肠道微生物群在中药治疗非酒精性脂肪性肝病中的作用

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摘要: 非酒精性脂肪性肝病 (NAFLD) 是一种与遗传和环境因素密切相关的代谢性疾病, 可发展为肝纤维化、肝硬化, 以致肝细胞癌。近年来, NAFLD的患病率逐年上升, 目前还缺乏明确的药物治疗方法。中药在NAFLD防治中具有很大潜力但相关机制研究较少。越来越多的证据表明, 肠道菌群与NAFLD的发生发展密切相关, 肠道菌研究为阐明中药的作用机制开辟了新的视野。本文旨在介绍肠道菌群与NAFLD发生、发展的关系, 解析肠道菌群调节在以中药为基础的NAFLD治疗中的作用及机制, 以期为相关研究提供参考。

关键词: 肠道菌群; 非酒精性脂肪性肝病; 作用机制; 中药

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Role of gut microbiota in the treatment of nonalcoholic fatty liver disease with traditional Chinese medicine

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is a genetic and environmental factor-associated metabolic disease that can lead to fibrosis, cirrhosis and hepatocellular carcinoma. In recent decades the prevalence of NAFLD has increased, but effective pharmacotherapy is limited. Treatment regimens in traditional Chinese medicine (TCM) have made significant contributions to the control of NAFLD, but underlying mechanisms are far less elucidated. Increasing evidence suggests that gut microbiota play a crucial role in the pathogenesis and development of diseases including NAFLD. The outcomes of such research open a new approach in identifying the molecular mechanisms of TCM. Here we review the evidence that gut microbiota might be a target in the treatment NAFLD using TCM.

Key words: gut microbiota; nonalcoholic fatty liver disease; mechanism; traditional Chinese medicine

近几十年来, 非酒精性脂肪性肝病 (nonalcoholic fatty liver disease, NAFLD) 的患病率逐年增加, 已经影响到全球约四分之一的人口[1], 在患有2型糖尿病和肥胖人群中, NAFLD患者的数量分别超过70%和90%[2]。NAFLD的主要特征为肝脏中甘油三酯 (triglyceride, TG) 的异常堆积, 在没有炎症和肝细胞损伤的情况下, 被定义为脂肪变性或非酒精性脂肪肝; 在慢性NAFLD患者的肝脏中, 可能会出现肝小叶炎症和肝细胞损伤, 这种情况被称为非酒精性脂肪性肝炎 (nonalcoholic steatohepatitis, NASH)。NASH易诱发肝纤维化、肝硬化和肝细胞癌等多种严重并发症。除了与肝脏相关的并发症外, NAFLD还可能增加心血管疾病的发病风险[3]。目前NAFLD的发病机制还不是十分清楚, 越来

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越多的证据表明, 肠道菌群失调是导致肝损伤的一个关键因素, 肝脏通过门静脉从肠道接受大部分营养供应, 是第一个接受肠源有毒物质 (包括细菌及其代谢产物) 的器官[4], 肠道菌群失调可能导致肠通透性增加、肠道菌易位以及进入门静脉的毒素增加, 致使肝脏中产生大量的炎性因子。因此, “肠−肠道菌群−肝轴”可能在包括NAFLD在内的许多肝病中发挥重要作用[5]。

