

中医治疗肝衰竭60年：从临床洞见到科学发现

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摘要: 肝衰竭作为高致死率的临床危重症,其治疗面临巨大挑战。本文系统回顾、梳理了我国中医药治疗肝衰竭领域60年传承创新的成果。临床研究方面:早期探索阶段,发现茵陈蒿汤联合西医治疗效果明显,灌肠疗法初显成效,为后续研究奠定基础;循证医学时代,基于对肝衰竭“本虚标实”的认识,创新构建“脾虚邪陷发黄”“气虚瘀黄”“脾肾阳虚发黄”等中医病机理论;基于中医证候动态演变研究,发现HBV相关慢加急性肝衰竭呈现“早实晚虚”的证型特征,据此建立分期辨治框架:早期祛实(解毒化瘀)、晚期补虚(温阳固脱)。技术创新层面:人工肝联合中药、结肠灌洗及针灸凸显多靶点协同优势。基础研究方面:揭示茵陈蒿汤通过肠道菌群-代谢轴调控肝功能,赤芍-附子药对重塑巨噬细胞极化,五味子木脂素与五味子多糖靶向GSH/GPX4调节脂质稳态,电针刺刺激足三里(ST36)激活肝再生信号等,阐明“清热解毒”“温阳固脱”等治则的分子机制。当前面临的挑战包括临床证据异质性、证候-生物标志物关联不足及前沿技术整合瓶颈。未来需构建“临床-基础”双向闭环研究范式,聚焦肠道微生态-免疫-能量代谢网络,推动中医药精准化治疗升级。

关键词: 肝功能衰竭; 中医药疗法; 中西医结合疗法; 针灸疗法

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Traditional Chinese medicine treatment of liver failure for 60 years: From clinical insights to scientific discoveries

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Abstract: Liver failure is a critical illness with a high fatality rate, and its treatment still faces great challenges. This article systematically reviews the achievements of inheritance and innovation in the field of traditional Chinese medicine (TCM) treatment of liver failure in China for the past 60 years. As for clinical research, it was found in the early exploration stage that Yinchenhao decoction combined with Western medicine treatment had a marked therapeutic effect, and enema therapy had shown a certain therapeutic effect, laying a foundation for subsequent research. In the era of evidence-based medicine, the TCM pathogenesis theories were established based on the understanding of “deficiency in origin and excess in superficiality” in liver failure, such as “jaundice due to spleen deficiency and invasion of pathogenic factors”, “Qi-deficiency and blood-stasis jaundice”, and “jaundice due to spleen-kidney Yang deficiency”. Based on the dynamic evolution of TCM syndromes, it is found that HBV-related acute-on-chronic liver failure presents the characteristics of “early excess and late deficiency”, and a framework of staged syndrome differentiation-based treatment has been established as removing excess in the early stage (detoxifying and resolving stasis) and tonifying deficiency in the late stage (warming Yang and securing collapse). As for technological innovation, artificial liver combined with TCM, colonic lavage, and acupuncture and moxibustion has highlighted the advantages of the synergistic effect between multiple targets. Basic research has revealed that Yinchenhao Decoction regulates liver function through the intestinal flora-metabolism axis, the drug combination of Radix Paeoniae Rubra-Radix Aconiti Lateralis Preparata reshapes macrophage polarization, Schisandra chinensis lignans and Schisandra polysaccharides target GSH/GPX4 to modulate lipid homeostasis, and electroacupuncture

stimulates ST36 (zusanli) to activate liver regeneration signal, thereby clarifying the molecular mechanism of the treatment principles such as “clearing heat and detoxicating” and “warming Yang and securing collapse”. Current challenges include the heterogeneity of clinical evidence, insufficient association between syndromes and biomarkers, and the bottleneck of cutting-edge technology integration. In the future, it is necessary to establish a two-way closed-loop research paradigm for clinical and basic research, focus on the intestinal microecology-immunity-energy metabolism network, and promote the upgrading of precise TCM treatment.

