

非酒精性脂肪性肝病的发病机制与中药多靶点干预机制的研究进展*

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摘要:非酒精性脂肪性肝病(Nonalcoholic fatty liver disease, NAFLD)是一种以脂质在肝脏中过度堆积引起的慢性肝病,其发病率逐年增加,已成为日益严重的公共卫生问题。NAFLD的发病机制复杂,目前尚未完全阐明,主要与遗传、代谢、肠道菌群及免疫反应等多因素环节有关。为了探讨中医药治疗NAFLD的用药规律及作用机制,为中医药治疗NAFLD及新药研发提供参考,本文对NAFLD的中医病机(如“痰瘀互结”或“肝郁脾虚”等)及现代病因病机(如胰岛素抵抗、脂质紊乱、线粒体功能障碍、氧化应激等)进行了归纳,并整合近年来国内外临床研究及实验数据,分析了中医药通过多靶点干预NAFLD的病理进程,包括改善胰岛素抵抗与脂代谢紊乱、抑制氧化应激与线粒体功能障碍等。中医药在NAFLD防治中展示出独特优势,但其机制解析深度及临床研究水平仍需提升,未来需要结合多组学技术深化机制研究,以加速中医药现代化发展。

关键词:非酒精性脂肪肝病 中药 病因病机 作用机制 研究进展

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非酒精性脂肪性肝病(Nonalcoholic fatty liver disease, NAFLD)是一种以脂质在肝脏中过度堆积引起的慢性肝病。随着人口老龄化及慢性代谢疾病的发生,导致NAFLD的发病率呈指数性增加,已成为日益严重的公共卫生问题。NAFLD从肝脂肪变性进展到非酒精性脂肪性肝炎,部分患者可能会发展为不可逆的肝硬化,最后发展为肝癌^[1-2]。NAFLD的发病机制复杂且尚未完全阐明,目前认为是多因素作用的结果,涉及遗传、代谢、肠道菌群及免疫反应等多个环节。NAFLD治疗不仅治疗费用高、周期长,而且存在预后不良、副作用显著等问题,严重影响患者的生活质量水平并增加社会负担。

近年来,随着现代药理学的不断发展,中药干预NAFLD正得到深入研究,大量的中药及有效组分在NAFLD的临床治疗和实验研究中显示出良好的治疗效果。中药具有多成分、多靶点、多途径作用特点以及副作用低等独特优势,中医根据患者体质和NAFLD发病机制等因素进行个体化给药,为NAFLD患者治疗提供有利选择。本综述系统概述了NAFLD的中医发病机制、现代病因病机、中医药治疗NAFLD的用药规律及中药作用机制,为中医药治疗NAFLD作用机制的阐释和新药开发提供参考。

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1 NAFLD的中医发病机制

NAFLD病位在肝,肝主疏泄,调节全身气机,若肝失疏泄,则气、血、津、液输布异常,则可痰湿内生,郁而化热,病程迁延不愈,形成瘀、痰、湿、热等病机互结,则浊毒内生,故“肝失疏泄、气机失调、浊毒内生”是NAFLD的核心病机^[3]。《非酒精性脂肪性肝病中西医诊疗专家共识》(2025年)将其分型为肝郁脾虚证、痰浊内阻证、湿热蕴结证、痰瘀互结证等^[4]。症候的辨识是中医的基础,部分中医认为NAFLD以肝郁脾虚为主,情志不畅(如焦急、抑郁)或外邪侵袭可致肝气郁结,肝郁导致脾虚,则脾胃运化失常,水湿痰饮内积,阻碍气血运行,最终导致NAFLD发生^[5]。此症候在女性患者中尤为常见,因女性情绪波动较大,易致肝气不舒,进而影响脾胃功能^[6]。湿热蕴结证患者因多食肥腻,脾胃运化不畅,湿热蕴结,气机升降不畅,湿热浊气上冲,导致肝失疏泄,湿热聚集于肝内引起NAFLD^[7]。痰瘀互结证患者多因脾虚失运,痰湿内生,肝郁气滞,痰血内停,痰瘀互结,痹阻肝络引起NAFLD^[8]。总之,肝、脾、肾为NAFLD主要病位,病性证素为湿、气滞、热、痰、气虚及血瘀相互交织,进而发病^[9]。

