

· 综述 ·

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黄连温胆汤干预代谢相关脂肪性肝病脂质堆积的作用机制

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摘要: 代谢相关脂肪性肝病(MAFLD)的核心特征为肝脏脂质堆积,与脂质代谢紊乱、胰岛素抵抗及炎症反应等因素密切相关,而异常的脂质堆积又可加剧上述因素,从而进一步加重脂质堆积,形成恶性循环。黄连温胆汤在改善 MAFLD 脂质堆积方面展现出独特优势,但其作用机制较为复杂。本文结合最新文献证据,系统总结黄连温胆汤从调节脂质代谢、改善胰岛素抵抗和抗炎等 3 个方面改善脂质堆积的作用机制以及相关中药活性成分的药理作用,为黄连温胆汤治疗 MAFLD 的临床应用提供理论依据。

关键词: 代谢相关脂肪性肝病; 黄连温胆汤; 脂类代谢

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Mechanism of action of Huanglian Wendan decoction in treatment of lipid accumulation in metabolic dysfunction-associated fatty liver disease

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD) has the core pathological feature of liver lipid accumulation, which is closely associated with the factors such as lipid metabolism disorders, insulin resistance, and inflammation, and abnormal lipid accumulation can exacerbate these factors and further intensify lipid accumulation, thereby forming a vicious circle. Huanglian Wendan decoction has shown unique advantages in alleviating lipid accumulation associated with MAFLD, but its mechanism of action is relatively complex. With reference to the latest literature evidence, this article systematically summarizes the mechanism of action of Huanglian Wendan decoction in improving lipid accumulation by regulating lipid metabolism, ameliorating insulin resistance, and exerting an anti-inflammatory effect, as well as the pharmacological actions of related active components, in order to provide a theoretical basis for the clinical application of Huanglian Wendan decoction in the management of MAFLD.

Key words: Metabolic Dysfunction-Associated Fatty Liver Disease; Huanglian Wendan Decoction; Lipid Metabolism

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代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)全球总患病率约为32.4%,且呈逐年上升趋势^[1]。目前尚无MAFLD靶向药

物,临床治疗主要依赖生活方式干预、代谢调控及有限的对症药物,疗效仍有待提高^[2-3]。中医学将MAFLD归属于“胁痛”“肝癖”“肥气”“痰浊”等范畴^[4]。其核心特

征为膏脂瘀积,肝体受损^[5]。其病机包括肝脾失调,痰浊内蕴;饮食不节,脾虚精瘀;湿热阻滞,毒瘀互生等。黄连温胆汤出自清代陆廷珍所作的《六因条辨》,由黄连、半夏、竹茹、枳实、陈皮、茯苓、甘草、生姜组成,具有调和肝脾、化痰降浊、清热解暑除湿等功效。本文将对黄连温胆汤改善MAFLD脂质堆积的作用机制开展归纳评述。

1 黄连温胆汤治疗MAFLD的中医理论

中医认为五脏各分体用,体用互为阴阳,肝体受损可导致肝用失常,反之肝用失调亦可损及肝体,此乃阴阳互根互用之理。《黄帝内经》云:“肝欲散,急食辛……用辛补之,酸泻之。”此句针对肝用而论。黄连温胆汤中半夏味辛,枳实味酸,二者同用补泻兼施,调肝用以复其体,由阳治阴。半夏配黄连还可共奏辛开苦降之法,半夏开郁化痰,散结降浊;黄连清热燥湿,泻火解毒。陈皮、枳实,一升一降,助其辛开苦降之力,强其行气化痰泻浊之功。四药合用,使肝内瘀积之痰浊脂膏可随大便而去,正应“肝通阳明”之理,此为治其肝体。茯苓、陈皮利湿燥湿,健脾运脾,助脾升清,可散瘀滞之脾精,绝痰源之化生,诸药配合,肝脾同调。竹茹味甘微寒,可清肝胆之热,亦具化痰之功。与半夏同用,一温一清,相反相成,加强化痰降浊之力。生姜横散,走而不守,辛温通络;甘草守乎中气,二药配合,散中有守,助毒瘀之疏通而不失其缓,驱邪而不伤正。由此可见,黄连温胆汤可通过改善膏脂瘀积以复肝体。