在人类的胃肠道中, 分布着数以万亿的微生物, 包括细菌、古生菌、病毒和真核微生物, 其中绝大多数为细菌。在消化道的不同部位, 细菌的组成和数量各不相同 (表 1)[6,7], 主要包括拟杆菌门、厚壁菌门、变形杆菌门和放线菌门, 约占肠道细菌总量的90%, 其中又以拟杆菌门和厚壁菌门最为丰富[8]。研究表明, 拟杆菌门与厚壁菌门的比率与个体对疾病 (如肥胖) 的易感性有关。此外, 人类结肠是大肠杆菌、空肠弯曲杆菌、肠沙门氏菌、霍乱弧菌和脆弱拟杆菌等致病菌的寄居地, 这些致病菌的丰度在机体健康状态下较低[9,10]。肠道菌群的组成和功能可能受到诸多因素影响, 包括宿主基因、性别、年龄、分娩方式、外界环境、饮食及药物干预等[11,12]。如最近一项研究表明给予大鼠高脂饮食 (high fat diet, HFD) 6周后, 其肠道内的革兰氏阳性菌数量增加[13]。反过来肠道菌群会影响宿主的代谢表型, 参与食物和药物代谢, 改善机体免疫[14]。在健康状态下, 宿主和肠道菌群之间相互受益, 这一状态被称为菌群平衡[15]。在病理条件下共生菌和致病菌的比例异常, 肠道菌群发生结构和功能的紊乱, 被称为菌群失调。将健康受试者和不同病理状态患者的肠道菌群组成相比较, 发现菌群失调与炎症和代谢紊乱包括心血管疾病、肥胖、糖尿病、代谢综合征和NAFLD等肝病之间可能存在直接联系[16-19]。此外, 临床研究表明中药治疗NAFLD具有很好的疗效, 随着对中药作用机制研究的不断深入, 发现肠道菌群组成和特定菌群含量的改变在中药治疗NAFLD中发挥着重要的作用, 现有研究不仅包括单体化合物、单味药及其提取物, 还包括中药组方。因此, 本文对近年来关于NAFLD与肠道菌群之间的关系, 以及肠道菌群调节在中药治疗NAFLD中的作用的研究进行整理与介绍, 以期为相关研究提供参考。

Table 1 The composition and density of the gut microbiota in different parts of gastrointestinal tract[6,7]

Part of gastrointestinal tract	The composition of the gut microbiota	Bacterial density (per gram of content)
Esophagus	*Bacteroides*, *Gemella*, *Megasphaera*, *Pseudomonas*, *Prevotella*, *Rothia* sps., *Streptococcus*, *Veillonella*	10^1−10^3
Stomach	*Streptococcus*, *Lactobacillus*, *Prevotella*, *Enterococcus*, *Helicobacter pylori*	
Small intestine	*Bacteroides*, *Clostridium*, *Streptococcus*, *Lactobacillus*, *γ-Proteobacteria*, *Enterococcus*	10^4−10^7
Cecum	*Lachnospira*, *Roseburia*, *Butyrivibrio*, *Ruminococcus*, *Fecalibacterium*, *Fusobacteria*	10^{11}−10^{12}
Colon	*Bacteroides*, *Clostridium*, *Prevotella*, *Porphyromonas*, *Eubacterium*, *Ruminococcus*, *Streptococcus*, *Enterobacterium*, *Enterococcus*, *Lactobacillus*, *Peptostreptococcus*, *Fusobacteria*	

1 NAFLD的产生机制

“二次打击”假说表明, 肝细胞中TG的堆积可能使肝脏遭受继发性损伤, 主要是氧化应激, 产生慢性损伤, 从而使肝脏的功能发生障碍, 最终发展为NASH[20], NAFLD被认为是代谢紊乱的肝脏表现, 胰岛素抵抗 (insulin resistance, IR) 和代谢综合征与肝病的进展密切相关。此外, 脂肪组织、肌肉和肠道等其他组织器官在NAFLD的进展中也发挥了重要的作用[3]。肥胖和高胰岛素血症与IR有关, IR在NAFLD中较为常见, 是其发病机制之一。IR能增加脂肪组织中的脂解作用, 使转运到肝脏的游离脂肪酸 (free fatty acids, FFA) 增加, 导致肝脏脂肪变性, 而过量的FFA会引起脂质过氧化, 导致细胞因子和炎症的产生[21,22], 炎症细胞因子、FFA积累、氧化应激和线粒体功能障碍最终导致脂肪性肝炎[23]。近年来还有人提出了“多次打击学说”[24]。

NAFLD的主要信号通路之一是核因子活化β细胞κ轻链增强子 (nuclear factor kappa-light-chain-enhancer of activated β cells, NF-κB) 通路, 在NASH中NF-κB通路被激活。这导致肝脏细胞因子的产生增加, 特别是肿瘤坏死因子α (tumor necrosis factor alpha, TNF-α) 和白细胞介素6 (interleukin-6, IL-6), 这些细胞因子通过减少肝胰岛素受体的表达, 从而促进了IR[25]。有研究发现富含胆固醇 (cholesterol, CHO)、饱和脂肪、多元不饱和脂肪、纤维和抗氧化剂的饮食与NAFLD有关[26]。此外, 果糖除了增加内脏脂肪和血浆TG外, 还增加肝脏炎症和纤维化[27,28]。

