。肠道菌群也参与人体的胆汁酸代谢, 大部分胆汁酸经由“肝肠循环”在肠壁被重新吸收进入肝脏。仅有1%～2%的胆汁酸在结直肠内经过肠道细菌代谢转化后生成次级胆汁酸被排出体外。而在使用抗生素后具有代谢能力的细菌数量减少, 导致未被吸收的初级胆酸无法被代谢成次级胆酸, 初级胆酸如鹅脱氧胆酸为强刺激物, 长期滞留肠道内可导致患者出现分泌性腹泻[62]。

质子泵抑制剂 (proton pump inhibitor, PPI) 如泮托拉唑、奥美拉唑等主要用于治疗胃酸相关疾病, 如消化性溃疡、胃食管反流和消化不良, 以及预防非甾体抗炎药诱导的胃十二指肠肿大和出血。大型队列研究表明, PPI是除抗生素之外与肠道微生物组结构改变最相关的药物[63,64]。总体而言, PPI使用者的菌群特征表现为肠杆菌科、肠球菌科和乳酸杆菌科的丰度增加以及瘤胃球菌科和双歧杆菌科的丰度减少。而PPI诱导的微生物组变化可能导致临床上的严重不良反应。例如导致艰难梭菌、弯曲杆菌和沙门氏菌等致病菌在肠道内的定植能力增强, 进而诱发感染。此外, PPI也可能通过肠道微生物群的变化影响代偿性肝硬化的临床病程[65,66]。

2.2 不良习惯 除了药物会影响人体肠道菌群的结构外, 一系列不良的生活习惯也会对肠道菌群的结构产生影响。例如饮酒、吸烟等。广泛的研究证实, 过量饮酒会加速肝脏疾病的发展进程: 从肝脂肪变性发展为脂肪性肝炎, 并最终发展为危及生命的肝硬化[67-69]。但是Martino等[70]证实乙醇并不会直接被肠道菌群代谢, 而是会刺激肠道菌群产生乙酸盐。乙酸盐是一种细胞代谢的营养素, 在食欲调节、能量消耗和免疫反应中起作用。在适量水平下, 能促进人体健康, 但在过量时, 它与肝损伤、癌症等疾病呈正相关, 是潜在的风险因素[71-73]。

吸烟是众多疾病的主要危险因素之一。香烟烟雾是一种复杂的混合物, 包括尼古丁、醛类、多环芳烃和重金属等。Bai等[74]研究显示, 与不吸烟的小鼠相比, 暴露于香烟烟雾中的小鼠结直肠肿瘤发病率明显增加, 肠道微生物也出现明显失调, 包括长尾蛋菌 (*Eggerthella lenta*) 的富集和副芽孢杆菌 (*Parabobacterides distasonis*) 和乳酸菌 (*Lactobacillus* spp) 的减少。代谢组学分析显示, 烟雾暴露小鼠结肠中牛磺脱氧胆酸 (TDCA) 显著增加, 后续实验也表明TDCA下游的MAPK/ERK信号通路也出现显著增强。而无菌小鼠移植了烟雾暴露小鼠的粪便后表现出与模型组相同的特征。说明吸烟引起的肠道菌群失调改变了肠道的胆汁酸代谢, 激活了结肠上皮中致癌的MAPK/ERK

Table 1 Typical toxic metabolism reactions induced by characteristic enzyme of gut microbiota

Compound	Metabolic process	Metabolic type
Amygdalin		Hydrolysis
Digitoxin		Hydrolysis
Geniposide		Hydrolysis
Cycasin		Hydrolysis
Irinotecan		Hydrolysis
Brivudine		Hydrolysis
Metronidazole		Nitroreduction
Nitrazepam		Nitroreduction
Choline		Lysis
Tryptophan		Decarboxylation, deamination
Tyrosine		Decarboxylation, deamination