Key words: Liver Failure; Traditional Chinese Medicine Therapy; Integrated Chinese Traditional and Western Medicine Therapy; Acupuncture Moxibustion Therapy

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肝衰竭是由多种病因引发的严重肝功能失代偿综合征,以凝血功能障碍、黄疸、肝性脑病及多器官衰竭为特征^[1]。随着病因谱的不断扩展(如病毒、药物、代谢性疾病等),其临床治疗复杂性与挑战性显著增加。根据病程进展差异,肝衰竭可分为急性、亚急性、慢加急性和慢性4类^[1]。我国每年新发肝衰竭患者达30万人以上,28天病死率为30%~40%,总体病死率达60%~80%^[2],高病死率提示肝衰竭治疗领域仍存在巨大未满足的临床需求,这为中医药发挥多靶点干预优势提供了重要契机。其中,慢加急性肝衰竭(ACLF)特指慢性肝病基础上4周内出现的急性恶化,表现为黄疸(血清胆红素>5 mg/dL)、严重凝血异常(INR>1.5或PTA<40%),并伴腹水或肝性脑病,28天病死率超过50%^[3]。我国作为HBV高流行区,HBV相关ACLF占比超80%,其次为药物性及酒精性肝损伤相关ACLF^[4]。

当前治疗依赖“内科综合-人工肝-肝移植”体系,尽管强有力的证据表明人工肝系统可改善急性肝衰竭患者的无移植生存率^[5],但对晚期肝衰竭的疗效欠佳^[6],且无法降低ACLF患者的病死率^[5]。肝移植虽是终极治疗手段,但受限于全球性的供体短缺,仅不足1%患者可以接受肝移植治疗^[7]。新兴疗法如干细胞移植虽具潜力^[8],仍面临细胞来源及技术瓶颈的难题,并需要突破细胞生物学、材料科学、临床医学的多学科壁垒^[9]。

值得注意的是,近60年肝衰竭研究发现,中医药通过多靶点调控在缓解症状(如退黄、改善凝血)、抑制炎症风暴及降低病死率方面展现出独特优势。本文系统综述中医药治疗肝衰竭的临床实践与机制研究进展,以期优化诊疗策略提供新视角。

1 中医药治疗肝衰竭临床实践

1.1 早期临床摸索 20世纪60年代,中西医结合疗法首次应用于急性传染性肝炎合并肝昏迷的治疗^[10],西医方案包括高糖饮食、保肝药物、谷氨酸钠及激素,中医分

期辨证施治:昏迷期以清热解毒为主,清醒后改用茵陈蒿汤(茵陈、栀子、大黄)利湿退黄,15例患者黄疸指数有效消退、肝脏合成能力与炎症反应改善。20世纪70年代,进一步研究将中药鼻饲(茵陈蒿汤化裁送服安宫牛黄丸)与西医综合治疗(能量合剂与谷氨酸钠静脉滴注、水合氯醛灌肠等)结合,成功救治1例亚急性肝坏死合并肝昏迷患者,其神志转醒、黄疸渐退、肝功能转复^[11]。另有研究采用通腑泻热、凉血解毒法(大黄6~12 g后下、枳实9 g、厚朴6 g、茵陈30 g、元参15~24 g、连翘24 g、黄连6 g、赤芍15 g、丹参15 g、生地15 g、郁金9 g、丹皮9 g,水煎灌服或鼻饲,每日2剂)结合西医支持治疗(补液、纠正电解质紊乱),21例肝昏迷患者有效率达58.3%^[12]。一项回顾性分析101例重症肝炎病例的研究提出“分阶段辨证”策略^[13]:早期以清热、解毒、利湿、退黄为主,酌情应用活血化痰,稳定后祛邪扶正并重,恢复期以扶正为主,联合“清肝注射液”(茵陈、栀子提取物)静脉滴注,使生存率从1973年的20%跃升至1977年的64%,大体反映了这个时期的中医治法。