此外,形乃神宅,形为神主。调神可以复其形体,复形亦可调其神气,形与神亦为一对阴阳。方中半夏可交通阴阳,配合生姜化痰开窍,引阳入阴以安神。茯苓宁心,枳实通魄,竹茹安眠,陈皮芳香辟秽醒神,甘草调和诸药。诸药合用,共奏安神定志之功。由此可见,黄连温胆汤还可通过调神改善患者的睡眠和情绪障碍,亦有助于肝体的修复。

2 黄连温胆汤改善MAFLD脂质堆积的作用机制

现代医学认为,MAFLD的核心特征是肝脏中脂质的过度堆积,而这种堆积与脂质代谢紊乱、胰岛素抵抗及炎症反应等因素密切相关,可直接损伤肝细胞^[3]。同时,异常的脂质堆积又可加剧脂质代谢紊乱、胰岛素抵抗和炎症反应,从而形成一种恶性循环,使脂质堆积持续加重(图1),进一步发展为肝纤维化,甚至肝硬化^[3]。因此,现代医学干预MAFLD的关键在于调节脂质代谢,改善胰岛素抵抗及抗炎等以改善脂质堆积。

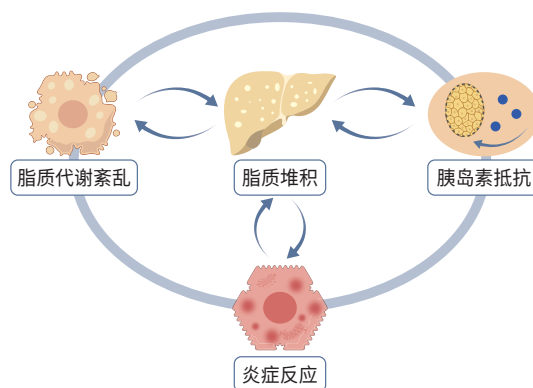


图1 脂质堆积与其影响因素的作用关系

Figure 1 The interplay between lipid accumulation and contributing factors

2.1 调节脂质代谢 脂质代谢紊乱是脂质异常堆积的核心环节^[6]。胆固醇代谢紊乱是脂质代谢紊乱的核心组成部分。胆固醇代谢紊乱在MAFLD发生发展中具有重要作用,可通过直接沉积、干扰相关代谢通路、破坏脂蛋白稳态等多种机制,驱动胆固醇本身及甘油三酯在血管壁、肝脏等组织的病理性堆积^[7]。临床上,MAFLD患者血清和肝脏中甘油三酯和总胆固醇水平显著升高^[8]。

过氧化物酶体增殖物激活受体 α (peroxisome-proliferator-activated receptor alpha, PPAR α)作为脂肪酸氧化代谢的关键调控因子,主导机体在能量应激状态下的脂质分解与利用,在肝脏中表达最为丰富^[9]。肝X受体 α (liver X receptor alpha, LXR α)作为细胞内胆固醇的“传感器”,能够感知胆固醇水平升高并启动清除程序以维持稳态,在肝脏、脂肪组织、肠道及巨噬细胞等组织中高度表达^[10]。LXR基因敲除小鼠在高胆固醇饮食诱导下,会出现肝脏胆固醇酯大量蓄积及脂代谢紊乱^[10]。三磷酸腺苷结合盒转运蛋白A1 (ATP-binding cassette transporter A1, ABCA1)是ABC转运家族的一员,在胆固醇逆向转运及新生高密度脂蛋白生成的过程中发挥关键的限速作用,负责将细胞内的胆固醇和磷脂转运至贫脂的载脂蛋白A1,从而启动高密度脂蛋白的组装^[10]。经此途径,胆固醇最终被转运至肝脏并降解形成胆汁酸,从而完成其代谢过程。PPAR α 可通过改变细胞内脂质环境,间接激活LXR α ^[11];LXR α 被激活后,可直接上调ABCA1的表达^[12],从而在功能上构成了一条PPAR α -LXR α -ABCA1信号通路,该通路在维持机体的胆固醇平衡过程中具有核心作用。研究显示,黄连温胆汤可激活大鼠的PPAR α -LXR α -ABCA1信号通路,提高各靶点信