研究表明, 肠道微生物组成和特定菌群含量的改变与NAFLD的发生、发展密切相关[29]。NAFLD患者与健康受试者相比, 其肠道革兰氏阴性菌数量较多而革兰氏阳性菌较少[30]。Boursier等[31]的研究发现, 肝纤维化患者肠道内的瘤胃球菌数目增加。另一项研究表明, NAFLD患者与非NAFLD患者的厚壁菌门及链球菌属的序列数存在显著差异[32], 而成年NASH患者的拟球梭菌比例明显高于NAFLD患者[29]。Le Roy等[33]

将患有NAFLD小鼠的肠道菌群移植到无菌小鼠体内, 发现无菌小鼠出现了NAFLD的疾病特征, 包括高血脂和肝细胞脂肪变性, 此外还有研究发现肠道菌群可显著影响肝脏脂质的代谢, 且与肥胖无关。以上研究说明肠道菌群的改变与失调在NAFLD发展过程中起到重要作用。

2 肠道菌群影响NAFLD的作用机制

目前研究认为, 肠道菌群可以通过多种机制改善或加剧NAFLD, 包括影响肠道通透性、调节饮食中能量的吸收、改变肠道菌代谢产物如短链脂肪酸 (short chain fatty acids, SCFAs)、胆碱和胆汁酸的代谢、在肠道中产生乙醇以及影响免疫炎症等[34]。

2.1 影响肠道通透性

肠道通透性增加是NAFLD发生发展的重要表型及致病因素, 肠道微生物可以对其进行调节。正常状态下, 黏液层、抗菌肽和紧密连接蛋白等多种因素共同作用维持肠道屏障的功能, 调节其通透性, 限制细菌通过肠黏膜上皮层易位[35]。当菌群失调时, 肠道通透性增加, 导致大量细菌及衍生物经门静脉到达肝脏及进入体循环。在NAFLD患者和HFD喂养的小鼠体内, 肠壁紧密连接蛋白ZO-1 (zona occludens) 的表达下降, 肠道屏障完整性受到破坏, 通透性增加, 导致内毒素等细菌成分易位增加[36,37]。此外, 肠道通透性还与NAFLD的严重程度相关, 研究发现诊断为脂肪性肝炎儿童的肠道通透性高于肝脂肪变性的儿童[38]。有研究表明肠道屏障功能的改变可能导致促炎因子的通过, 而NAFLD发展的后期通常与血液中较高浓度的细菌内毒素有关[39,40]。Verdam等[41]发现NASH患者血浆中的脂多糖 (lypopolisaccharide, LPS) 抗体水平高于健康对照组, 且随着肝病严重程度的增加而增加。因此, 保护肠道屏障功能是治疗NAFLD及其相关疾病的重要途径[42]。

2.2 调节饮食中能量的吸收

能量摄取和储存的增加是导致肥胖和NAFLD的又一发病机制, 而肥胖与NAFLD的发生发展密切相关[43]。Backhed等[44]将正常小鼠的粪便微生物移植到无菌小鼠体内后, 发现无菌小鼠体内总脂肪含量增加57%, 并发生了IR, 研究认为肠道菌群将不可消化的碳水化合物发酵成可吸收的形式, 从而促进单糖的吸收和能量的摄取, 并抑制脂肪组织中的脂蛋白脂肪酶, 促进脂肪组织中TG的堆积, 从而导致肥胖的发生。此外, 肠道细菌还可能通过降低小肠血管生成素样蛋白的合成和分泌, 导致脂蛋白脂肪酶活性增强, 从而使肝脏脂肪的储存增加[45], 最终导致NAFLD的形成。

