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Review 综述

丹参与微生态调节剂：临床干预酒精性肝病的研究前景

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摘　要：酒精性肝病(alcoholic liver disease, ALD)是全球最常见的慢性肝病之一，也是肝硬化和肝癌的重要诱因。当前 ALD 诊疗面临诊断延迟、戒酒依从性差、特效药物匮乏等挑战，开发新的干预策略意义重大。近年来，药用植物丹参(*Salvia miltiorrhiza*, *Sal*)对 ALD 的干预作用受到广泛关注。其粗提物及活性单体可通过抗炎、调节脂质代谢等途径缓解 ALD 病理进程，但单药疗效存在局限性，因此联合用药成为 ALD 治疗的重要策略。本文综述 *Sal* 联合天然产物、抗氧化剂、保肝药物、微生态调节剂等联合策略干预 ALD 的研究进展。发现 *Sal* 联合用药可调控肠道菌群丰度，经肠道菌群介导发挥协同保肝作用。相关研究证实，益生菌、益生元、后生元及合生元等微生态调节剂也可通过“肠-肝轴”调控机制改善 ALD，是 *Sal* 干预 ALD 的潜在临床联合策略，具有良好的临床前景。靶向 ALD 肠道菌群稳态调控，开发 ALD 微生态调节剂不仅可为开发高效低毒的生物活性制剂提供全新思路，还对改善 ALD 疗效缓解 ALD 预后具有潜在的临床价值，是未来 *Sal* 联合干预 ALD 新策略的重要研发方向。

关键词：酒精性肝病；微生态调节剂；肠道菌群稳态；丹参；联合用药

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Salvia miltiorrhiza and microecological regulators: research prospects for clinical intervention in alcoholic liver disease

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Abstract: Alcoholic liver disease (ALD) is one of the most common types of chronic liver diseases globally and an important cause of liver cirrhosis and liver cancer. Currently, the diagnosis and treatment of ALD face challenges such as delayed diagnosis, poor compliance with alcohol abstinence, and a lack of specific drugs. Therefore, it is of great significance to develop new intervention strategies. In recent years, the intervention effect of the medicinal herb *Salvia miltiorrhiza* (*Sal*) on ALD has received extensive attention. The crude extracts and active components of *Sal* can alleviate the pathological process of ALD through anti-inflammatory and lipid metabolism regulation, while the efficacy of single *Sal* treatment has limitations. Thus, combination medication has become an important strategy for ALD treatment. This article reviews the research progress in the combination strategies of *Sal* with natural products, antioxidants, liver-protecting drugs, and microecological regulators in the intervention of ALD. It is found that the combination medication with *Sal* can regulate the abundance of the gut microbiota and play a synergistic liver-protecting role through the mediation of gut microbiota. Relevant studies have confirmed that microecological regulators such as probiotics, prebiotics, postbiotics, and synbiotics can also ameliorate ALD by regulating the "gut-liver axis", and they can be combined with *Sal* to intervene in ALD, demonstrating good clinical prospects. Developing microecological regulators targeting the gut microbiota homeostasis in ALD can not only provide new ideas for the development of bioactive preparations with high efficiency and low toxicity, but also have potential clinical value in improving the therapeutic efficacy and prognosis for ALD. It is an important research and development direction for new combination intervention strategies with *Sal* for ALD in the future.

Keywords: alcoholic liver disease; microecological regulator; gut microbiota homeostasis; *Salvia miltiorrhiza*; combination medication

酒精性肝病(alcoholic liver disease, ALD)已成为全球重大公共卫生难题，全球疾病、伤害和风险因素负担研究(global burden of diseases, injuries, and risk factors study, GBD)数据库2023年明确将酒精使用(alcohol use)纳入健康危险因素评估[1]。根据世界卫生组织2022年的数据统计，全球癌症新发案例近2 000万例，肝癌位列第六(占4.3%)；新增死亡病例970万例，肝癌位列第三(占7.8%)[2]。酒精过度使用给个人健康与社会医疗体系带来沉重负担，当前临床针对ALD