使RNA及其蛋白表达,改善胆固醇代谢紊乱^[10]。

此外,细胞色素P450家族7亚家族A成员1(cytochrome P450 family 7 subfamily a member 1, CYP7A1)作为胆固醇代谢重要的限速酶,也是LXR α 的靶基因之一。激活LXR α 可直接上调CYP7A1的表达,催化肝脏内的胆固醇转变为胆汁酸并排出体外,从而降低肝脏中胆固醇的堆积^[13]。因此,黄连温胆汤还可能通过激活该通路,改善胆固醇代谢紊乱。

然而,LXR α 激活的同时可上调脂肪生成转录因子——固醇调节元件结合蛋白1c(sterol regulatory element-binding protein-1c, SREBP-1c)^[14],从而可能促进肝脏脂肪酸与甘油三酯的合成,这一副作用限制了单纯肝X受体激动剂的临床应用。然而,黄连温胆汤在调节脂质代谢中展现出多靶点协同的优势。虽然尚无研究直接证实黄连温胆汤复方对SREBP-1c的调控作用,但多项研究发现,无论是温胆汤复方,还是黄连的核心成分小檗碱,均可显著下调SREBP-1c的表达^[15-16]。因此,笔者推测黄连温胆汤可能对LXR α 信号通路具有“偏向性激活”效应,在激活胆固醇逆向转运相关基因的同时,还可抑制SREBP-1c的表达,从而规避了促进脂质合成的副作用。此外,黄连温胆汤还可通过激活PPAR α 信号通路上调肉碱棕榈酰转移酶1的表达,通过增强脂肪酸 β -氧化,有效降低血清中甘油三酯与游离脂肪酸水平^[9]。这种多通路协同、扬长避短的作用模式,充分体现了中医药在调控复杂脂质代谢网络时整体性强、副作用小的独特优势。

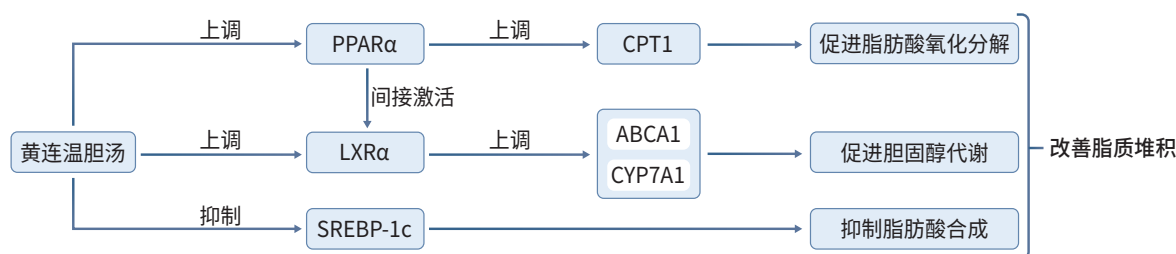
综上所述,总结黄连温胆汤通过调节脂质代谢改善脂质堆积的作用机制见图2。

2.2 改善胰岛素抵抗 胰岛素抵抗可破坏糖脂代谢稳态并驱动肝细胞脂肪异常蓄积,显著影响MAFLD的发生发展^[17]。

磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase,

PI3K)/蛋白激酶B(protein kinase B, Akt)信号通路作为胰岛素信号传导的主要途径,与体内葡萄糖和脂质代谢密切相关,在胰岛素抵抗的发生中发挥重要作用^[18]。在胰岛素抵抗状态下,肝脏PI3K/Akt信号通路的传导受损引发了一系列代谢紊乱,这种紊乱并非通路的完全关闭,而是一种“选择性失灵”:即其对葡萄糖代谢的调控功能显著减弱,而其对脂质合成的驱动作用却被保留或异常增强。首先,受损的Akt信号无法有效磷酸化并抑制转录因子——叉头框蛋白质O1(forkhead box protein O1, FOXO1),导致其持续入核,启动糖异生相关基因的表达,加剧空腹高血糖,为脂质合成提供过剩的碳源^[19-20]。其次,在全身性高胰岛素血症的驱动下,或通过其他替代信号途径,其下游的哺乳动物雷帕霉素靶蛋白复合物1被异常激活^[21]。活化的哺乳动物雷帕霉素靶蛋白复合物1可促进脂肪生成的关键转录因子——SREBP-1c的成熟,从而驱动肝脏脂肪的从头合成急剧增加^[21]。而黄连温胆汤可作用于胰岛素受体底物等上游靶点,增强PI3K及其下游信号分子Akt的磷酸化激活,磷酸化并抑制FOXO1,从而减少肝糖输出^[22],加之前述黄连温胆汤成分具有下调SREBP-1c表达的作用,因此,黄连温胆汤可有效改善胰岛素抵抗,并减轻肝脏脂质堆积。