灌肠疗法在此阶段初显成效,中医药联合人工肝治疗也开展了初步探讨。一项对照研究显示,活性炭联合大黄煎剂灌肠治疗肝性脑病,治疗组每日灌肠1~2次,连续7天,病死率从70%降至25.5%,血氨水平从148.6 μmol/L降至102.1 μmol/L($P<0.05$)^[14]。另一项临床实践将茵陈蒿汤配伍消食化滞中药(茵陈30 g,栀子6 g,神曲、谷麦芽、山楂各12 g)联合安宫牛黄丸保留灌肠,联合小剂量血浆置换(单次置换量3 L,每例1~6次),应用于44例重型肝炎患者,结果显示TBil及凝血酶原时间(PT)均显著下降^[15]。上述代表性研究基本体现了这一时期中医药治疗肝衰竭的发展情况。

1.2 规范化研究

1.2.1 循证医学推动中西医结合方案标准化 一项研究采用中药多途径给药:在对照组治疗基础上,治疗组加用茵栀黄、清开灵及复方丹参注射液每日静脉滴注,茵虎汤

口服每日1剂,退黄灌肠液保留灌肠每日1次,结果显示治疗组治愈显效率为57.14%,总有效率为82.14%,显著优于对照组($P<0.05$),且肝肾综合征发生率明显降低^[16]。另一项研究证实,醋制大黄30g、乌梅30g煎煮灌肠联合人工肝治疗,可降低内毒素水平($P<0.05$),且血氨下降幅度较对照组明显^[17]。一项解毒化瘀颗粒(赤芍、茵陈、白花蛇舌草、郁金、大黄、石菖蒲)治疗重型肝炎的随机对照试验显示,治疗组肝性脑病改善率显著高于安宫牛黄丸组($P<0.05$)^[18]。进一步研究采用解毒化瘀颗粒联合西医综合治疗(抗病毒、保肝),治疗组90天生存率显著提高,MELD评分明显降低($P<0.05$)^[19]。上述以“瘀热”论治的医疗实践,继承发扬了《伤寒杂病论》关于“黄疸”的辨证论治思想。

1.2.2 辨证分型进一步细化 基于HBV-ACLF属本虚标实之证的认识,有学者提出“脾虚为本,湿热毒瘀互结为标”的理论,构建了“解毒凉血重通腑,健脾化湿顾中焦”的治疗原则,开展临床分型辨治:瘀热毒结证用解毒凉血方(茵陈30g、大黄6~15g、栀子15g、黄芩15g、蒲公英30g、生地黄15g、赤芍30g、丹参15g、牡丹皮15g、紫草15g、郁金15g、麸炒白术15g、茯苓15g、陈皮15g),湿热毒蕴证用解毒凉血利湿方(茵陈15g、龙胆15g、栀子15g、黄芩15g、升麻15g、车前子30g、生地黄15g、泽泻15g、牡丹皮15g、丹参15g、麸炒白术15g、茯苓15g),脾虚湿热证用解毒凉血健脾方(黄芪30g、党参15g、茵陈30g、麸炒白术30g、茯苓30g、赤芍30g、生地黄15g、升麻15g、陈皮15g、法半夏9g、山楂30g、大黄10g),均取得显著疗效^[20]。其中,解毒凉血健脾方创新性引入“脾虚邪陷”的治疗理念,为后续研究提供了启发。

1.2.3 不同证型肝衰竭的中医药治疗进展

在这一时期,肝衰竭的中医药治疗研究引入了循证医学理念,对不同证型的临床疗效验证取得了系统性进展。

1.2.3.1 对湿热蕴结证的循证医学研究 经典方剂复方茵陈蒿汤通过现代制剂开发,已形成或延伸为赤丹退黄颗粒、茵栀黄颗粒/口服液、苦黄颗粒等标准化中成药体系^[21-22]。一项涵盖19项随机对照试验2029例黄疸型病毒性肝炎患者的网状Meta分析显示,苦黄颗粒联合常规治疗的总有效率达92.57%,较茵栀黄口服液(81.46%)和茵栀黄颗粒剂(79.61%)具有显著优势,为湿热证型药物选择提供了较高级别证据支持^[22]。