2 现代医学对NAFLD发病机制的认识

现代医学认为,NAFLD的进展是由多环节的“多重打击”所引发的,其症状通常是非特异性的,包括疲劳、消化不良、肝脏区域钝痛及代谢异常(如超重、内脏肥胖和脂质失调)。NAFLD的发病机制主要涉及胰岛素抵抗与脂质紊乱、线粒体功能障碍与氧化应激、炎症与免疫反应、肠道菌群失调、遗传与表观遗传因素等。

2.1 胰岛素抵抗与脂质紊乱

NAFLD中肝脂肪变性是由于肝细胞中甘油三酯(Triglyceride, TG)合成过多引发。TG合成大约由60%白色脂肪组织(White adipose tissue, WAT), 26%的从头脂肪生成(De novo lipogenesis, DNL)以及15%的高脂或高糖饮食组成。胰岛素介导TG在脂肪组织中储存,并促进脂肪酸(Fatty acid, FA)的酯化和储存。因此,胰岛素抵抗(Insulin resistance, IR)是NAFLD发病的关键驱动因素,尤其是在肥胖和代谢综合征患者中更为显著。过量的游离脂肪酸(Free fatty acid, FFA)以TG的形式储存在肝脏中,形成脂质异位沉积导致

NAFLD。此外,DNL是脂质累积的重要代谢途径,其受胆固醇调节元件结合蛋白-1c(Sterol regulatory element binding protein 1, SREBP-1c)和糖类反应元件结合蛋白的调控,IR激活SREBP-1c以促进DNL增加^[10-11]。因此,由于胰岛素失调引起的脂质代谢紊乱是NAFLD发生和进展的关键因素。

2.2 线粒体功能障碍与氧化应激

NAFLD中线粒体动力相关蛋白1介导的线粒体分裂异常增加会促进肝脏中脂肪沉积和氧化应激,肝脏中过剩活性氧(Reactive oxygen species, ROS)诱导的氧化应激也会导致线粒体损伤^[12-13]。除此之外,NAFLD还与线粒体功能障碍相关的三磷酸腺苷(Adenosine triphosphate, ATP)生成以及线粒体通透性转换孔(Mitochondrial permeability transition pore, mPTP)开放相关。例如,在线粒体内,丰富的乙酰辅酶A(Acetyl coenzyme A, acetyl-CoA)和ATP可通过乙酰辅酶A羧化酶(Acetyl-CoA carboxylase, ACC)的酶促作用合成丙二酰辅酶A(Malonyl coenzyme A, malonyl-CoA),从而在脂滴中合成TG^[14]。当过量的TG和FFA异常沉积在肝细胞中,脂质代谢紊乱诱导的脂毒性会导致过度的氧化应激和线粒体功能障碍。在肝脂肪变性期间,mPTP异常开放,会损伤线粒体呼吸链功能,从而导致ROS积累^[15]。因此,提高线粒体的功能,恢复其清除ROS的能力,以减轻氧化应激,调控脂类代谢与凋亡可有效控制NAFLD发展^[16]。

2.3 炎症和免疫反应

NAFLD发病过程中,肝内免疫细胞由免疫耐受向免疫原性转化,这种表型的转换可促使大量促炎因子和趋化因子如白细胞介素-6(Interleukin 6, IL-6)进入循环系统,加剧全身慢性炎症反应^[17]。此外,肝细胞凋亡被认为是肝脏炎症和纤维化的主要原因,同时巨噬细胞和炎症细胞在受损的肝细胞释放危险信号时被激活,触发促炎因子的分泌,从而进一步加重肝细胞损伤和死亡。在NAFLD中,革兰氏阴性菌和ROS激活Toll样受体4(Toll-like receptor 4, TLR4),使肝细胞中的TLR4/核因子- κ B(Nuclear Factor- κ B, NF- κ B)上调炎症细胞因子分泌,导致肝脏慢性炎症。在肥胖患者中,NF- κ B的激活促进炎症因子的表达,而IL-6和肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)等炎症因子的大量释放又进一步增强了NF- κ B的活性。重要的是,TNF- α 对脂蛋白脂肪酶具有较强的抑制作