信号通路, 进而促进了结直肠癌的发生发展。

3 药物引起肠屏障受损导致毒物移位

肠道作为人体内最大的免疫器官对健康有着重要影响。肠黏膜屏障的受损是级联炎症反应和多器官功能障碍综合征的重要原因[75,76]。化疗药物在使用过程中对免疫功能的损伤已有许多报道。许多化疗药物可以引起免疫细胞数量变化, 导致免疫调控异常, 如$CD4^+/CD8^+$ T淋巴细胞比例失调, IgA^+浆细胞水平下降, 进而释放炎性介质, 造成肠黏膜免疫功能紊乱[77]。也可以通过直接损伤肠黏膜或上皮细胞的方式, 致使肠道细胞间的紧密连接被破坏, 肠道屏障通透性增加, 使得致病菌和细菌产生的毒素能够穿过肠壁, 移位至其他器官, 产生次级损伤。在这一过程中, 组织损伤产生的大量活性氧自由基也会破坏各类细胞的膜结构, 导致细胞死亡[78]。Manzano等[79]在动物模型上发现经5-氟尿嘧啶处理后肠腔内谷胱甘肽循环被破坏, 机体内的抗氧化平衡机制被打破, 对自由基清除能力下降。也有研究发现5-氟尿嘧啶可以通过p53依赖机制引起大肠黏膜细胞凋亡进而损伤肠屏障, 引起下游的级联反应[80-82]。

4 肠道菌群通过调控肝脏代谢酶间接导致药物毒性

对乙酰氨基酚 (acetaminophen, APAP) 作为最常用的解热镇痛类非处方药, 长期使用引起的肝毒性受

到广泛关注。许多研究者认为APAP的毒性是由代谢引起的[83,84]。APAP在体内主要通过两种途径代谢, 一是葡萄糖醛酸化和硫酸化途径, 大部分APAP会酯化形成葡萄糖酸苷和硫酸盐, 进而被排出体外; 二是CYP450氧化途径, 当酯化能力达到饱和后, CYP2E1会催化APAP生成具有毒性的中间代谢产物*N*-乙酰对苯醌亚胺 (*N*-acetyl-*p*-benzo-quinone imine, NAPQI), NAPQI可以与细胞内的谷胱甘肽 (GSH) 结合成无毒的巯基尿酸随尿液排出体外; 但当GSH耗竭时, NAPQI会通过半胱氨酸残基直接与细胞蛋白结合, 破坏细胞完整性从而导致肝细胞坏死[85-89]。

近年来, 肠道菌群影响宿主对APAP产生肝毒性敏感性的理论也受到越来越多的关注, Lee等[90]发现抗生素干预后, APAP在血液中的代谢物出现APAP-GSH结合物增多而APAP-硫酸盐结合物减少的现象, 说明肠道菌群在APAP的代谢中可能起到重要作用。Toda等[91]研究证实, 肠道细菌产生的次级胆汁酸LCA可以通过激活核转录因子孕烷X受体 (PXR) 和组成型雄甾烷受体 (constitutive androstane receptor, CAR), 从而增加肝脏CYP的表达。而外源性饮食干预也能够通过影响肠道菌从而导致APAP肝损伤敏感性改变, Cho等[92]发现果糖干预下小鼠肠道菌群的组成会显著改变, 进而减轻APAP导致的肝损伤, 其分子机制与影响CYP450酶的表达相关, 果糖饮食会增加粪厌氧棒杆菌属的丰度, 该菌与肝脏 *Cyp2e1* 和 *Cyp1a2* mRNA水平负相关, 与GSH水平正相关。说明补充果糖可以通过降低代谢APAP的CYP450酶活性从而减轻肝损伤。

5 总结与展望

药物的毒性制约了药物在临床的应用。为了尽可能避免毒性并安全地使用药物, 就需要对药物的毒性产生机制有更全面的认识。肠道菌群研究已经成为药物研发领域的热点, 而当前不断发展的基因组学、转录组学、蛋白质组学和代谢组学等技术也为进一步认识“肠道微生物–宿主–药物”三者之间互作调控提供了关键技术[93,94]。基于肠道菌的研究可作为一个全新的视角来认识和评价药物的毒性, 为阐明药物毒性物质基础及分子机制提供了新思路。未来调节肠道微生物或菌源药物代谢酶将有可能成为临床上降低药物毒副作用的新手段。

宿主、肠道菌和药物三者之间的相互作用是药物发挥药效作用的重要途径, 但是药物与肠道菌的相互作用是一把双刃剑。一方面, 肠道菌可以将原本无活性的药物转化产生活性代谢物; 另一方面, 肠道菌也有可能导致药物原有药效的降低, 甚至造成多脏器损伤。鉴于肠道菌群对药物药效和毒性的潜在影响, 因此, 肠道微生物群对药物体内代谢/药效/毒性作用的评估应当成为药物整个开发过程中的一个重要组成部分。