1.2.3.2 对气虚瘀黄证的循证医学研究 一项前瞻性队列研究评估了中西医结合治疗对HBV-ACLF患者临床

结局的影响,该研究共纳入934例患者,依据实际接受的治疗方案分为两组,中西医结合治疗组($n=593$)根据中医辨证分型给予相应方剂治疗,湿热瘀黄证患者予凉血解毒化瘀方加减、气虚瘀黄证予益气解毒化瘀方加减;对照组($n=341$)接受标准西医治疗。结果显示,中西医结合治疗组48周累积病死率为27.0%,显著低于对照组的32.0%($P<0.05$)^[23]。

1.2.3.3 对脾肾阳虚证的探索 2012年一项前瞻性、横断面研究分析324例不同阶段HBV-ACLF患者中医辨证分布,结果显示HBV-ACLF中医证型分布呈现显著的“早实晚虚”动态演变特征。在HBV-ACLF早期($n=140$),实证占比突出,其中热毒瘀结证发生率高达58.57%(82/140);晚期阶段($n=78$)则以虚证为主,阳气虚衰证占比升至41.03%(32/78),显著高于中期(22/106,20.75%)和早期(12/140,8.57%)($P<0.003$)^[24]。这一结果提示,HBV-ACLF的临床治疗需紧密结合病程阶段特征,早期以清热化瘀(针对热毒瘀结证)为主,晚期则需强化温补阳气(针对阳气虚衰证)以改善预后,为温阳法治疗肝衰竭提供了中医理论依据。在前期结果的基础上,该研究团队通过一项回顾性队列研究观察加味四逆汤(附子、干姜、甘草、人参、乌梅)治疗HBV-ACLF的临床疗效^[25],结果表明,观察组在标准综合治疗基础上联合中药干预后,多项肝功能和预后指标显著改善,提示加味四逆汤通过多靶点调控肝功能代谢及凝血功能,为HBV-ACLF晚期的中医治疗提供了重要线索。同期的另一项研究^[26]对比凉血解毒、清热化湿与凉血解毒、健脾温阳法,发现后者治疗慢性重型肝炎阴阳黄证疗效更优。随后的一项随机对照临床试验^[27]探讨了茵陈四逆汤治疗ACLF阴黄证患者的临床疗效,将260例符合诊断标准的ACLF阴黄证患者随机分为对照组($n=130$,接受标准西医综合治疗)和治疗组($n=130$,在西医综合治疗基础上加用茵陈四逆汤(茵陈30~60g、炮附子10g先煎、干姜10g、炙甘草10g)辨证加减治疗],疗程8周。结果显示,治疗组中医证候总有效率(87.90% vs 60.83%, $P<0.05$)和8周临床总有效率(91.54% vs 53.85%, $P<0.01$)均显著高于对照组;在实验室指标方面,治疗组血清TBil、ALT、Alb、PTA及MELD评分的改善幅度均显著优于对照组(P 值均 <0.01);12周随访时治疗组存活率亦显著高于对照组($P<0.05$),表明茵陈四逆汤辨证治疗可显著改善ACLF阴黄证患者的临床症状、生化指标及短期预后。上述研究在传承《金匮要略》“瘀热发黄”理论精髓的同时,创造性聚焦《伤寒论》“少阴病”本质,提出“少阴阳衰为本,湿毒瘀

热为标”的肝衰竭核心病机观,更通过“回阳救逆”的治则突破,填补了肝衰竭晚期“阴阳离决”阶段的中医辨治空白,为逆转肝衰竭“阳衰毒陷”的危重病势提供了关键性治疗方法,为肝衰竭的中医治疗提供了崭新的视角,有助于完善中医药治疗肝衰竭的全链条诊疗框架。

在这一时期,中医药治疗重症酒精性肝炎研究也取得了进展。在强的松治疗的基础上加用固脱解酒方(人参、葛根、黄芩等组成)治疗,相较于仅接受强的松治疗的患者相比,前者在生存率、生化指标、MDF评分、MELD评分、CTP分级及中医临床症状积分等方面均显著优于后者。