的治疗手段存在明显局限性，难以满足临床需求[3-4]。因此，开发 ALD 新药对于缓解 ALD 临床局限性、改善患者预后具有重要的临床意义。药用植物丹参(*Salvia miltiorrhiza*, *Sal*)是唇形科(Labiatae)鼠尾草属(*Salvia*)直立草本植物，具有活血化瘀的药理功效，临床上常用于治疗心血管系统疾病[5]。研究发现，*Sal* 对多种肝脏疾病也具有良好的效果[6-7]，本文系统性综述了 *Sal* 粗提物、其活性单体，以及它们联合天然产物(natural products)、抗氧化剂(antioxidant)等药物缓解 ALD 的机制研究，同时梳理了微生态调节剂(microecological regulator)及其联合 *Sal* 治疗 ALD 的相关研究，以期为开发 *Sal* 缓解 ALD 的联合用药新策略提供新思路。

1 ALD 的临床简介和研究进展

ALD 是长期过量饮酒导致的肝脏疾病，可诱导肝脂肪变性，严重时可诱发肝硬化甚至肝癌[8]。有数据预测表明：2019–2039 年肝硬化的数量和发病率将持续上升[9]。目前临床筛查 ALD 主要依赖饮酒史、肝功能指标及影像学检查，干预策略常包括酒精戒断、感染监测、抗生素治疗、营养补充和肝移植等[10]，然而，晚期 ALD 硬化及重症肝炎预后较差，死亡风险高[11]。糖皮质激素是目前唯一被证实对重症 ALD 有效的药物，但死亡率仍有 10%[12-13]，并且，ALD 发病机制复杂，酒精可诱导肝脏多种病理改变，例如氧化应激[14]、脂质代谢异常和脂质积累[15]、内质网应激[16]、细胞自噬[17]、细胞焦亡[18]、细胞铁死亡[19]、细胞坏死[20]和细胞凋亡[21]等，还可诱导肠道微生物群失调[22-23]，共同介导肝细胞损伤、肝脂肪变性、肝纤维化甚至肝癌的发生发展[24-27]。因此，开发 ALD 新的干预策略是缓解其临床局限性的重要研究方向。

2 *Sal* 治疗 ALD 的作用机制研究进展

2.1 *Sal* 粗提物治疗 ALD 的研究进展

Sal 为临床常用活血化瘀中药[28]，其主要活性成分包括水溶性酚酸类[丹酚酸 A (salvianolic acid A, SalA)、丹酚酸 B (salvianolic acid B, SalB)、迷迭香酸(rosmarinic acid, RA)等]与脂溶性酮类[丹参酮IIA (tanshinone IIA, Tan IIA)、隐丹参酮(cryptotanshinone, CTS)、丹参酮I (tanshinone I, Tan I)等]。近年来，*Sal* 在 ALD 防治中展现出多靶点、多通路的保护作用，已成为 ALD 新药研发的重要方向。其粗提物能够降低丙氨酸氨基转移酶(alanine aminotransferase, ALT)、天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)水平，减少肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、白细胞介素-1 (interleukin-1, IL-1)等炎症因子释放，减轻肝脏炎症[29-30]。同时，*Sal* 可通过激活过氧化物酶体增殖物激活受体 α (peroxisome proliferator activated receptor α, PPARα)，促进 4-羟基壬烯醛(4-hydroxynonenal, 4-HNE)降解，并下调 Toll 样受体 4 (Toll-like receptor 4, TLR4)和血红素氧化酶-1 (heme oxygenase-1, HO-1) mRNA 的表达，缓解 ALD 肝脂肪变性[31-32]。

2.2 *Sal* 活性单体治疗 ALD 的研究进展

相较于粗提物，*Sal* 水溶性活性单体作用明确、机制清晰，在 ALD 精准治疗研究中更受关注。丹酚酸 A 是 *Sal* 一种水溶性活性成分，可调控沉默信息调节因子 1 (silent information regulator 1, Sirt1)介导的细胞自噬，降低 ALT、AST、甘油三酯(triglyceride, TG)和胆固醇(total cholesterol, TC)水平，增强肝细胞活力、减轻肝细胞凋亡与脂肪变性[33-34]。丹酚酸 B 是 *Sal* 的另一种水溶性活性成分，其通过激活 *Sirt1*，介导 C 反应蛋白(C-reactive protein, CRP)表达，降低 TNF-α、白细胞介素-6 (interleukin-6, IL-6)等促炎

