

中医药调控肠道菌群治疗代谢相关脂肪性肝病的机制

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[摘要] 代谢相关脂肪性肝病(MAFLD)为多系统代谢功能紊乱累及肝脏的表现,其疾病谱不仅包括脂肪性肝炎、肝纤维化、肝硬化、肝恶性肿瘤等肝脏疾病,还包括2型糖尿病、动脉粥样硬化性疾病、慢性肾脏病等肝脏外疾病,是全球范围内最常见的慢性肝病,发病机制复杂,目前缺乏有效的药物治疗。随着人们生活水平的提高及老龄化进程的加快,MAFLD的发病未来有继续增加的可能,其发生发展及防治受到广泛的关注及重视。近年来研究表明肠道菌群组成及比例异常可影响肠道菌群代谢物的变化,胆汁酸、胆碱等代谢紊乱可进一步加剧肠道菌群失调,由此形成恶性循环破坏肠道屏障功能,使肠道通透性增高,脂多糖、细菌及病毒等通过“肠肝轴”进入肝脏,促进肝脏炎症反应及脂质沉积,通过菌群移位、调节宿主能量吸收、糖脂代谢、炎症反应等一个或多个因素相互作用参与MAFLD的发生发展。中医药通过多靶点调节肠道菌群的结构和功能,促进有益菌生长,抑制有害菌形成,使肠道微生态恢复平衡,改善肠黏膜屏障功能,抑制肝脏炎症反应和脂肪变性,进而影响肝脏代谢和免疫应答,达到防治MAFLD的作用。该文通过文献检索及归纳总结,系统综述以肠道菌群为靶点的中医药治疗MAFLD的机制,以期为中医药治疗MAFLD提供思路和参考。

[关键词] 肠道菌群; 代谢相关脂肪性肝病; 非酒精性脂肪肝; 研究进展; 中医药; 机制

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Mechanism of Traditional Chinese Medicine in Regulating Gut Microbiota in Treating Metabolic-associated Fatty Liver Disease

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[Abstract] Metabolic-associated fatty liver disease (MAFLD) is a manifestation of multi-system metabolic dysfunction that affects the liver. Its disease spectrum not only includes fatty liver hepatitis, liver fibrosis, cirrhosis, liver malignancies, and other liver diseases but also includes extrahepatic diseases such as type 2 diabetes, atherosclerosis diseases, and chronic kidney disease. It is the most common chronic liver disease worldwide, with a complex pathogenesis and a lack of effective pharmacological treatments. With the improvement of people's living standards and the acceleration of the aging process, the incidence of MAFLD may continue to increase in the future, and its occurrence, development, prevention, and treatment have received widespread attention. Recent studies have shown that abnormal composition and proportion of gut

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microbiota can affect the changes in gut microbiota-derived metabolites. Metabolic disorders of bile acids and choline can further exacerbate gut microbiota imbalance, leading to a vicious cycle that destroys intestinal barrier function, increases intestinal permeability, and allows lipopolysaccharides, bacteria, viruses, and other substances to enter the liver through the "gut-liver axis". This process promotes liver inflammation and lipid deposition. Factors such as gut microbiota shift, regulation of host energy absorption, glucose and lipid metabolism, and inflammatory response interact to participate in the occurrence and development of MAFLD. Traditional Chinese medicine regulates the structure and function of gut microbiota through multiple targets, promoting the growth of beneficial bacteria, inhibiting the formation of harmful bacteria, restoring the balance of gut microbiota, improving intestinal mucosal barrier function, inhibiting liver inflammation and lipid degeneration, and influencing liver metabolism and immune response. This ultimately contributes to the prevention and treatment of MAFLD. This article systematically reviewed the mechanism of traditional Chinese medicine (TCM) treatment of MAFLD targeting gut microbiota through a literature search, aiming to provide ideas and references for TCM treatment of MAFLD.