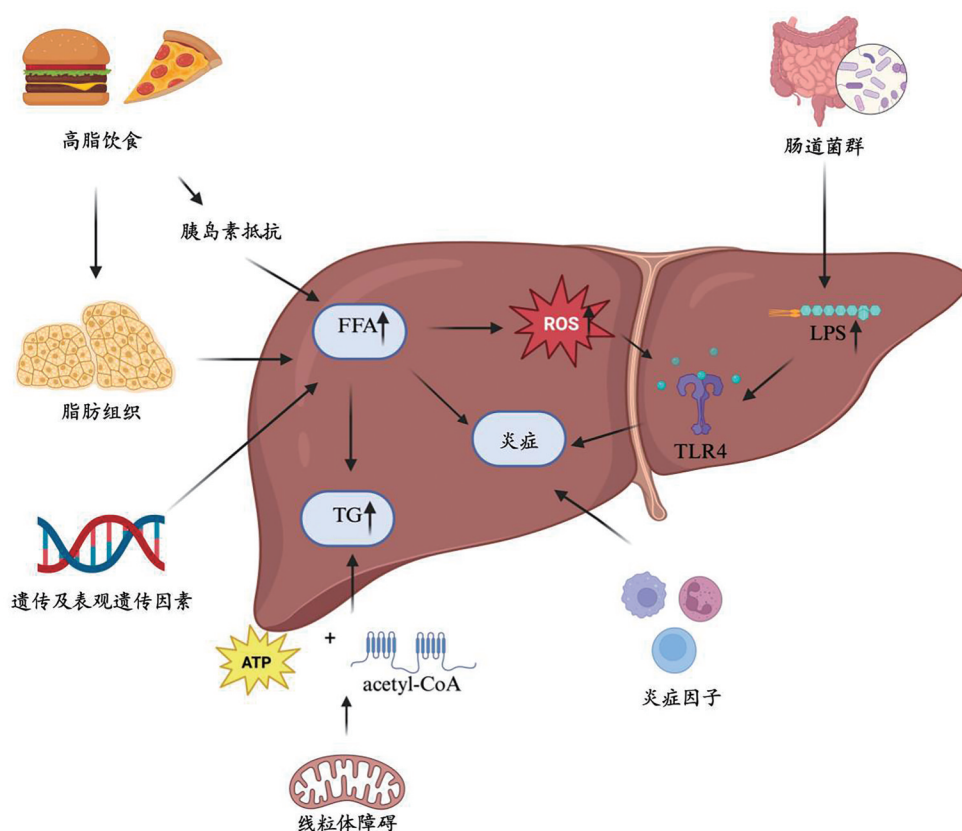


图1 NAFLD发病机制

Fig. 1 The pathogenesis of NAFLD

用,可减少外周脂肪组织的分解代谢,促进肝组织中TG的合成,并诱导脂质积累^[18]。先前研究发现,NAFLD小鼠中肝细胞淋巴瘤素- β 受体和NF- κ B均能激活肝内浸润的自然杀伤T细胞及CD8⁺T细胞的活化,从而促进NASH向肝癌的转变^[19]。

2.4 肠道菌群失调

肠-肝轴是肠道及其微生物与肝脏间的双向交流通路,通过胆道系统、肝门静脉和体循环实现。肠道菌群失调通过肠-肝轴的多途径交互(代谢产物、免疫激活、胆汁酸信号)驱动NAFLD进展,如肠菌代谢物脂多糖(Lipopolysaccharide, LPS)进入肝脏并激活TLR4,导致炎症反应。实验证明,脆弱拟杆菌会诱导肠道菌群失调,特别是Desulfovibrionaceae显著增加,导致内毒素水平升高,从而加剧了糖代谢与脂质代谢紊乱^[20]。大量研究表明,额外的益生元和益生菌有助于宿主代谢,其通过重塑肠道微生物群来缓解NAFLD^[21]。短链脂肪酸是肠道菌群的重要代谢产物,其可通过肠-肝轴参与肝脂肪变性和炎症的调节,在缓解NAFLD中起重要作用,如丁酸对肝脏有保护作用,可抑制微小RNA(MicroRNA,