2.3 改变SCFAs、胆碱和胆汁酸的代谢

越来越多的证据表明肠道菌代谢产物在NAFLD中起着重要作用[46]。例如, 拟杆菌数量的增加与SCFAs和氨基酸水平的变化有关[47]。结肠中的微生物通过发酵植物来源多糖产生SCFAs[48], 在饮食中补充SCFAs已被证明对NAFLD有保护作用[49], 从氨基酸分解代谢中得到的代谢物 (如谷氨酰胺) 对肝功能有保护和治疗作用。有研究发现口服补充谷氨酰胺能保护小鼠免受由HFD引起的门静脉中内毒素及TNF-α水平的升高, 减少肝损伤[50]。

饮食中的胆碱对极低密度脂蛋白 (very low density lipoprotein receptor, VLDL) 的产生和肝脂质转运至关重要。因此在动物模型中, 常用胆碱缺乏的饮食来诱导NAFLD, 降低VLDL输出水平, 减少β氧化, 导致肝细胞脂肪酸和CHO堆积、氧化应激改变、细胞因子和脂肪因子释放, 致使肝脏中出现轻微的炎症和纤维化[51,52]。肠道菌群参与胆碱向二甲胺和三甲胺的转化[53], 导致体内胆碱缺乏, 对肝脏的正常生理产生影响。研究证实HFD饮食小鼠的肠道菌群能够增加胆碱向甲胺转化, 降低胆碱的生物利用度, 导致NAFLD和IR[54]。

胆汁酸是由肝脏中的CHO生成的, 能够促进脂质在胃肠道的吸收, 肠道菌群能将初级胆汁酸转化为20多种不同的次级胆汁酸[55]。胆汁酸除了促进脂肪的吸收, 还在其自身代谢中起到信号分子的作用, 并通过肠细胞上的法尼酯X受体 (farnesoid X receptor, FXR) 和G蛋白偶联胆汁酸受体1 (G protein-coupled bile acid receptor 1, TGR5) 调节能量代谢[56]。肠道菌群参与胆汁酸代谢既可以有益于健康也可以促进疾病的发生发展, 这取决于所产生次级胆汁酸的种类和数量。

2.4 促进肠道中产生乙醇

一些肠道菌群可以产生氨、乙醇和乙醛, 而这些物质经肠道吸收后主要在肝脏中代谢, 并与Kupffer细胞和炎症因子信号通路的激活有关, 从而促进NAFLD的发生[57]。在对肥胖小鼠进行的一项研究中发现, 虽然小鼠没有摄入任何酒精, 但在其呼出的气体中检测到了乙醇[58]。与健康人或NAFLD儿童相比, NASH患儿血液中乙醇的浓度升高, 这表明内源性乙醇可能通过激活炎症信号而加重肝脏损伤[57]。

2.5 影响免疫炎症

细菌及其代谢产物可激活肠道免疫细胞, 从而提高炎症细胞因子的产生, 进一步破坏肠上皮屏障的完整性, 并加剧肠道炎症, 继而经“肠–肝轴”增加肝脏炎症[59,60]。肠道菌产生的LPS是Toll样受体4 (toll-like receptor 4, TLR4) 的配体, 能够激活TLR4, 从而产生促炎因子和趋化因子, 高水平的LPS通过招募炎症细胞导致肝损伤, 从而导致NASH的形成[61]。研究发现, HFD喂养TLR4缺失的小鼠肝脏不会出现脂肪变性和

炎症, 这表明激活TLR4依赖的信号通路与肝脏炎症的产生密切相关[62]。以5-氨基水杨酸治疗HFD诱导的肠炎小鼠, 发现不仅减少了肠道炎症, 还减少了肝脏脂肪变性和IR, 说明肠道炎症是NAFLD发病的一个重要因素[63]。