[Keywords] gut microbiota; metabolic-associated fatty liver disease; non-alcoholic fatty liver; research progress; traditional Chinese medicine; mechanism

代谢相关脂肪性肝病(MAFLD)是由2020年国际专家提出的取代非酒精性脂肪性肝病的新名词^[1],这一更名强调了代谢因素在脂肪性肝病诊断和治疗中的重要性。随着全球经济的快速发展和人们生活方式的改变,MAFLD在全球的患病率逐渐升高且呈低龄化趋势^[2-3],一项系统评价和荟萃分析提示全球MAFLD患病率从1990至2006年的25.26%增加到2016至2019年的38.00%,增幅50.4%,值得注意的是儿童MAFLD患病率已达到约10%,青少年高达17%,肥胖儿童高达40%~70%,且MAFLD的发病未来有继续增加的可能^[4],该病严重影响人们的身体健康并带来沉重的医疗负担,应引起社会足够的重视与关注。MAFLD的疾病谱不仅包括脂肪性肝炎、肝纤维化、肝硬化、肝恶性肿瘤等肝脏疾病,还包括2型糖尿病、动脉粥样硬化性疾病、心脑血管疾病、慢性肾脏病等肝脏外疾病^[5],目前针对MAFLD的治疗药物尚在研究中^[6]。MAFLD的病理生理机制至今尚未完全阐明,近年来研究表明肠道菌群在MAFLD的发病过程中有重要作用^[7-8]。中医药通过多靶点、多途径调控肠道菌群治疗MAFLD取得良好的临床疗效^[9-10]。本文系统检索中医药靶向调控肠道菌群治疗MAFLD的相关文献,从肠道菌群与MAFLD关系、肠道菌群失调在MAFLD发病中的作用机制、中医药调节肠道菌群治疗MAFLD等方面进行综述,以期为临床治疗MAFLD及新型药物开发提供思路和参考。

1 肠道菌群与MAFLD关系

肠道菌群是指定居在胃肠道中各种微生物的

总称,肠道菌群及其代谢产物对机体消化、吸收、代谢及免疫等诸多环节发挥重要作用,被称为机体新陈代谢的核心调节器^[11]。肠道和肝脏通过“肠-肝轴”双向通讯,正常情况下,肠道菌群和肝脏保持相对平衡的状态,病理状态下肠道菌群紊乱,导致肠道通透性增高及细菌移位,随门静脉循环进入肝脏,激活炎症级联反应致使肝损伤,而肝脏释放的炎症因子反过来又造成肠道损害^[12-13]。随着对MAFLD研究的不断深入,越来越多的证据证实肠道菌群通过肠肝循环对MAFLD的发生发展及转归关系密切^[14-16]。这为从肠道菌群角度治疗MAFLD提供思路和方向。

2 肠道菌群失调在MAFLD发病中的作用机制

肠道菌群组成比例及代谢产物失调引起肠壁通透性增强、肝脏炎症反应、胰岛素抵抗等多重改变,为MAFLD的发病奠定病理基础,影响MAFLD的发生发展及预后。

2.1 肠道菌群组成和比例是MAFLD发生、发展的重要因素 肠道菌群由近百万亿个细菌、病毒及真菌等构成,受宿主遗传基因和外环境改变等诸多因素影响,肠道菌群的定植部位、菌群组成和比例对维持机体微生态平衡发挥重大作用^[11]。研究表明,MAFLD肠道菌群物种丰度减少,在门、属、科和种方面有其不同的特征^[17]。厚壁菌门和拟杆菌门与肥胖相关,其比率升高可导致低水平的炎症反应,促炎因子过度合成,增加脂肪酸流入肝细胞,加重肝脂肪变性^[18]。MAFLD严重程度与肠道菌群组成和比例有关,拟杆菌属丰度增加与脂肪性肝炎严

重程度相关,瘤胃球菌和变形菌门丰度增加与肝纤维化程度呈正相关^[14]。肠杆菌科和绒毛杆菌科丰度与非肥胖型MAFLD患者的肝纤维化严重程度呈正相关^[19]。目前,肠道菌群组成和比例变化如何影响MAFLD的具体作用机制研究仍处于初始探索阶段,以上研究结果提示肠道菌群在预测MAFLD病情进展方面具有临床应用价值。

2.2 肠道菌群代谢产物是影响MAFLD发生、发展的关键环节 肠道菌群可衍生多种代谢产物(如短链脂肪酸、胆汁酸、胆碱、脂多糖、内源性乙醇等)与宿主相互作用,通过不同作用机制导致肝脏炎症及脂肪沉积,影响MAFLD的发生发展。