此外, 在精准医疗走向微观化的时代, 基于对单一个体的菌群研究, 可以帮助加深对宿主–菌群–药物的互作的理解, 结合组学技术, 实现对菌群的精准干预、预测个体对药物反应等。这些都有助于更好实现个性化治疗[95-98]。这也意味着未来或许可以通过改变微生物群, 来提高药物疗效或减少不良反应。比如, 可以通过改变饮食习惯, 或是采取粪菌移植的方式来改变肠道微生物群, 进而延缓疾病进程[99-101]。

然而, 由于肠道微生物的种类具有多样性、微生物之间以及微生物与宿主代谢之间关系极其复杂, 目前对于肠道微生物组成和功能的认识还存在欠缺。尽管研究人员已经发现和证实了肠道微生物如何影响数十种临床上常用药物的代谢与毒性产生[102-104], 但是相对于数千种临床药物来说, 肠道微生物是否以及如何影响药物的代谢过程与毒性效应的机制还有待深入的探索与研究。

作者贡献: 王琰负责整体文章的设计与指导; 胡家淳负责全文的撰写; 叶孟亮负责图表的设计与制作; 宋建业负责文献的查阅; 蒋建东和王琰负责对论文进行修改。

利益冲突: 所有作者无任何利益冲突。

References

[1] Lee WM. Acetaminophen (APAP) hepatotoxicity-isn't it time for APAP to go away? [J]. J Hepatol, 2017, 67: 1324-1331.

[2] Zhai XR, Zou ZS, Wang JB, et al. Herb-induced liver injury related to *Reynoutria multiflora* (Thunb.) Moldenke: risk factors, molecular and mechanistic specifics [J]. Front Pharmacol, 2021, 12: 738577.

[3] Haas JF. A problem-oriented approach to safety issues in drug development and beyond [J]. Drug Saf, 2004, 27: 555-567.

[4] Danesi R, De Braud F, Fogli S, et al. Pharmacogenetic determinants of anti-cancer drug activity and toxicity [J]. Trends Pharmacol Sci, 2001, 22: 420-426.

[5] Basile AO, Yahi A, Tatonetti NP. Artificial intelligence for drug toxicity and safety [J]. Trends Pharmacol Sci, 2019, 40: 624-635.

[6] Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management [J]. Lancet, 2000, 356: 1255-1259.

[7] Tosca EM, Bartolucci R, Magni P, et al. Modeling approaches for reducing safety-related attrition in drug discovery and development: a review on myelotoxicity, immunotoxicity, cardiovascular toxicity, and liver toxicity [J]. Expert Opin Drug Discov, 2021, 16: 1365-1390.

[8] Pognan F, Beilmann M, Boonen HCM, et al. The evolving role of investigative toxicology in the pharmaceutical industry [J].

Nat Rev Drug Discov, 2023, 22: 317-335.

[9] Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota [J]. Nat Rev Gastroenterol Hepatol, 2019, 16: 35-56.

[10] Lynch SV, Pedersen O. The human intestinal microbiome in health and disease [J]. N Engl J Med, 2016, 375: 2369-2379.

[11] Kåhrström CT, Pariente N, Weiss U. Intestinal microbiota in health and disease [J]. Nature, 2016, 535: 47.

[12] Meijers B, Evenepoel P, Anders HJ. Intestinal microbiome and fitness in kidney disease [J]. Nat Rev Nephrol, 2019, 15: 531-545.

[13] Rosshart SP, Vassallo BG, Angeletti D, et al. Wild mouse gut microbiota promotes host fitness and improves disease resistance [J]. Cell, 2017, 171: 1015-1028.

[14] 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.

[15] Weersma RK, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome [J]. Gut, 2020, 69: 1510-1519.

[16] Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, et al. Mapping human microbiome drug metabolism by gut bacteria and their genes [J]. Nature, 2019, 570: 462-467.

[17] Javdan B, Lopez JG, Chankhamjon P, et al. Personalized mapping of drug metabolism by the human gut microbiome [J]. Cell, 2020, 181: 1661-1679.