mRNA)水平和ATP柠檬酸裂解酶的活性,进而减少acetyl-CoA的供应,改善NAFLD的发展^[22]。

2.5 遗传与表观遗传因素

遗传和表观遗传因素与环境因素相互作用使NAFLD的患病率增加。美国NAFLD的发病率存在显著的种族和民族差异。近年来全基因组关联研究揭示了遗传多态性在NAFLD进展中的重要性,特别是磷脂酶结构域3和跨膜6超家族成员2是肝纤维化、肝硬化、肝炎以及肝细胞癌相关的遗传标记^[23-24]。肝脏中17 β -羟基类固醇脱氢酶13(17 β -hydroxysteroid dehydrogenase 13, HSD17B13)的丢失已被证明会增加肝脏中FFA的合成,导致脂肪变性和炎症。据报道,NASH患者通过肝X受体 α 中SREBP-1c上调可导致HSD17B13的表达下调,导致脂肪变性。事实上,肝脏葡萄糖激酶活性的增强会刺激糖酵解通量,从而促进肝脏葡萄糖代谢和malonyl-CoA浓度增加,由于malonyl-CoA的 β 氧化阻断能力,导致肝脏脂肪储存。总之,罕见的遗传与表观遗传因素可导致NAFLD发展^[25]。

3 中药治疗NAFLD的用药规律

中医治疗NAFLD通常基于整体观和辨证的方法,旨在协调身体的阴阳平衡。对于NAFLD患者,应依据临床病情确定主方,结合体质特征和证候加减用药,并随疾病发展变化,以辨体为主,结合辨病辨证,调节体质,巩固疗效^[26]。通过数据挖掘,临床上NAFLD患者证型主要为湿热内蕴证、肝郁脾虚证、肝郁气滞证、气滞血瘀证。回归分析得出黄芩、茵陈、川木通、车前子、连翘等多用于治疗湿热内蕴证,柴胡、半夏、茯苓、白芍、白术等是治疗肝郁脾虚证的常用药物,治疗肝郁气滞证常使用当归、牡丹皮、川芎等^[27]。黄彬教授认为NAFLD发病机制多为肝郁脾虚证,疏肝健脾益气药物多以甘草、柴胡、党参、白术、陈皮等为主;痰湿瘀血皆为病理产物,不通则痛,而具有利湿、化瘀、行气、止痛功效的中药多以白芍、枳壳、茯苓、川芎等使用频率较高^[28]。

4 中药治疗NAFLD的作用机制

中药在治疗慢性疾病方面具有独特的理论和实践经验,已被广泛用于治疗各种肝脏疾病。中药具有多成分、多靶点的作用特点,与NAFLD的复杂发病机制相吻合。大量研究表明,中药具有调节胰岛素抵抗、脂质代谢、改善线粒体功能、抗炎和抗氧化及调节肠道菌群等作用,为治疗NAFLD提供新视角。

4.1 改善胰岛素抵抗与脂质紊乱

NAFLD是一种复杂的代谢类疾病,在众多发病机制中,“二次打击”假说被作为研究重点。肝脏中的脂质积累、胰岛素抵抗是导致NAFLD的主要因素。长期摄入高糖和高脂肪加上胰岛素抵抗,会导致肝脏脂质积累和NAFLD形成。豌豆蛋白是一种优质的植物蛋白,其特点是调节氨基酸谱平衡。研究发现,豌豆蛋白具有增加腺苷酸活化蛋白激酶 α 和ACC的磷酸化,降低固醇调节元件结合转录因子1和脂肪酸合酶的表达,增强甘油三酯脂肪酶、PPAR α 和过氧化物酶体增殖物激活受体 γ (Peroxisome proliferator-activated receptor γ , PPAR γ)的表达,减少从头脂肪生成、促进TG水解和线粒体FA氧化等作用,从而缓解NAFLD小鼠肝脏脂质累积^[29]。据报道,银杏内酯C通过影响葡萄糖代谢改善胰岛素信号传导,并通过单磷酸腺苷活化蛋白激酶(Adenosinemonophosphate-activated protein kinase, AMPK)抑制脂肪生成^[30]。此外,紫草素可直接作用于PPAR γ 和基质金属蛋白酶-9(Matrix metalloproteinases-

9, MMP-9)/金属蛋白酶组织抑制剂-1(Metalloproteinases-1, TIMP-1)轴,改善肝脏脂质失调和纤维化,显著降低高脂饮食所致的肝组织中PPAR γ 和MMP-9表达以及增加TIMP-1表达,改善NAFLD^[31]。