肠道菌群可将难以消化的膳食多糖、碳水化合物等加工成短链脂肪酸(SCFAs),SCFAs具有代谢免疫调节及维护肠道屏障功能稳定等作用^[20],可通过阻断炎症反应及影响免疫功能参与MAFLD进程^[21-22]。肠道菌群中富含的胆汁酸水解酶可通过解偶联和去羟基化影响胆汁酸代谢^[23],胆汁酸能促进脂类物质的吸收,同时,作为法尼醇X受体(FXR)的配体,胆汁酸与FXR结合后,可增强胰岛素敏感性,抑制肝糖异生,增加能量消耗^[24]。胆碱具有维持肝细胞膜完整性、调节脂代谢的作用,主要从饮食中获取^[25],部分肠道菌群可分解胆碱,降低其生物利用度,导致肝细胞损伤及脂肪蓄积,从而诱发MAFLD^[26]。肠道菌群失调可增强肠黏膜通透性,破坏肠道屏障功能^[27],肠道菌群代谢产物脂多糖通过门静脉系统释放入肝脏,诱发肝脏炎症和脂肪变性^[28]。肠道菌群对碳水化合物的发酵可产生内源性乙醇,内源性乙醇过量产生可通过增加肠黏膜通透性及脂多糖水平,诱发肝脏炎症反应,进而促进MAFLD发生发展^[29]。

3 中医药调节肠道菌群治疗MAFLD

祖国传统医学并无MAFLD病名,现代医家多将其归属于“积聚”“肥胖”等范畴,MAFLD多因饮食失节、损脾碍胃所致,病位虽在肝脏,但与脾胃密切相关。中医脾胃功能与西医肠道菌群密切相关^[30],《黄帝内经·灵枢》云:“大肠、小肠皆属于胃”,肠道菌群与饮食物的消化吸收密切相关,是中医“脾胃”功能的具体体现,可归属于中医藏象学说中的脾胃范畴。中医藏象学说认为肝脾“克而互用、经络相通”,在现代解剖学中,肝是距离肠道最近的器官之一,肝脏通过肠肝轴与肠道菌群及其代谢产物接触,肠道微环境失衡可改变肝脏内稳态,从而引发肝脏相关疾病^[31]。有学者研究发现,MAFLD

轻症患者多表现为肝郁脾虚证,而中重度MAFLD多表现为湿热内蕴证^[32]。吴珊珊等^[33]通过临床试验研究发现,肝郁脾虚型与湿热内蕴型MAFLD患者肠道菌群拟杆菌门丰度减少,厚壁菌门及变形菌门丰度增加,不同中医证型的MAFLD患者肠道菌群结构亦存在差异,肝郁脾虚型有益菌酸杆菌门丰度较湿热内蕴型多,临床中可针对不同的中医证型精准靶向调节肠道微生态平衡。中药经过胃肠道消化吸收,与肠道菌群相互作用,中药有效活性成分或中药复方通过调节肠道菌群及其代谢物、改善肠黏膜屏障等发挥治疗MAFLD作用。

3.1 调节肠道菌群组成和比例,保持肠道微生态平衡 小檗碱(BBR)是从中药黄连中提取的活性成分,有研究报告,BBR可增加MAFLD小鼠双歧杆菌的相对丰度,降低厚壁菌门丰度,重建肠道细菌群落,通过促进支链氨基酸分解代谢,降低支链氨基酸产生菌的相对丰度缓解胰岛素抵抗^[34],此外,BBR还可通过减少拟杆菌死亡,减少肠道菌群代谢产物脂多糖的产生,抑制肝脏炎症和脂肪变性,减轻肝损伤^[35]。荷叶碱是荷叶的有效成分,通过改变高脂饲料喂养的MAFLD大鼠模型肠道菌群的组成,升高肠道阿克曼菌丰度,增加牛磺酸代谢相关菌群,减少 7α -脱羟基化菌属,改善脂质代谢^[36-37]。白藜芦醇(RSV)是从中药决明子、虎杖等提取的天然多酚类化合物,研究发现,RSV可改变高脂饮食诱导的肥胖小鼠的肠道菌群组成,包括降低厚壁菌门、毛螺菌科的相对丰度,升高副杆菌属、拟杆菌属的相对丰度,通过抗生素实验进一步证明RSV被肠道菌群转化为有益菌群代谢物,具有抗氧化、改善脂质代谢等生物效应^[38]。绞股蓝(GP)含有黄酮、皂苷等多种生物活性成分,研究表明,从GP中提取的GP皂苷可降低厚壁菌门的丰度,增加拟杆菌门丰度,重塑肠道菌群,减轻肝脏脂肪变性,从而对高脂饮食诱导的MAFLD小鼠模型有治疗作用^[39-40]。齐墩果酸是从中药女贞子的果实中提取的化合物,可通过重塑高脂饮食诱导的MAFLD大鼠肠道菌群的组成,发挥抗氧化、抗炎及益生元整合反应,治疗肥胖相关的MAFLD^[41]。四妙方由苍术、黄柏、牛膝、薏苡仁组成,具有清热利湿作用,有研究表明,四妙方可改变肠道菌群的组成和丰度,减轻高脂高糖小鼠肝脏脂肪变性,提高对胰岛素敏感性,通过肠肝轴调控肠道菌群组成改善MAFLD^[42]。苓桂术甘汤由茯苓、白术、桂枝、甘草组成,临床试验表明该方治疗脾阳虚衰的MAFLD患者疗效显著^[43],有