[18] Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, et al. Separating host and microbiome contributions to drug pharmacokinetics and toxicity [J]. Science, 2019, 363: 9931.

[19] Chen ZQ, Tang S, Zhang CX, et al. Research progress on the interactions between gut bacterial β-glucuronidases and Chinese herbal medicines [J]. Acta Pharm Sin (药学学报), 2022, 57: 3465-3479.

[20] Kannan P, Shafreen MM, Achudhan AB, et al. A review on applications of β-glucosidase in food, brewery, pharmaceutical and cosmetic industries [J]. Carbohydr Res, 2023, 530: 108855.

[21] Ouyang B, Wang G, Zhang N, et al. Recent advances in β-glucosidase sequence and structure engineering: a brief review [J]. Molecules, 2023, 28: 4990.

[22] He XY, Wu LJ, Wang WX, et al. Amygdalin - a pharmacological and toxicological review [J]. J Ethnopharmacol, 2020, 254: 112717.

[23] Barakat H, Aljutaily T, Almujaydil MS, et al. Amygdalin: a review on its characteristics, antioxidant potential, gastrointestinal microbiota intervention, anticancer therapeutic and mechanisms, toxicity, and encapsulation [J]. Biomolecules, 2022, 12: 1514.

[24] Ochs HR, Smith TW. Reversal of advanced digitoxin toxicity and modification of pharmacokinetics by specific antibodies and Fab fragments [J]. J Clin Invest, 1977, 60: 1303-1313.

[25] Dey P. The pharmaco-toxicological conundrum of oleander: potential role of gut microbiome [J]. Biomed Pharmacother, 2020, 129: 110422.

[26] Hou YC, Tsai SY, Lai PY, et al. Metabolism and pharmacokinetics of genipin and geniposide in rats [J]. Food Chem Toxicol, 2008, 46: 2764-2769.

[27] Khanal T, Kim HG, Choi JH, et al. Biotransformation of geniposide by human intestinal microflora on cytotoxicity against HepG2 cells [J]. Toxicol Lett, 2012, 209: 246-254.

[28] Morgan RW, Hoffmann GR. Cycasin and its mutagenic metabolites [J]. Mutat Res, 1983, 114: 19-58.

[29] Laqueur GL, Spatz M. Toxicology of cycasin [J]. Cancer Res, 1968, 28: 2262-2267.

[30] Sieber SM, Correa P, Dalgard DW, et al. Carcinogenicity and hepatotoxicity of cycasin and its aglycone methylazoxymethanol acetate in nonhuman primates [J]. J Natl Cancer Inst, 1980, 65: 177-189.

[31] de Man FM, Goey AKL, van Schaik RHN, et al. Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics, and pharmacogenetics [J]. Clin Pharmacokinet, 2018, 57: 1229-1254.

[32] Alexander JL, Wilson ID, Teare J, et al. Gut microbiota modulation of chemotherapy efficacy and toxicity [J]. Nat Rev Gastroenterol Hepatol, 2017, 14: 356-365.

[33] Johan UUM, Rahman RNZRA, Kamarudin NHA, et al. An integrated overview of bacterial carboxylesterase: structure, function and biocatalytic applications [J]. Colloids Surf B Biointerfaces, 2021, 205: 111882.

[34] Chen F, Zhang B, Parker RB, et al. Clinical implications of genetic variation in carboxylesterase drug metabolism [J]. Expert Opin Drug Metab Toxicol, 2018, 14: 131-142.

[35] Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage [J]. Proc Natl Acad Sci U S A, 2004, 101: 15718-15723.

[36] Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy [J]. Nat Rev Clin Oncol, 2023, 20: 429-452.

[37] Chrysostomou D, Roberts LA, Marchesi JR, et al. Gut microbiota modulation of efficacy and toxicity of cancer chemotherapy and immunotherapy [J]. Gastroenterology, 2023, 164: 198-213.

[38] Collins SL, Patterson AD. The gut microbiome: an orchestrator of xenobiotic metabolism [J]. Acta Pharm Sin B, 2020, 10: 19-32.

[39] Williams EM, Little RF, Mowday AM, et al. Nitroreductase gene-directed enzyme prodrug therapy: insights and advances toward clinical utility [J]. Biochem J, 2015, 471: 131-153.