因子表达，减少血清及肝脏脂质积累，抑制血清转氨酶升高，缓解 ALD 肝损伤[35]。

除水溶性酚酸外，*Sal* 的脂溶性活性单体同样对干预 ALD 发挥关键作用。隐丹参酮是 *Sal* 中的脂溶性单体，可激活腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)、*Sirt1* 通路及核因子 E2 相关因子 2 (nuclear factor erythroid 2-related factor 2, Nrf2)磷酸化，同时抑制细胞色素 P450 2E1 (cytochrome P450 2E1, CYP2E1)的表达，抑制酒精诱导的肝脂肪变性、炎症反应及氧化应激损伤[36-37]。丹参酮IIA 是 *Sal* 的另一种脂溶性单体，可通过逆转乙醇诱导的视黄醇 X 受体 α (retinoid X receptor-alpha, RXRα)的异常表达，抑制脂肪酸合成并促进其氧化分解，减少酒精介导的肝脏脂质积累[38]。

综上所述，*Sal* 的粗提物和多种活性单体对 ALD 具有良好的生物学活性，可缓解 ALD 诱导的肝脂肪变性、炎症反应、氧化应激损伤、细胞自噬等病理改变。*Sal* 及其活性单体治疗 ALD 的作用机制总结如表 1 所示，与单一用药相比，*Sal* 与多种天然产物、抗氧化剂及其他药物联合应用在改善 ALD 患者肝功能、减轻肝脏病理损伤等方面更具优势，是临床干预 ALD 的重要手段。

3 *Sal* 联合用药缓解 ALD 的临床应用

3.1 *Sal* 联合天然产物缓解 ALD 的临床应用

复方甘草甜素(compound glycyrrhizin, CG)，又称复方甘草酸苷，是从甘草中提取的复方制剂，其主要成分为 2% 甘氨酸、0.2% 甘草酸苷及 0.1% 盐酸半胱氨酸，目前已纳入医保目录，为临床治疗肝脏疾病的常用药物，临床研究发现，其可与还原型谷胱甘肽(glutathione, GSH)联用用于治疗儿童急性肝损伤，且 CG 联合用药组疗效明显优于对照组[39]。一项调查报告(2014−2016 年)显示，给予 60 例 ALD 患者复方甘草酸苷和 *Sal* 注射液联合治疗，可明显改善 ALD 患者血清 AST 和 ALT 水平[40]。另一项临床研究发现，92 例 ALD 患者在严格戒酒基础上联合 *Sal* 治疗可明显改善患者肝功能指标[41]。

水飞蓟(*Silybum marianum*, *SIL*)是菊科水飞蓟属的草本植物，原产地在南欧或北非地区，其制剂可成为一种护肝类膳食补充剂，主要用于改善肝损伤等病症。研究表明，水飞蓟和葛根(*Pueraria lobata*, *PUE*)联用可激活肝激酶 B1 (liver kinase B1, LKB1)/AMPK/乙酰辅酶 A 羧化

表1 *Sal*及其活性单体治疗ALD的机制总结

Table 1 Summary of the mechanism of *Sal* and its active monomers in the treatment of alcoholic liver disease

Drugs	Targets	Results	References
Sal	PPARα, TLR4, HO-1	Its crude extract can reduce ALT and TG levels, alleviate liver inflammation and ALD-related liver damage, activate PPARα to promote 4-HNE degradation, and down-regulate the mRNA expression of TLR4 and HO-1	[31-32]
SalA	Sirt1	SalA can regulate the Sirt1 expression, reduce the levels of ALT, AST, TG, and TC, enhance hepatocyte vitality, and alleviate ALD	[33-34]
SalB	Sirt1, CRP, TNF-α, IL-6	SalB can activate Sirt1, inhibit the expression of CRP, reduce the levels of pro-inflammatory factors such as TNF-α and IL-6, inhibit the increase of serum transaminase, and alleviate ALD	[35]
CTS	AMPK, Sirt1, Nrf2, CYP2E1	CTS can activate AMPK, Sirt1 pathways, and phosphorylate Nrf2, meanwhile, it can also inhibit CYP2E1 expression, suppress alcohol-induced hepatic steatosis, liver inflammatory response and oxidative stress injury, and alleviate ALD damage	[36-37]
Tan IIA	RXRα	Tan IIA can reverse abnormal RXRα expression, promote fatty acid oxidation, reduce hepatic lipid accumulation, and alleviate ALD-induced liver injury	[38]