3 以肠道微生物为靶点的NAFLD的治疗方法

研究表明, 通过健康饮食、多种微生物补充剂和移植健康粪便微生物群来调节肠道菌群, 可以促进有益微生物群的生长, 从而改善NAFLD患者的菌群失调和预后[64]。

益生菌是指活的细菌或酵母菌, 食用后对健康有益。在啮齿动物模型中, 给予干酪乳杆菌 *Shirota* 后, NASH动物肠道内原本增多的肠球菌的数量减少[65]。此外, 经鼠李糖乳杆菌治疗后, HFD喂养大鼠肠道内的紧密连接蛋白的表达量增加[66]。益生菌还可能通过作用于LPS/TLR4信号, 下调血清LPS和肝脏TLR4的表达, 从而延缓NAFLD的进展[67]。总之, 益生菌可以减少NAFLD患者的肝脏炎症及脂肪变性, 然而目前关于益生菌对肝纤维化影响的报道很少, 需要进一步的研究来阐明益生菌在NAFLD中的作用及机制。

益生元是指促进益生菌生长和活性的膳食补充剂。肠道中益生菌利用益生元产生活性的主要作用机制是发酵[68]。益生元可以改变肠道菌群, 降低肝脏脂肪生成和血中TG的水平[69]。此外, 肠道菌群通过益生菌发酵增加盲肠和门静脉血液中SCFAs的浓度[70]。

将益生菌和益生元结合在一起的膳食补充剂被定义为合生元。对于NASH患者, 长双歧杆菌与低聚果糖合用可以降低血清中TNF-α、肝酶及内毒素的水平, 改善脂肪变性和降低NASH指数[71]。此外, 有研究发现合生元能够改善NAFLD, 可以用于预防和辅助治疗NAFLD[72]。然而, 合生元治疗作用的确切机制仍需进一步研究。

通过使用抗生素减少肠道细菌是减少微生物及其产物易位的有效方法[73]。抗生素可以清除有害细菌, 有效治疗肝病[74]。使用抗生素进行短期治疗可能会对宿主产生治疗效果。在NASH大鼠模型的研究中, 庆大霉素可以显著降低血清丙氨酸转氨酶 (alanine aminotransferase, ALT)、天冬氨酸转氨酶 (aspartate aminotransferase, AST) 和TNF-α的水平[75]。多粘菌素B和新霉素可降低高糖饮食诱导小鼠的肝脏脂肪堆积[76]。诺氟沙星与新霉素交替治疗6个月, 可减少小肠细菌过度生长, 改善肝硬化患者的肝脏功能[77]。而在NAFLD小鼠模型中发现, 长期口服抗生素可抑制肠道细菌生长, 降低门静脉中次级胆汁酸的含量, 减轻肝脏炎症和纤维化[78]。此外, 联合应用新霉素、杆菌肽和链霉素4个月, 可降低小鼠肝脏中TG、脂质堆积和血清神经酰胺的生成[79]。然而, 抗生素治疗方法还存在争议, 如可能引起菌群失调, 长期使用存在抗生素耐药风险等。

粪便微生物群移植 (faecal microbiota transplantation, FMT) 是指将含有细菌的粪便物质从健康供体转移到患者体内, 以重建一个平衡的肠道微生物群[80]。FMT已被证明能够有效治疗艰难梭菌感染, 同时也可应用在代谢紊乱等非胃肠道疾病的治疗中[81]。有研究表明FMT治疗8周后, 小鼠肝内脂肪堆积和血清转氨酶水平显著降低, 小叶炎症程度和肝细胞气球样变明显减轻, 这提示FMT对HFD诱导的代谢紊乱具有一定的治疗作用[82]。

4 中药治疗NAFLD的肠道菌调节机制研究

临床研究表明中药治疗NAFLD具有很好的疗效, 但由于其成分复杂, 作用机制仍不明确。随着对中药作用机制的深入探索, 越来越多的研究表明肠道菌调节在中药治疗NAFLD中发挥着重要的作用, 现有研究不仅包括单体化合物、单味药及其提取物, 还包括中药组方。