研究表明,苓桂术甘汤通过增加肠道中有益菌丰度,强化脂肪酸氧化功能并抑制肝脏脂质沉积,恢复肠道微生态,进而改善MAFLD^[44]。茵陈蒿汤由茵陈、栀子、大黄组成,是《伤寒论》中治疗湿热黄疸的经典方剂,研究表明,茵陈蒿汤可通过增加肠道中益生菌数量、抑制致病菌属的数量对MAFLD起到治疗作用^[45]。刘悦^[46]通过临床随机观察实验验证茵陈蒿汤治疗湿热证MAFLD患者的临床疗效,结果发现茵陈蒿汤治疗后实验组肠杆菌、肠球菌等有害菌数量较治疗前减少,乳酸杆菌、双歧杆菌等有益菌数量较前增加,且肝功能、血脂、炎症指标水平均有所改善,表明茵陈蒿汤通过恢复肠道微生态、减轻炎症反应、保护肝功能达到治疗MAFLD的作用。谢维宁等^[47]运用随机对照研究方法,观察柴胡疏肝散治疗肝郁脾虚型MAFLD患者的临床疗效及其对肠道菌群的影响,结果发现柴胡疏肝散干预后可增加肠道有益菌双歧杆菌及乳杆菌丰度,降低有害菌大肠埃希菌及肠球菌丰度,通过调节肠道菌群组成和比例达到治疗MAFLD的作用。

3.2 调节肠道菌群代谢物,改善肝脏炎症和脂肪变 姜黄素是天然多酚类物质,可以从中药郁金、姜黄、莪术等根茎中提取,具有抗炎、抗氧化等多种药理作用^[48]。在治疗MAFLD过程中,可以与肠道菌群双向互动增效,一方面,姜黄素通过调节肠道菌群改善高脂饮食诱导的大鼠肠道炎症,减轻肝脂肪变性^[49],另一方面,肠道菌群对姜黄素进行生物转化,产生的新代谢产物具有更强的生物学效应^[50-51]。黄芩苷是从中药黄芩中提取的活性成分,通过增加肠道菌群代谢物SCFAs的产生,调控FXR胆汁酸受体进而调节胆汁酸代谢等方式发挥治疗MAFLD的作用^[52]。灵芝酸A(GA)从中药灵芝中提取,GA干预高脂饮食诱导的MAFLD小鼠模型,可提高肠道SCFAs水平,促进胆汁酸排泄,减轻小鼠体质量,改善血脂及肝脏脂质积累^[53]。黄芪多糖(APS)是从中药黄芪中提取的化合物,具有调控血脂、调控血糖及调节免疫等多种作用,是治疗MAFLD的颇有前景的天然药物^[54],进一步研究表明,APS通过调节肠道菌群组成结构,改变肠道菌群代谢产物进而影响宿主谷胱甘肽代谢和嘌呤代谢,改善肝脏脂肪变进而治疗MAFLD^[55]。参苓白术散能增加MAFLD大鼠肠道有益菌如双歧杆菌、厌氧杆菌等丰度,促进SCFAs产生,减少脂多糖产生,阻断肝脏炎症反应和脂质沉积治疗MAFLD^[56]。