葡萄糖转运蛋白4(glucose transporter 4, GLUT4)是一种葡萄糖转运蛋白,在胰岛素刺激后GLUT4会发生膜转位,从而发挥转运葡萄糖的功能^[23]。PI3K/Akt通路是胰岛素调控GLUT4转位的核心桥梁,其功能的失灵将直接导致GLUT4向细胞膜转运失败,使骨骼肌和脂肪组织这2个主要的葡萄糖处理器官无法有效清除血液中的葡萄糖,是外周胰岛素抵抗发生发展的根本原因之一^[24]。黄连温胆汤含药血清可有效激活胰岛素抵抗的3T3-L1脂肪细胞的PI3K/Akt信号通路,并上调GLUT4的基因表达,从而改善胰岛素抵抗^[25]。而瘦素是由脂肪细胞分泌的一种蛋白质激素,其通过影响胰岛素在脂肪细胞的



注:PPAR α ,过氧化物酶体增殖物激活受体 α ;CPT1,肉碱棕榈酰转移酶1;LXR α ,肝X受体 α ;ABCA1,三磷酸腺苷结合盒转运蛋白A1;CYP7A1,细胞色素P450家族7亚家族A成员1;SREBP-1c,固醇调节元件结合蛋白1c。

图2 黄连温胆汤通过调节脂质代谢改善脂质堆积的作用机制

Figure 2 Mechanism by which Huanglian Wendan decoction improves lipid accumulation via lipid metabolism regulation

信号转导、葡萄糖转运和脂肪合成等途径影响糖脂代谢,导致胰岛素抵抗^[23];对代谢综合征大鼠模型进行黄连温胆汤中药灌胃后,可见大鼠血清瘦素水平明显降低^[23]。因此,黄连温胆汤亦可通过抑制瘦素,改善胰岛素抵抗。

作为肠道菌群的关键代谢产物,短链脂肪酸(short-chain fatty acid, SCFA)在维持机体葡萄糖稳态中扮演着重要角色。SCFA作为上游信号分子,能够激活肠道内的G蛋白偶联受体(G protein-coupled receptor, GPR)41/43,进而刺激L细胞分泌胰高血糖素样肽1(glucagon-like peptide1, GLP1)与YY肽(peptide YY, PYY),从而促进胰岛素的分泌,提高胰岛素敏感性并减少糖异生。黄连温胆汤可通过增加肠道SCFA含量,调控SCFA-GPR41/43-GLP1/PYY信号轴,改善胰岛素抵抗^[26]。

综上所述,总结黄连温胆汤通过改善胰岛素抵抗改善脂质堆积的作用机制见图3。

2.3 抗炎 炎症因子可以加重肝细胞内的脂质堆积,并引起细胞的损伤^[27]。核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白(nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein, NLRP)炎症小体是细胞内感知危险信号的核心传感器,其异常激活是驱动MAFLD炎症恶性循环的关键环节。被激活的NLRP3炎症小体通过活化其下游的胱天蛋白酶1(cysteine aspartic acid specific protease, Caspase-1),切割并释放强效促炎因子白细胞介素(interleukin, IL)1 β 与IL-18,并介导细胞焦亡,从而启动并持续放大肝脏的炎症级联反应^[28-29]。而黄连温胆汤含药血清能有效靶向抑制NLRP3/Caspase-1信号通路,显著降低IL-1 β 与IL-18的水平,并减轻细胞焦亡,从而发挥其抗炎作用^[30]。