4.1 单体化合物

4.1.1 小檗碱 小檗碱 (berberine, BBR) 是一种从黄连中分离得到的药用生物碱, 其口服后肠道吸收差, 生物利用度低[83]。目前已经有许多研究发现BBR能够通过调节肠道菌群抑制与腹泻相关的菌群失调。通过HFD喂养动物, 诱导NAFLD模型, 给予BBR治疗后可以显著升高HFD引起的双歧杆菌、有益乳酸菌以及拟杆菌与厚壁菌比值的降低, 减少粪杆菌数量, 显著降低体重、内毒素、肠道脂肪酸结合蛋白、血清中LPS、转氨酶和胰岛素的水平, 下调内毒素受体及其下游IL-6、IL-1和TNF-α等炎症因子的表达, 增加闭合蛋白的表达, 改善HFD诱导的肝脂肪变性及回肠绒毛断裂、缺失及间隙增大[84-86]。张园园等[87]也发现BBR能够通过增加拟杆菌数量, 改善菌群失调, 显著减少HFD引起的肝脏脂质堆积及LPS生成, 抑制相关炎症因子的释放。肠道菌群给予BBR后, 乙酸、丙酸和丁酸合成的关键酶乙酸激酶 (acetate kinase, ACK)、甲基丙二酰乙酰辅酶A脱羧酶 (methylmalonyl-CoA decarboxylase, MMD) 和丁酰辅酶A: 醋酸盐辅酶A转移酶 (butyryl-CoA: acetate-CoA transferase, BUT) 的表达量显著增加[88]。因此, BBR可能通过调节肠道菌群结构及修复肠道屏障功能, 继而改善NAFLD。

4.1.2 白藜芦醇 白藜芦醇是一种天然多酚类化合物, 具有抗氧化、抗炎、抗肿瘤、保护心血管的作用。在HFD诱导的动物模型中, 给予白藜芦醇能够显著降低

模型小鼠的血糖、血脂和内脏脂肪含量, 改善HFD引起的肠道菌群失调, 包括增加拟杆菌门与厚壁菌门的比值, 显著抑制粪肠球菌的生长, 促进乳酸菌和双歧杆菌的生长。白藜芦醇可以显著增加脂蛋白脂肪酶抑制剂禁食诱导脂肪因子 (fasting induced adipose factor, Fiaf) 在肠道内的表达, 降低脂蛋白脂肪酶 (lipoprotein lipase, Lpl)、硬脂酰辅酶A去饱和酶 (stearoyl-CoA desaturase 1, Scd1)、过氧化物酶体增生物激活受体γ (peroxisome proliferator-activated receptor γ, Ppar-γ)、乙酰辅酶A羧化酶 (acetyl-CoA carboxylase 1, Acc1) 和脂肪酸合酶 (fatty acid synthase, Fas) 等与脂肪酸合成及脂肪生成相关的基因表达, 通过改善肠道菌群紊乱和抑制与脂肪生成相关的代谢通路来减少肥胖[89]。此外, 白藜芦醇还可以通过调节肠道菌群, 增加闭合蛋白的表达, 抑制TNF-α等炎症因子, 恢复肠黏膜屏障功能, 从而改善NAFLD[90]。临床实验表明NAFLD患者服用白藜芦醇12周后, 血浆中ALT、IL-6、NF-κB及C反应蛋白的水平明显降低, 肝细胞脂肪变性减少[91]。另一项临床试验表明, 白藜芦醇可以改善IR并降低总CHO水平[92]。因此, 白藜芦醇可能通过改善肠道菌群紊乱, 抑制脂肪生成, 减少炎症因子而发挥抗NAFLD的作用。

4.2 单味药及其提取物

4.2.1 五味子及其提取物 五味子为木兰科植物五味子的干燥成熟果实。有研究发现五味子可以减轻四氯化碳诱导的肝硬化大鼠的肝损伤及肠道菌群失调[93]。林可霉素可以减少小鼠肠道内双歧杆菌和乳杆菌丰度, 增加肠球菌和大肠杆菌的数量, 五味子多糖能够改善上述菌群失调, 恢复正常的菌群结构, 表明五味子多糖对小鼠的肠道菌群紊乱具有一定的调节作用[94]。因此, 五味子及其提取物可能通过调节肠道菌群失调, 延缓NAFLD的疾病进展。