1.3 创新疗法与技术融合

1.3.1 人工肝与中药协同增效 陆霓虹等^[29]采用生大黄灌肠(30 g煎汁200 mL)联合非生物型人工肝治疗急性肝衰竭,总有效率为89%,肝功能改善率为83%,凝血功能明显改善,并发症发生率显著低于单纯人工肝组($P<0.05$)。王振东等^[30]应用双重血浆分子吸附系统(DPMAS)联合“辛开苦降”法(安宫牛黄丸口服+大黄、桃仁灌肠),患者TBil、凝血功能及90天生存率均显著改善(P 值均 <0.05)。此类研究开创性地将中医病机理论与现代血液净化技术结合,但其提升疗效的调节机制尚需验证。

1.3.2 结肠灌洗技术革新 商斌仪等^[31]采用结肠治疗仪联合新石军方(大黄30 g、石菖蒲15 g、乌梅30 g、败酱草30 g)灌肠治疗慢性肝衰竭,病死率为8.8%,显著低于保肝对症治疗组的45.5%($P<0.05$)。曹慧等^[32]通过结肠透析机高位灌肠(茵陈60 g、栀子15 g、生大黄30 g)治疗肝衰竭早期湿热瘀黄证,好转率为65%,消化系统症状改善时间缩短($P<0.05$)。李秀惠团队^[33]采用清肝利肠方(生地、蒲公英、大黄等)结肠透析,显著降低了慢性乙型重型肝炎病死率。

1.3.3 针灸与免疫调节 李爱民等^[34]通过针刺肝俞、足三里等穴位联合高氧液治疗急性肝衰竭合并低氧血症,患者ALT、TBil及血氨下降速度显著优于吸氧联合药物治疗组(P 值均 <0.05)。Jia等^[35]研究证实,短期甲泼尼龙治疗($1.5\text{ mg}^{-1}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ 递减)可提高HBV-ACLF患者6个月生存率(32.4% vs 42.5%, $P=0.0037$)。Tong等^[36]采用粒细胞集落刺激因子治疗HBV-ACLF,180天生存率提升至72.2%,促进单核细胞M2表型转化,并显著减少炎症因子分泌($P<0.05$)。

1.4 肝衰竭的非药物疗法

1.4.1 中药灌肠疗法 基于中医“肝与大肠相通”理论,王融冰教授^[37]创新性地提出了“调肠治肝”的治疗思路,其采用复方大黄煎剂(生大黄、芒硝、乌梅)高位灌肠法,

以釜底抽薪、清热泄毒为治疗原则,在治疗内毒素血症、ACLF及肝性脑病等疾病中均取得了显著的临床疗效。李海凤等^[38]采用赤芍承气汤(赤芍、厚朴、枳实、乌梅、生大黄)高位保留灌肠治疗ACLF,结果显示,治疗组肠道双歧杆菌等有益菌显著增加、TBil水平明显下降、PTA水平升高(P 值均 <0.05)。易臻等^[39]进一步验证了大黄乌梅汤(大黄、乌梅)灌肠治疗的总有效率为86.67%,肝衰竭患者临床疗效及生化指标均明显好转($P<0.05$)。

1.4.2 针灸与物理疗法 田凌云等^[40]将消胀灵(桂枝、冰片、丁香、柴胡)贴敷于期门、神阙穴治疗肝硬化腹水,治疗组腹水完全消退率显著高于单纯保肝对症治疗组($P<0.05$)。李爱民等^[41]采用高氧液静脉输注联合针灸、穴位贴敷治疗慢性肝衰竭,患者血氨显著下降,氧分压显著改善($P<0.05$)。