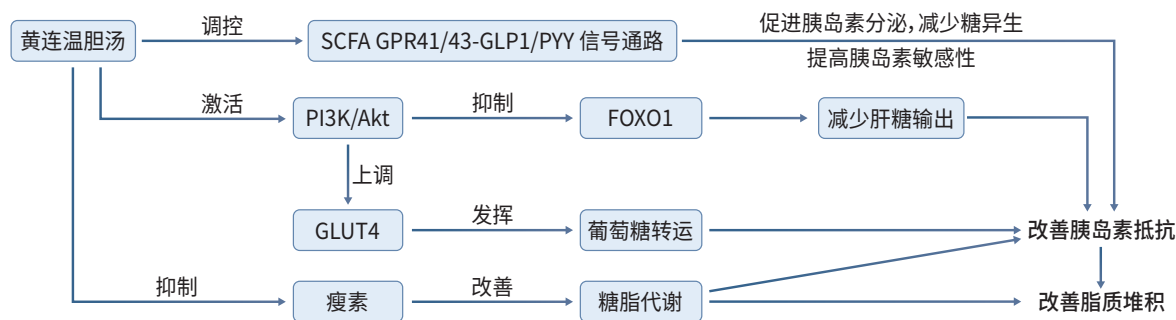
作为炎症应答过程中的关键调控因子,核因子 κ B(nuclear factor κ B, NF- κ B)家族能够激活IL-6和肿瘤坏死因子 α 等主要促炎介质的基因表达,同时促进血管细胞黏附分子1等细胞表面黏附分子的表达。G蛋白偶联受体5(G protein-coupled receptor 5, GPR5)对NF- κ B通路具有核心抑制作用^[31],PPAR α 也可部分抑制NF- κ B通路^[32]。黄连温胆汤不仅能够直接剂量依赖性抑制多发性硬化大鼠模型的主动脉NF- κ B活化,还可通过上调TGR5与PPAR α 表达,间接抑制主动脉NF- κ B活化,从而降低IL-6、肿瘤坏死因子 α 和血管细胞黏附分子1等炎症相关因子表达,缓解炎症反应^[9,33]。

此外,肠道菌群紊乱可引起肠道屏障的破坏,导致脂多糖通过肝门静脉入肝^[34],而细胞膜定位的Toll样受体4(Toll-like receptor 4, TLR4)可通过识别脂多糖激活髓系分化初级反应蛋白质88,进而通过IL-1受体相关激酶1/4-肿瘤坏死因子受体相关因子6-转化生长因子 β 活化激酶-I κ B激酶级联反应,最终激活NF- κ B信号通路,导致炎症反应^[35]。而黄连温胆汤不仅能够提高大鼠肠道菌群的丰度及多样性,改善大鼠的肠道菌群稳态,还可下调TLR4的表达,从而抑制NF- κ B信号通路的激活,改善炎症反应^[36-38]。

综上所述,黄连温胆汤可能通过抗炎改善脂质堆积(图4)。

3 黄连温胆汤主要活性成分改善MAFLD脂质堆积的药理作用

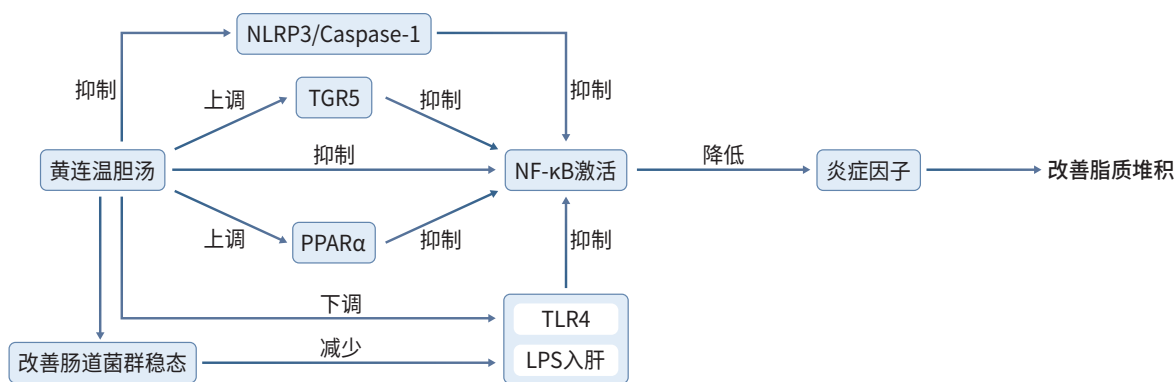
黄连温胆汤的核心成分包括:半夏水提取物、荜茇素、新橙皮苷、柚皮苷、茯苓提取物、甘草查尔酮A、姜辣素、小檗碱等,以上成分可通过调节脂质代谢、改善胰岛素抵抗、抗炎等协同改善MAFLD的脂质堆积(表1)。