4.2.2 绿茶及其提取物 绿茶富含多酚类化合物, 如表没食子儿茶素没食子酸酯 (epigallocatechin gallate, EGCG) 和表没食子儿茶素 (epigallocatechin, EGC), 已被证明具有抗代谢的作用, 可降低体内脂肪含量, 减少肝脏TG及CHO堆积[95]。茶多酚被认为对健康有益, 如提高葡萄糖耐量、减少肝脏脂肪堆积、改善菌群多样性及显著升高拟杆菌门与厚壁菌门的比值。此外, 茶多酚还可以以剂量依赖的方式有效延缓由饮食引起的体重及体脂增加、脂肪细胞肥大和肝脏脂肪变性, 降低血清中总CHO、TG、低密度脂蛋白、葡萄糖和胰岛素水平, 显著提高乙酸和丁酸水平, 这些可能有助于治疗肥胖及相关的代谢性疾病, 如NAFLD[96,97]。乳酸菌发酵绿茶中的EGCG、EGC和绿原酸含量高于未发酵茶, 且能够通过刺激脂肪分解抑制成熟的3T3-L1脂肪细胞的堆积[98]。并且绿茶发酵提取物可以在不改变食物摄入的情况下减少体重和脂肪量, 降低与脂肪和炎症生成相关基因的表达, 恢复肠道菌群的正常结构[99]。总的来说, 绿茶及其提取物可以改善肥胖及其相关症状, 调节肠道菌群的组成。因此, 它可能作为一种新的有效成分来控制NAFLD和与代谢紊乱相关的疾病。

4.3 中药组方

4.3.1 四君子汤 四君子汤由茯苓、人参、白术、炙甘草组成, 出自《太平惠民和剂局方》, 在《医方集解补养之剂》中写道“人参甘温, 大补元气而为君。白术苦温, 燥脾补气为臣。茯苓甘淡, 渗湿泻热为佐。甘草甘平, 和中益土为使也”, 主治脾胃气虚证[100]。在动物实验中, 四君子汤可以使小鼠血浆中的二胺氧化酶水平下降, 肠道菌群分析结果显示, 四君子汤具有一定调节肠道菌群失调的作用, 增加乳酸杆菌及双歧杆菌数量, 减轻肠黏膜损伤[101]。在临床试验中, 胃肠道术后患者服用四君子汤后, 血浆中*D*-乳酸水平明显降低[102]; 肠道菌群失调所致腹泻的患者服用四君子汤后, 发现粪常规及菌群分析恢复正常[103], 将180例NAFLD患者随机分为治疗组与对照组, 发现四君子汤治疗后病人血浆中ALT及谷氨酰转肽酶水平降低, 血脂血糖也有所改善[104]。研究认为四君子汤可能通过降低肠黏膜通透性、调节肠道菌群、修复受损肝细胞和调节肝内脂肪代谢, 而发挥治疗NAFLD的作用。

4.3.2 祛湿化瘀方 祛湿化瘀方是由茵陈、虎杖、萎黄、栀子、田基黄组成, 具有清热利湿解毒, 活血散瘀的功效。在HFD诱导的NAFLD动物模型中, 祛湿化瘀方可以显著上调保护肠黏膜屏障的细菌*parabacteroides*菌属丰度, 改善模型动物肝脏和结肠病理损伤以及由HFD引起的肝细胞肿胀、脂肪变性、炎细胞浸润及脂质堆积, 降低血清中ALT、AST、血清LPS结合蛋白、肝TG水平, 增加ZO-1 mRNA的表达[105,106]。表明祛湿化瘀方可能通过调节肠道菌群、保护肠黏膜屏障完整、减轻肝脏炎症及肠道通透性, 从而延缓NAFLD的发生发展。

4.3.3 消脂汤 消脂汤由山楂、何首乌、决明子、丹参、虎杖、白术、泽泻、柴胡组成。研究显示, 消脂汤可以显著降低NAFLD模型小鼠空腹血糖、空腹胰岛素、IR指数、总CHO、TG, 减少小鼠肝组织TLR4、NF-κB mRNA及蛋白的表达, 肠道菌群分析结果显示, 消脂汤可增加小鼠肠道梭杆菌属、普氏菌属、双歧杆菌及乳酸杆菌数量, 并减少大肠埃希菌丰度。研究表明消脂汤可通过调整肠道菌群结构改善IR、减少肝脏脂肪堆积和炎症反应, 从而缓解NAFLD的进展[107]。