[40] Searle PF, Chen MJ, Hu L, et al. Nitroreductase: a prodrug-activating enzyme for cancer gene therapy [J]. Clin Exp Pharmacol Physiol, 2004, 31: 811-816.

[41] Lamp KC, Freeman CD, Klutman NE, et al. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials [J]. Clin Pharmacokinet, 1999, 36: 353-373.

[42] Edwards DI. Mechanisms of selective toxicity of metronidazole and other nitroimidazole drugs [J]. Br J Vener Dis, 1980, 56:

285-290.

[43] Dingsdag SA, Hunter N. Metronidazole: an update on metabolism, structure-cytotoxicity and resistance mechanisms [J]. J Antimicrob Chemother, 2018, 73: 265-279.

[44] Kim DH. Gut microbiota-mediated drug-antibiotic interactions [J]. Drug Metab Dispos, 2015, 43: 1581-1589.

[45] Takeno S, Hirano Y, Kitamura A, et al. Comparative developmental toxicity and metabolism of nitrazepam in rats and mice [J]. Toxicol Appl Pharmacol, 1993, 121: 233-238.

[46] Konishi K, Fukami T, Gotoh S, et al. Identification of enzymes responsible for nitrazepam metabolism and toxicity in human [J]. Biochem Pharmacol, 2017, 140: 150-160.

[47] Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease [J]. Nature, 2011, 472: 57-63.

[48] Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease [J]. Circ Res, 2020, 127: 553-570.

[49] Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders [J]. Gut, 2021, 70: 1174-1182.

[50] Tang WH, Wang Z, Kennedy DJ, et al. Gut microbiota-dependent trimethylamine *N*-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease [J]. Circ Res, 2015, 116: 448-455.

[51] Fang Q, Liu N, Zheng B, et al. Roles of gut microbial metabolites in diabetic kidney disease [J]. Front Endocrinol (Lausanne), 2021, 12: 636175.

[52] Ma SR, Tong Q, Lin Y, et al. Berberine treats atherosclerosis *via* a vitamine-like effect down-regulating choline-TMA-TMAO production pathway in gut microbiota [J]. Signal Transduct Target Ther, 2022, 7: 207.

[53] Yang T, Richards EM, Pepine CJ, et al. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease [J]. Nat Rev Nephrol, 2018, 14: 442-456.

[54] Feng YL, Cao G, Chen DQ, et al. Microbiome-metabolomics reveals gut microbiota associated with glycine-conjugated metabolites and polyamine metabolism in chronic kidney disease [J]. Cell Mol Life Sci, 2019, 76: 4961-4978.

[55] Wang X, Yang S, Li S, et al. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents [J]. Gut, 2020, 69: 2131-2142.

[56] Koppe L, Soulage CO. The impact of dietary nutrient intake on gut microbiota in the progression and complications of chronic kidney disease [J]. Kidney Int, 2022, 102: 728-739.

[57] Vanholder R, Schepers E, Pletinck A, et al. The uremic toxicity of indoxyl sulfate and *p*-cresyl sulfate: a systematic review [J]. J Am Soc Nephrol, 2014, 25: 1897-1907.

[58] Chi XY, Lin Y, Jiang JD. Research progress of intestinal microecological disorders caused by antibiotics and the treatment [J]. Acta Pharm Sin (药学学报), 2023, 58: 1981-1987.

[59] Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections [J]. Clin Infect Dis, 2010, 50 (Suppl 1): S16-S23.

[60] Laiman V, Lo YC, Chen HC, et al. Effects of antibiotics and metals on lung and intestinal microbiome dysbiosis after subchronic lower-level exposure of air pollution in ageing rats [J]. Ecotoxicol Environ Saf, 2022, 246: 114164.

[61] Yang B, Lu P, Li MX, et al. A meta-analysis of the effects of probiotics and synbiotics in children with acute diarrhea [J]. Medicine (Baltimore), 2019, 98: 16618.

[62] Johnston BC, Goldenberg JZ, Parkin PC. Probiotics and the prevention of antibiotic-associated diarrhea in infants and children [J]. JAMA, 2016, 316: 1484-1485.