3.3 调节肠道菌群,保护肠黏膜屏障 肠黏膜屏障

功能在MAFLD的发生发展中具有重要作用^[57],调节肠道菌群可以保护肠黏膜屏障从而达到治疗MAFLD的作用^[58]。木犀草素是天然黄酮类化合物,可从中药金银花、野菊花、紫苏等提取,可通过调节肠肝轴,改善肠黏膜通透性,降低脂多糖水平,恢复肠黏膜屏障完整性达到治疗MAFLD作用^[59]。二苯乙烯苷(TSG)是从中药何首乌中提取的有效成分,王艳芳等^[60]采用TSG治疗高脂饮食诱导的MAFLD大鼠模型,结果表明TSG可调节肠道菌群代谢物SCFAs的表达,改善肠黏膜屏障功能,同时减轻脂多糖介导的慢性低度炎症反应及肝脏脂质沉积,达到防治MAFLD的作用。枸杞多糖是中药枸杞子的主要活性成分,可以通过恢复肠道菌群、改善肠道黏膜屏障等实现改善MAFLD的作用,被认为是新型的益生元^[61]。甘草酸二铵(DG)从中药甘草中提取,DG可增加肠道菌群的多样性,促进SCFAs产生,改善胆汁酸代谢,补充DG可增加杯状细胞数量和黏蛋白分泌,改善肠黏膜通透性,增强肠道屏障功能,抑制肝脏脂肪变性,达到治疗MAFLD作用^[62-63]。大黄泽泻汤由《金匮要略》泽泻汤(泽泻、白术)加制大黄组成,具有健脾利湿、祛痰泄浊的功效,可有效治疗MAFLD,进一步机制研究表明,大黄泽泻汤通过降低MAFLD大鼠肠道致病菌比例,升高肠道有益菌比例,改善肠道菌群的结构,调节紧密连接蛋白的表达及分布,使肠黏膜通透性降低,减少致病菌通过肠肝轴进入肝脏,达到改善MAFLD的作用^[64]。祛湿化痰方由茵陈、栀子、虎杖、姜黄、田基黄组成,临床治疗痰瘀互结型MAFLD疗效显著^[65],该方通过调节MAFLD大鼠肠道菌群,恢复肠道微生态,增强肠屏障功能,减少肠黏膜损伤,改善慢性炎症反应进而改善肝脂肪变性达到治疗作用^[66]。苗兰等^[67]发现祛瘀化痰通脉方通过调节肠道菌群改善肠道微生态,改善脂代谢紊乱,对MAFLD的防治有积极意义。

综上,中药有效成分或中药复方防治MAFLD的作用与调节肠道菌群组成、调节肠道菌群代谢产物、保护肠道黏膜屏障等有关,具体调节关系及实验设计见增强出版附加材料。

4 总结与展望

MAFLD是最常见的慢性肝病,进一步发展可导致脂肪性肝炎、肝纤维化、肝硬化、肝癌及心脑血管疾病,严重危害人类健康,目前尚无有效的药物治疗法^[3]。随着研究的逐步深入,肠道菌群在MAFLD发病中的作用越来越得到重视。肠道菌群组成及

比例异常可影响肠道菌群代谢物的变化,胆汁酸、胆碱、SCFAs、内源性乙醇等肠道菌群代谢物与肠道菌群失调相互影响,由此形成恶性循环破坏肠道屏障功能,使肠道通透性增高,脂多糖、细菌及病毒等通过“肠肝轴”进入肝脏,促进肝脏炎症反应和脂质沉积,参与MAFLD的发生与进展。中医药通过调节肠道菌群平衡、促进优势菌群生长、改善肠黏膜屏障功能,从而减少致病菌产生及菌群产物易位,达到治疗或减轻MAFLD的作用。但人体肠道菌群组成复杂,目前中药通过调节肠道菌群防治MAFLD的研究大多集中于丰度相对较高的菌群且动物实验较多,仍有大部分菌群有待检测与分析并在临床研究中以验证。肠道菌群易受各种因素影响,不同饮食、不同个体肠道菌群亦存在差异,且肠道细菌及其代谢物种类和数目繁多,相互关系错综复杂,口服中药后肠道菌群的变化也可能只是中药干预机体出现的结果,而并不一定是其治疗MAFLD的途径。肠道菌群的多样性和中药成分的复杂性使相关研究具有一定的难度和挑战,未来可结合各种组学技术研究阐明各种菌群单独及协同作用治疗MAFLD的机制,为MAFLD的精准靶向治疗提供依据。

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