4.3.4 皂术茵陈方 皂术茵陈方由皂角刺、炒白术、茵陈蒿、大黄和栀子组成。临床试验将80例NASH患者, 随机分为治疗组和对照组, 研究结果发现, 给予皂术茵陈方治疗的患者血清中ALT、AST及内毒素水平明显下降, 肠道菌群分析结果显示, 治疗组患者肠道内的双歧杆菌、乳酸杆菌及拟杆菌丰度增加, 而肠球菌和肠杆菌丰度显著降低。由此提示皂术茵陈方可能通过调节肠道菌群数量及结构, 改善肝脏功能, 可用于NASH的临床治疗[108]。

4.3.5 益气清化方 益气清化方由黄芪、丹参、炒白术、陈皮、荷叶、绞股蓝、茯苓、玉米须组成。灌胃给予HFD诱导的NAFLD大鼠益气清化方, 结果表明, 与模型组相比, 益气清化方能够降低NAFLD大鼠血清中ALT、AST及LPS水平, 并明显减少肝细胞炎症和坏死, 肠道菌群分析结果显示, 益气清化方可增加模型动物肠道菌群多样性, 纠正HFD引起的肠道菌群失调。表明益气清化可能通过调节肠道菌群减轻NAFLD大鼠肝细胞的损伤和脂肪沉积[109]。

5 总结和展望

中医中药是中华民族灿烂文化的重要组成部分, 中药以其特有疗效与作用为人类的健康作出了积极的贡献, 在防病治病、康复保健方面显示出了独特优势和魅力, 阐明其药效物质基础及分子机制是现代中药研究的关键科学问题之一。中药多来源于结构类型多样的植物和微生物产物 (如多糖、生物碱、黄酮、苷类等), 常采用口服方式给药, 普遍存在疗效确切而口服生物利用度低的矛盾。随着科技的不断进步, 肠道菌与人体健康及疾病的关系得到阐述, 成为当今生命科学界研究的热点, 肠道菌研究也为解析传统中药作用机制开辟了新的视野。越来越多的证据表明肠道菌与中药成分能够发生相互作用, 在疾病的治疗过程中起到重要作用。中药能改变肠道菌群组成, 改善与疾病相关菌群失衡, 反之肠道菌群及生物酶能将中药化学成分转化为不同生物活性/毒性或具不同生物利用度的代谢产物, 也能介导中药及组方中不同成分间的相互作用。如有研究发现, 灵芝主要成分灵芝多糖可调节肠道菌群组成, 降低厚壁菌门/拟杆菌门比值, 减少变形菌门含量, 减少条件致病菌 *M. schaedleri*, *E. fergusonii*, *Enteroroccus*, *L. lactis*, *C. lactatifermentans*, *O. valericigenes* 丰度, 增加益生菌 *P. goldsteinii*, *Bacteroides*, *A. colihominis*, *R. hominis*, *C. methylpentosum*, *E. coprostanoligenes* 丰度, 由此降低肝中促炎症因子分泌, 增加肠壁屏障功能, 起到减轻体重减少脂肪堆积作用[110]。又如BBR可经肠道硝基还原酶转化为二氢小檗碱, 被肠上皮细胞吸收后经氧化转化回BBR, 继而进入体内发挥药效[111]; 甘草酸经大肠细菌代谢生成甘草次酸, 然后被机体吸收发挥药理活性; 柴胡皂苷a经*β*-*D*-葡萄糖苷酶及*β*-*D*-岩藻糖苷酶作用转化为b1和g的二烯皂苷而发挥药理作用等[110]。本文从NAFLD的角度, 介绍了以肠道菌群调节为基础的中药药效及机制研究进展。中药与肠道菌的研究正在成为研究热点, 仍有许多问题需要探索, 如中药 (及其化学成分) 如何调节肠道菌群进而改善疾病状态, 其靶点及信号通路是什么; 肠道菌如何利用中药成分生成哪些代谢活性/毒性产物, 肠道菌群对中药各种成分的代谢特征是什么, 与传统中医药理论如何结合等。将传统中医药理论实践与现代生物和化学技术相结合, 将促进中药在疾病治疗中取得新的进展, 并使之得到广泛的认可。

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