综上可见,中医药治疗肝衰竭历经经验积累、循证规范到技术创新的跨越式发展。早期以茵陈蒿汤联合西医支持治疗为主,使重症肝炎生存率从20%跃升至64%^[13],大黄灌肠降低血氨^[14],奠定“肠-肝轴”干预基础。21世纪后,循证研究推动辨证分型细化,解毒化瘀颗粒可改善肝性脑病^[18],中西医结合治疗可显著提高生存率^[19]。针对晚期“阳气虚衰”证的温阳法突破传统治疗理念,加味四逆汤使HBV-ACLF患者12周生存率达62.9%^[25],茵陈四逆汤将阴黄证治疗有效率提升至91.54%^[27],揭示“少阴阳衰为本”的核心病机。技术创新融合多学科优势,人工肝联合辛开苦降法改善90天预后^[30],结肠灌洗使病死率降至8.8%^[31],针灸联合高氧液显著降低血氨^[34],赤芍承气汤调节肠道菌群^[38],凸显多靶点协同治疗机制。未来研究需突破小样本局限,深化“病-证-效”机制解析,尤其在肠道微生态-免疫网络层面,以实现疗效瓶颈突破,推动中医药传承创新。

值得注意的是,肝衰竭相关诊断标准的动态修订,以及不同医疗中心在收治标准、评估体系及区域中医证候学特征等方面存在多维差异,导致现有研究队列呈现显著的临床异质性。这种异质性不仅使跨研究的疗效指标比较缺乏统一基准,更对系统性评价及荟萃分析构成实质性障碍。然而,各研究数据均真实记录了特定诊疗场景下的干预路径与预后轨迹,其科学价值在于通过多维度临床实证,揭示肝衰竭病理进程的时空变异规律,为构建精准化诊疗策略提供实证依据。

2 基础研究进展:从经验总结到分子机制解析

2.1 1960—1990年:传统理论与初步实验验证 肝衰

竭的中医理论体系根植于古代医籍对“急黄”“肝瘟”“鼓胀”等病症的深刻认知。张仲景在《金匱要略》中提出“黄家所得,从湿得之”,巢元方进一步阐释“热毒致黄”的急性病机,叶天士则从“湿从热化,瘀热在里”角度论述肝胆功能失调的病理本质,形成以“湿、热、疫毒、瘀”为核心的四维病机框架^[42-45]。20世纪60—80年代,中医研究从经验医学迈入实验科学阶段,学者通过临床实践与基础研究相结合,系统验证经典理论的科学性。茵陈蒿汤作为治疗肝衰竭的代表方剂,其作用机制首次通过正交设计实验被揭示:全方配伍通过协同调节Oddi括约肌张力、降低血清转氨酶活性(ALT/AST)及促进肝糖原合成,从肝胆动力学与代谢调控双维度阐释了“疏肝利胆”的现代内涵^[46-47]。同期研究发现,山栀子提取物可显著降低黄疸模型大鼠的血清胆红素水平,提示中药组分研究需关注提取工艺对活性成分生物利用度的影响^[48]。针对慢性肝损伤,大黄蛰虫丸的抗纤维化效应被证实与羟脯氨酸和胶原合成抑制相关,同时通过改善肝组织学表现,为“活血通络”理论提供了量化实验依据^[49-50]。此阶段研究虽受限于技术条件,但已初步构建“辨证-方剂-机制”关联的研究范式。

2.2 1990—2010年:分子机制与药效物质基础突破

此阶段研究揭示了天然植物提取物在肝脏保护中的多靶点协同机制,涵盖抗氧化、炎症调控及凋亡抑制等关键通路,并初步验证了复方制剂的临床转化潜力。

2.2.1 抗氧化与调节谷胱甘肽 女贞子提取物通过激活 γ -谷氨酰半胱氨酸合成酶(γ -GCS),显著提升肝脏谷胱甘肽水平,缓解 CCl_4 诱导的氧化损伤^[51];芝麻油则通过增强线粒体乌头酶活性,协同谷胱甘肽系统减轻对乙酰氨基酚肝毒性^[52]。银杏叶提取物展现出双重作用,其黄酮苷成分清除自由基能力显著,同时拮抗血小板活化因子(PAF)受体,但因缺乏PAF受体敲除模型验证,临床转化受限^[53-54]。酸枣仁汤通过动态平衡氧化应激网络(超氧化物歧化酶活性提升,丙二醛降低,NO、T-NOS和iNOS降低),首次揭示中药复方代谢网络调控特性,但因缺乏代谢组学追踪,机制未明^[55]。