4.2 改善线粒体功能与激活抗氧化通路

线粒体功能障碍使FA氧化受损和ROS过量产生,导致肝脏脂肪过度堆积和氧化应激的发展,从而造成肝细胞损伤和慢性肝病。同时,NAFLD的发展将进一步损害线粒体呼吸链和线粒体超微结构的活性,导致肝细胞线粒体功能障碍^[32]。AMPK能够抑制肝脏葡萄糖原合成及促进糖原降解,从而维护肝脏糖脂代谢稳态。ACC是FA合成过程的重要调节节点,同时也是AMPK的直接下游靶基因。研究表明,毛兰素可通过活化AMPK,促进FA氧化和线粒体功能修复,从而发挥对肝脏功能的保护作用^[33]。NAFLD的发生发展与氧化应激现象紧密相连,氧化应激会加重肝内脂肪沉积。白头翁皂苷B4可调控NAFLD小鼠血糖、血脂水平,保护肝功能,并减轻肝脂沉积,其机制与激活AMPK介导的ACC/CPT1A通路有关,通过调控肝脏的FA代谢及抗氧化应激发挥防治NAFLD的作用^[34]。据报道,菊苣酸可以保护肝细胞免受H₂O₂诱导的氧化应激损伤,降低H₂O₂诱导的体外ROS和丙二醛水平。此外,菊苣酸在体内外增强了抗氧化酶并激活了Kelch样环氧氯丙烷相关蛋白1-核因子E2相关因子2和血红素氧合酶1的抗氧化途径^[35]。

4.3 改善炎症反应与调节免疫

炎症反应是NAFLD发生发展的关键环节,炎症因子的平衡失调是其发生发展的关键基础。胆固醇通过Th1型免疫反应促进促炎细胞因子谱,微循环中白细胞募集和肝星状细胞激活,导致微循环功能障碍。研究发现,NAFLD与微环境中的炎症因子密切相关,芍药苷可以降低LPS引起的RAW 264.7细胞增殖,并显著降低TNF- α 、IL-6、IL-1 β 的水平,并通过氧化应激缓解炎症进程^[36]。NF- κ B通路异常激活会加剧NAFLD中的肝脏炎症,抑制蛋白激酶B(Protein kinase B, PKB)活化及其偶联的NF- κ B信号,降低ROS介导的炎症反应。研究表明,舒肝祛脂胶囊能够减少磷酸化AKT,抑制AKT/NF- κ B信号通路的激活,从而减轻肝脏炎症^[37]。黄芪中富含大量黄芪多糖,其表现出明显的抗氧化、提高免疫力、保护肝损伤作用。研究证实黄芪多糖可通过抑制NF- κ B/NOD样受体信号通路

来减轻脂质积累和炎症反应^[38]。适应性免疫细胞(T淋巴细胞和B淋巴细胞)与NASH的发生和发展有关。其中T淋巴细胞在触发肝脏炎症中起到至关重要的作用,可将其分为CD8⁺和CD4⁺亚群。因此,在CD8⁺T细胞缺陷小鼠中可观察到NASH的改善以及肝功能的恢复和肝损伤减少^[39]。钩吻素子可提高高脂饮食诱导的大鼠肝脏中CD8⁺T细胞、CD4⁺T细胞和调节性T细胞比例,抑制IL-6、TNF- α 的产生,降低炎症反应^[40]。