[63] Reveles KR, Ryan CN, Chan L, et al. Proton pump inhibitor use associated with changes in gut microbiota composition [J]. Gut, 2018, 67: 1369-1370.

[64] Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complications and risks [J]. Nat Rev Gastroenterol Hepatol, 2017, 14: 697-710.

[65] Bajaj JS, Acharya C, Fagan A, et al. Proton pump inhibitor initiation and withdrawal affects gut microbiota and readmission risk in cirrhosis [J]. Am J Gastroenterol, 2018, 113: 1177-1186.

[66] Haastrup PF, Thompson W, Søndergaard J, et al. Side effects of long-term proton pump inhibitor use: a review [J]. Basic Clin Pharmacol Toxicol, 2018, 123: 114-121.

[67] Dubinkina VB, Tyakht AV, Odintsova VY, et al. Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease [J]. Microbiome, 2017, 5: 141.

[68] Wang R, Tang R, Li B, et al. Gut microbiome, liver immunology, and liver diseases [J]. Cell Mol Immunol, 2021, 18: 4-17.

[69] Leung C, Rivera L, Furness JB, et al. The role of the gut microbiota in NAFLD [J]. Nat Rev Gastroenterol Hepatol, 2016, 13: 412-425.

[70] Martino C, Zaramela LS, Gao B, et al. Acetate reprograms gut microbiota during alcohol consumption [J]. Nat Commun, 2022, 13: 4630.

[71] Deghima A, Righi N, Rosales-Conrado N, et al. Anti-inflammatory activity of ethyl acetate and *n*-butanol extracts from *Ranunculus macrophyllus* Desf. and their phenolic profile [J]. J Ethnopharmacol, 2021, 265: 113347.

[72] Portincasa P, Bonfrate L, Vacca M, et al. Gut microbiota and short chain fatty acids: implications in glucose homeostasis [J]. Int J Mol Sci, 2022, 23: 1105.

[73] Hernández MAG, Canfora EE, Jocken JWE, et al. The short-chain fatty acid acetate in body weight control and insulin sensitivity [J]. Nutrients, 2019, 11: 1943.

[74] Bai X, Wei H, Liu W, et al. Cigarette smoke promotes colorectal cancer through modulation of gut microbiota and related metabolites [J]. Gut, 2022, 71: 2439-2450.

[75] Nagasaka M, Sexton R, Alhasan R, et al. Gut microbiome and

response to checkpoint inhibitors in non-small cell lung cancer-a review [J]. Crit Rev Oncol Hematol, 2020, 145: 102841.

[76] Sougiannis AT, VanderVeen BN, Davis JM, et al. Understanding chemotherapy-induced intestinal mucositis and strategies to improve gut resilience [J]. Am J Physiol Gastrointest Liver Physiol, 2021, 320: G712-G719.

[77] Pellicci DG, Koay HF, Berzins SP. Thymic development of unconventional T cells: how NKT cells, MAIT cells and *γδ* T cells emerge [J]. Nat Rev Immunol, 2020, 20: 756-770.

[78] Niu B, Liao K, Zhou Y, et al. Application of glutathione depletion in cancer therapy: enhanced ROS-based therapy, ferroptosis, and chemotherapy [J]. Biomaterials, 2021, 277: 121110.

[79] Manzano M, Bueno P, Rueda R, et al. Intestinal toxicity induced by 5-fluorouracil in pigs: a new preclinical model [J]. Chemotherapy, 2007, 53: 344-355.

[80] Longley DB, Harkin DP, Johnston PG. 5-Fluorouracil: mechanisms of action and clinical strategies [J]. Nat Rev Cancer, 2003, 3: 330-338.

[81] Yang C, Song J, Hwang S, et al. Apigenin enhances apoptosis induction by 5-fluorouracil through regulation of thymidylate synthase in colorectal cancer cells [J]. Redox Biol, 2021, 47: 102144.

[82] Smeekens JM, Johnson-Weaver BT, Hinton AL, et al. Fecal IgA, antigen absorption, and gut microbiome composition are associated with food antigen sensitization in genetically susceptible mice [J]. Front Immunol, 2021, 11: 599637.

[83] Brune K, Renner B, Tiegs G. Acetaminophen/paracetamol: a history of errors, failures and false decisions [J]. Eur J Pain, 2015, 19: 953-965.