2.2.2 调控炎症 越南人参的主要皂苷成分MR2具有TNF- α 通路双重抑制作用,既能抑制活化的巨噬细胞生成TNF- α ,又直接抑制TNF- α 诱导的细胞凋亡^[56]。垂盆草提取物通过TLR4/MAPK/NF- κ B信号轴抑制IL-6、TNF- α 分泌,并阻断Caspase-3激活,从而有效预防暴发性肝衰竭;芦荟-水飞蓟复合物则通过抑制TIMP-1/TGF- β 1表达发挥抗纤维化作用^[57-58]。

2.2.3 调控凋亡 葛根异黄酮Daidzin通过稳定线粒体膜电位及减少谷胱甘肽耗竭实现肝细胞的双重保护^[59];虎眼万年青总皂苷通过下调HIF-1 α /Caspase-3通路发挥抗凋亡活性^[60]。

2.2.4 临床复方制剂的科学验证 三黄茵赤汤(含大黄、赤芍等)与安宫牛黄丸可显著降低急性肝衰竭大鼠ALT、TBil水平,缩短PT,抑制Caspase-3活性,证实了传统方剂在现代肝病治疗中的重要作用^[61]。

2.3 2010年至今:系统生物学与多组学整合 近年研究通过整合基因组、转录组、代谢组等多组学技术,系统解析中药复方多靶点作用网络。加味四逆汤、加味桃核承气汤、乌头水提取物及清肝活血方均显示出对HMGB1/TLR4/NF- κ B/Caspase-3信号轴的协同抑制作用,同时上调肝再生标志物增殖细胞核抗原(proliferating cell nuclear antigen, PCNA);值得注意的是,清肝活血方可显著改善急性肝衰竭大鼠肝功能并纠正凝血异常^[62-65]。犀角地黄汤通过激活NF- κ B依赖的抗凋亡通路,抑制TNF- α /D-GalN诱导的肝细胞凋亡,生地黄为其关键味药,其核心成分半乳糖通过阻断TLR/MAPK/NF- κ B炎症信号发挥保护作用^[66]。解毒凉血方通过调节TGF- β 1/Smad通路,抑制急性肝衰竭肝细胞凋亡;解毒化瘀颗粒对 H_2O_2 诱导的LO2肝细胞炎症反应有保护作用,其机制可能与TLR/MAPK/NF- κ B信号通路相关^[67-68]。

肠道微生物群-代谢轴研究揭示茵陈蒿汤可恢复梭菌目菌群丰度,调节3-羟基丁酸代谢物,提示茵陈蒿汤可能通过调节梭菌类群比例影响3-羟基丁酸的产生而发挥保肝作用,但其分子机制仍需阐明^[69]。五味子木脂素与五味子多糖的护肝作用可能依靠对GSH/GPX4介导的脂质代谢紊乱的调控,而牛角地黄解毒汤通过升高半胱氨酸、谷胱甘肽水平抑制铁死亡^[70-72]。免疫调节机制方面,赤芍-附子药对具有调节巨噬细胞极化,抑制促炎因子TNF- α 、IL-6分泌的作用^[73]。四逆加入人参汤可通过激活PPAR α 及CPT1A增强线粒体 β 氧化,并抑制HMGB1释放和NF- κ B活化;同时,四逆汤可通过MTOR/HIF-1 α 信号轴调控巨噬细胞代谢重编程与表型转化,为中西医结合治疗急性肝衰竭提供了创新性理论基础^[74-75]。芍药甘草汤则可通过促进线粒体自噬显著减轻对乙酰氨基酚诱导的肝损伤^[76]。电针刺激ST36穴位可通过激活胆碱能神经元-IL-6通路,促进肝细胞增殖^[77]。清热解毒、凉血化瘀中药联合干细胞移植通过调控Bcl-2/Bax/Caspase-3通路抑制肝细胞凋亡^[78]。