4.4 调节肠道菌群

肠道微生态失衡可导致肠黏膜损伤,肠道通透性增加,同时微生物代谢物通过“肠-肝轴”激活肝免疫,诱发炎症反应,进而加速NAFLD的发生发展^[41]。研究表明,藜麦麸多酚可有效减轻NAFLD小鼠的异常脂质代谢和肝脏脂肪堆积,通过增加有益菌 Clostridium_innocuum_group、Clostridium_sensu_stricto_13、Ruminococcus_gnavus_group、UBA1819 和 Coriobacteriaceae_UCG_002 的丰度来调节肠道菌群的组成^[42]。先前研究表明,高脂饮食会导致 Ruminococcus、Clostridium_XI V a 和 Barmesiella 丰度增加,导致脂质代谢紊乱和肝脂肪变性,从而促进NAFLD进展,银丹心脑通可通过增加肠道菌群的组成和多样性,降低 Ruminococcus、Clostridium_XI V a 和 Barmesiella 丰度,并降低 Firmicutes to Bacteroidota (F/B) 的比例,显著抑制促炎因子(如LPS)引起的炎症反应而改善NAFLD小鼠的肠道菌群紊乱^[43]。肠道菌群失调通过产生内源性乙醇、增加LPS等毒素水平来影响肠道通透性,其组成的改变也会扰乱BAs稳态,通过BAs受体(如FXR)发出信号传导,从而影响能量平衡和脂质代谢^[44]。FXR在维持BAs代谢中发挥着关键作用,其中成纤维细胞生长因子15(Fibroblast growth factor 15, FGF15)参与总BAs稳态的调控。研究证明,附子理中汤通过FXR-FGF15通路发挥作用,可提高NAFLD大鼠回肠及肝内

FXR蛋白和mRNA的表达,且FGF15及mRNA在回肠中的表达显著升高^[45]。

5 总结与展望

5.1 中医药治疗NAFLD的独特性与优势

NAFLD是全球最常见的慢性肝病之一。中医药基于整体观和辨证的方法,根据各种症候分型治疗NAFLD,且中药复方可灵活加减,精准应对NAFLD病因的复杂性,显示出其防治NAFLD的巨大潜力。相比较西药单一靶点,中医药则是通过调控脂质代谢、氧化应激及肠道菌群等多途径实现多靶点治疗NAFLD的。

5.2 中医药治疗NAFLD的局限性与突破方向

首先,中医应根据患者症状、体征等辨证分型,但辅助检查的客观标准及辨证分型结合的研究不足,无法进行具体关联^[46]。应建立“症候-多组学-影响表型”关联模型,推动辨证标准化。中药治疗NAFLD中涉及的靶点和通路信号较多,且与多种机制有关,因此不同信号通路之间是否存在协同关系是我们进一步需要探讨的问题,并需要借助多组学,如代谢组学、蛋白组学、转录组学、修饰组学等诠释更多活性成分的作用机制^[47]。这些组学分析方法的应用不仅体现了中医“辨证论治”的理念,也与中药的整体观相吻合,并与中医未来发展的趋势相一致,促进了中医药的现代化发展。此外,部分复方及单体成分缺乏安全性、药代动力学及临床研究数据,因此,未来需要进一步完善其药代动力学和毒副作用数据。

中医药在NAFLD防治中展示出独特优势,但其机制解析深度及临床研究水平需提升,未来需要结合多组学技术深化机制研究,以加速中医药现代化发展。

[利益冲突] 本文不存在任何利益冲突。

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Research Progress on the Pathogenesis of Non-Alcoholic Fatty Liver Disease and the Multi-Target Intervention Mechanism of Traditional Chinese Medicine

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease caused by excessive lipid accumulation in the liver. Its incidence rate is increasing year by year and has become an increasingly serious public healthy problem. The pathogenesis of NAFLD is complex and has not been fully clarified at present. It is mainly related to multiple factors such as genetics, metabolism, intestinal flora and immune response. In order to explore the medication rules and mechanism of action of traditional Chinese medicine (TCM) in the treatment of NAFLD, and to provide references for the treatment of NAFLD with TCM and the research and development of new drugs, this article summarizes the TCM pathogenesis of NAFLD (such as "phlegm and blood stasis interlacing", "liver depression and spleen deficiency", etc.) and modern etiology and pathogenesis (such as insulin resistance, lipid disorder, mitochondrial dysfunction, oxidative stress, etc.). The clinical research and experimental data at home and abroad in recent years were integrated to analyze the pathological process of NAFLD intervention by TCM through multiple targets, including improving insulin resistance and lipid metabolism disorders, inhibiting oxidative stress and mitochondrial dysfunction, etc. TCM has shown unique advantages in the prevention and treatment of NAFLD. However, the depth of its mechanism analysis and the level of clinical research still need to be improved. In the future, it is necessary to deepen the mechanism research by combining multi-omics technology to accelerate the modernization development of TCM.

Keywords: Nonalcoholic fatty liver disease, Traditional Chinese medicine, Etiology and pathogenesis, Mechanism of action research progress

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