注:SCFA,短链脂肪酸;GPR41/43,G蛋白偶联受体41/43;GLP1,胰高血糖素样肽1;PYY,YY肽;PI3K/Akt,磷脂酰肌醇3-激酶/蛋白激酶B;FOXO1,叉头框蛋白O1;GLUT4,葡萄糖转运蛋白4。

图3 黄连温胆汤通过胰岛素抵抗改善脂质堆积的作用机制

Figure 3 Mechanism by which Huanglian Wendan decoction reduces lipid accumulation via amelioration of insulin resistance



注: NLRP3, 核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白3; Caspase-1, 胱天蛋白酶1; TGR5, G蛋白偶联胆汁酸受体1; NF-κB, 核因子κB; PPARα, 过氧化物酶体增殖物激活受体α; TLR4, Toll样受体4; LPS, 脂多糖。

图4 黄连温胆汤通过抗炎改善脂质堆积的作用机制

Figure 4 Mechanism by which Huanglian Wendan decoction reduces lipid accumulation via anti-inflammatory action

表1 黄连温胆汤主要活性成分的药理作用

Table 1 Pharmacological actions of the main active constituents of Huanglian Wendan decoction

活性成分	归属中药	靶点/通路/途径	具体效应	参考文献
半夏水提取物	半夏	ATGL ↑	促进脂质分解	[39]
荭草素	竹茹	PI3K/Akt ↑, P38/MAPK ↑, 参与 GLUT2 转运	改善胰岛素抵抗	[40-41]
新橙皮苷、柚皮苷	枳实	NF-κB ↓	抗炎	[42]
茯苓提取物	茯苓	PPARα ↑, SREBP-1c ↓	调节脂质代谢	[43]
甘草查尔酮 A	甘草	NF-κB ↓	抗炎	[44]
姜辣素	生姜	PI3K/Akt ↑	改善胰岛素抵抗	[45]
小檗碱	黄连	SREBP-1c ↓	抑制脂质合成	[16]

注: ATGL, 脂肪甘油三酯脂肪酶; PI3K, 磷脂酰肌醇 3-激酶; Akt, 蛋白激酶B; P38/MAPK, 促分裂原活化的蛋白质激酶; GLUT2, 葡萄糖转运蛋白2; NF-κB, 核因子κB; PPARα, 过氧化物酶体增殖物激活受体α; SREBP-1c, 固醇调节元件结合蛋白1c。

4 小结

黄连温胆汤对 MAFLD 的脂质堆积具有良好的改善作用,并在多项研究中得以证实。在中医理论方面,黄连温胆汤可通过改善膏脂瘀积、调神以修复肝体。在现代医学作用机制方面,黄连温胆汤可从调节脂质代谢、改善胰岛素抵抗和抗炎等3个途径,改善 MAFLD 的脂质堆积。对于调节脂质代谢,黄连温胆汤具有上调 PPARα、LXRα、ABCA1、CYP7A1、肉碱棕榈酰转移酶1,抑制 SREBP-1c 等作用;对于改善胰岛素抵抗,黄连温胆汤具有激活 PI3K/Akt 信号通路,上调 GLUT4,抑制 FOXO1、瘦素,调控 SCFA-GPR41/43-GLP1/PYY 信号轴等作用;对于抗炎,黄连温胆汤具有抑制 NLRP3/Caspase-1 信号通路,上调 TGR5,下调 TLR4,抑制 NF-κB,改善肠道菌群稳态等作用。在药理作用方面,黄连温胆汤的主要活性成分可有效作用于相关靶点,亦可佐证上述观点。由此可见,黄连温胆汤具有多靶点、多通路协同改善 MAFLD 脂质堆积的作用优势,但其对 MAFLD 中铁代谢异常及线粒

体质量控制失衡等方面的作用仍有待揭示。未来研究需对其他方面进行深入探讨,以更全面地揭示其治疗 MAFLD 的潜力。

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