在ACLF治疗领域,温阳法研究取得了标志性突破。

四逆加人参汤被证实具有双重调控功能:通过抑制 HMGB1/NF- κ B 炎症轴阻断“炎症瀑布”,同时激活 PPAR α /CPT1A 代谢轴(ATP 水平显著升高)逆转线粒体能量崩溃^[74]。进一步研究揭示其通过抑制 MTOR/HIF-1 α 信号轴调控巨噬细胞代谢重编程,促进 M2 型巨噬细胞极化^[75],从免疫代谢角度阐释了“温阳固脱”的科学本质。临床研究显示,HBV-ACLF 晚期患者中“阳气虚衰证”占比达 41.03%^[24],与“少阴阳衰为本”的病机理论高度吻合;采用加味四逆汤干预后,患者 12 周生存率明显提升,ALT、AST 水平下降,PTA 显著改善^[25],其临床疗效与基础研究揭示的糖酵解调控强度形成显著量效关联,最终构建了“炎症/代谢靶点调控-阳虚证候特征-临床疗效终点”的全链条证据体系,实现了《伤寒论》“回阳救逆”治则与现代病理机制的跨时空对话。

历经 60 年系统研究,中医药治疗肝衰竭理论体系与现代医学机制已实现多维度深度融合,形成了从经典理论阐释到分子网络解析的完整科学证据链。

3 小结与展望

经过半个世纪的传承与创新,中医药研究已突破传统经验医学的边界,构建起“临床实践-机制解析-技术革新”深度融合的转化医学体系。在临床诊疗方面,从早期茵陈蒿汤降低黄疸指数、改善凝血功能的直观疗效,到灌肠疗法揭示“肠-肝轴”调控的生物学价值,直至温阳法显著提高 HBV-ACLF 患者 12 周生存率,中医药在“清热解毒”到“扶阳固本”的治则演进中,不仅验证了辨证分型与 MELD 评分等客观指标的结合价值,更以“少阴阳衰为本”的病机理论重塑了肝衰竭的治疗范式。技术创新层面,中西医多学科交叉促进突破性疗法:人工肝联合中药增效方案、靶向结肠道菌群的灌洗技术优化、电针刺激足三里等,展现出整合医学的独特优势。基础研究深度解析其科学内核:茵陈蒿汤通过肠道菌群-代谢轴调控肝功能;赤芍-附子药对重塑巨噬细胞极化;五味子木脂素与五味子多糖通过调节 GSH/GPX4 改善脂质代谢异常;四逆加人参汤双重调控 HMGB1/NF- κ B 炎症轴与 PPAR α /CPT1A 代谢轴、调控巨噬细胞代谢重编程,促进 M2 型极化等,系统揭示了“多成分-多靶点-多通路”协同作用的分子全景。

当前研究仍面临三重转化瓶颈:临床层面,疗效评价受限于临床研究的异质性;机制层面,“中医证候-生物标志物-干预靶点”的动态映射模型尚未建立,肠道菌群时序变化、免疫微环境空间异质性等新型指标与传统

辨证分型的关联缺乏量化标准;技术层面,类器官模型对中药多成分体系的响应模拟度不足,干细胞联合疗法的中西医整合方案亟待技术突破。破解这些难题需要构建“临床表型精准刻画-多组学生物网络解析-智能模型动态预测”三位一体的研究范式,重点聚焦肠道微生态-免疫代谢-细胞死亡网络的动态互作机制,通过人工智能驱动的真实世界证据整合(如全球肝病注册平台)、仿生器官芯片模拟系统(肝-肠-免疫多组织互作模型)及数据融合技术,推动中医药从“群体疗效”向“精准干预”跨越,为肝衰竭治疗贡献具有中国特色的解决方案。

利益冲突声明: 本文不存在任何利益冲突。

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