[84] Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure [J]. Hepatology, 1995, 22: 767-773.

[85] Heard K, Green JL, Anderson V, et al. Paracetamol (acetaminophen) protein adduct concentrations during therapeutic dosing [J]. Br J Clin Pharmacol, 2016, 81: 562-568.

[86] Zhao Y, Harmatz JS, Epstein CR, et al. Favipiravir inhibits acetaminophen sulfate formation but minimally affects systemic pharmacokinetics of acetaminophen [J]. Br J Clin Pharmacol, 2015, 80: 1076-1085.

[87] Miettinen TP, Björklund M. NQO2 is a reactive oxygen species generating off-target for acetaminophen [J]. Mol Pharm, 2014, 11: 4395-4404.

[88] Schneider KM, Elfers C, Ghallab A, et al. Intestinal dysbiosis amplifies acetaminophen-induced acute liver injury [J]. Cell Mol Gastroenterol Hepatol, 2021, 11: 909-933.

[89] Zeng Y, Wu R, Wang F, et al. Liberation of daidzein by gut microbial *β*-galactosidase suppresses acetaminophen-induced hepatotoxicity in mice [J]. Cell Host Microbe, 2023, 31: 766-780.

[90] Lee SH, An JH, Lee HJ, et al. Evaluation of pharmacokinetic differences of acetaminophen in pseudo germ-free rats [J]. Biopharm Drug Dispos, 2012, 33: 292-303.

[91] Toda T, Saito N, Ikarashi N, et al. Intestinal flora induces the expression of Cyp3a in the mouse liver [J]. Xenobiotica, 2009, 39: 323-334.

[92] Cho S, Tripathi A, Chlipala G, et al. Fructose diet alleviates acetaminophen-induced hepatotoxicity in mice [J]. PLoS One, 2017, 12: e0182977.

[93] Yuan X, Chen B, Duan Z, et al. Depression and anxiety in patients with active ulcerative colitis: crosstalk of gut microbiota, metabolomics and proteomics [J]. Gut Microbes, 2021, 13: 1987779.

[94] Adak A, Khan MR. An insight into gut microbiota and its functionalities [J]. Cell Mol Life Sci, 2019, 76: 473-493.

[95] Jia Q, Wang L, Zhang X, et al. Prevention and treatment of chronic heart failure through traditional Chinese medicine: role of the gut microbiota [J]. Pharmacol Res, 2020, 151: 104552.

[96] Nie Q, Chen H, Hu J, et al. Dietary compounds and traditional Chinese medicine ameliorate type 2 diabetes by modulating gut microbiota [J]. Crit Rev Food Sci Nutr, 2019, 59: 848-863.

[97] Li Y, Ji X, Wu H, et al. Mechanisms of traditional Chinese medicine in modulating gut microbiota metabolites-mediated lipid metabolism [J]. J Ethnopharmacol, 2021, 278: 114207.

[98] Yang Z, Liu Y, Wang L, et al. Traditional Chinese medicine against COVID-19: role of the gut microbiota [J]. Biomed Pharmacother, 2022, 149: 112787.

[99] Zhao Q, Chen Y, Huang W, et al. Drug-microbiota interactions: an emerging priority for precision medicine [J]. Signal Transduct Target Ther, 2023, 8: 386.

[100] Varesi A, Campagnoli LIM, Chirumbolo S, et al. The brain-gut-microbiota interplay in depression: a key to design innovative therapeutic approaches [J]. Pharmacol Res, 2023, 192: 106799.

[101] Gowen R, Gamal A, Di Martino L, et al. Modulating the microbiome for Crohn's disease treatment [J]. Gastroenterology, 2023, 164: 828-840.

[102] 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.

[103] Zhang ZW, Gao CS, Zhang H, et al. Morinda officinalis oligosaccharides increase serotonin in the brain and ameliorate depression *via* promoting 5-hydroxytryptophan production in the gut microbiota [J]. Acta Pharm Sin B, 2022, 12: 3298-3312.

[104] Zhao ZX, Fu J, Ma SR, et al. Gut-brain axis metabolic pathway regulates antidepressant efficacy of albiflorin [J]. Theranostics, 2018, 8: 5945-5959.