酶(acetyl-CoA carboxylase, ACC)信号通路，减轻酒精诱导的肝脂肪变性，同时抑制 TLR4 介导的核因子 κB (nuclear factor-κB, NF-κB)信号通路缓解 ALD 肝损伤[42]。一项 121 例非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)患者的临床试验结果显示，水飞蓟、葛根素和 *Sal* 联合给药的患者乙醛脱氢酶活性显著升高，治疗效果更优良，有助于促进酒精在肝脏的代谢，该方案已在美国临床试验注册平台上注册(NCT05076058)[43]。另一项临床研究发现，112 例 ALD 患者中 56 例水飞蓟宾胶囊和复方 *Sal* 滴丸联合治疗组总胆红素(total bilirubin, TBIL)及肝纤维化指标明显低于单独给药组，治疗期间未见明显不良反应，安全性较高[44]。

中草药三七(*Panax notoginseng*, *PN*)、芳香二苯醚(diphenyl ether, DPE)和 *Sal* 是用于治疗冠状动脉和脑梗死等心血管疾病的中药复方，可升高 PPARα mRNA 表达水平，抑制酒精诱导的肝脂肪变性，缓解 ALD 肝损伤[45]。

五味子(*Schisandra chinensis*, *SC*)、葛根、水飞蓟宾和 *Sal* 联用可降低血清透明质酸(hyaluronan, HA)、层粘连蛋白(laminin, LN)和羟脯氨酸(hydroxyproline, Hyp)水平，抑制肝脏金属蛋白酶-1 抑制剂(tissue inhibitor of metalloproteinase-1, TIMP-1)的表达，增加肝脏基质金属蛋白酶抑制剂-13 (matrix metalloproteinase-13, MMP-13)的表达，抑制肝脏转化生长因子-β (transforming growth factor-β, TGF-β)信号通路，减轻肝脏纤维化，缓解 ALD[46]。

肝舒诺丹(Ganshu Nuodan, GN)是一种由灵芝孢子粉(Ganoderma lucidum spore powder, GLSP)、葛根、黄芪(*Astragalus membranaceus*, *AM*)和 *Sal* 组成的护肝膳食补充剂，其中含有 21 种醌类、18 种黄酮类、11 种有机酸、7 种萜类、5 种酮类、4 种甾醇类、3 种香豆素类和 7 种其他化学成分，研究发现 GN 可降低急性 ALD 小鼠模型 AST、ALT 和丙二醛(malondialdehyde, MDA)水平，升高肝脏 GSH 含量和超氧化物歧化酶(superoxide dismutase, SOD)活力，调控环氧化物水解酶 2 (epoxide hydrolase 2, Ephx2)、白三烯 A4 水解酶(leukotriene a4 hydrolase, Lta4h)、丝裂原活化蛋白激酶激酶 1 (mitogen-activated protein kinase kinase 1, Map2k1)、信号转导与转录激活因子 3 (signal transducer and activator of transcription 3, STAT3)、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR 和二酰甘油酰基转移酶 1 (diacylglycerol O-acyltransferase 1, Dgat1)表达，抑制急性肝脏氧化应激、脂质积累和细胞凋亡，缓解急性 ALD 肝损伤[47]。

白桑(*Morus alba*, *MA*)、山楂(*Crataegus pinnatifida*, *CP*)、泽泻(*Alisma orientale*, *AO*)、黄芪、葛根和 *Sal* 联合用药为传统中药治疗组，可改善 ALD 大鼠 AST、ALT、TG 和 TC 血清含量，减少肝脏脂质积累，缓解 ALD 肝损伤[48]。另有研究证明，中药(白桑、山楂、泽泻、黄芪、葛根与 *Sal*)治疗可恢复酒精抑制的肝脏 PPARα 和微粒体甘油三酯转移蛋白(microsomal triglyceride transfer protein, MTP)水平，缓解 ALD[49]。综上所述，*Sal* 可联合多种天然产物协同干预 ALD 进程，具有良好的临床潜力。

3.2 *Sal* 联合抗氧化剂治疗 ALD 的临床应用

还原型 GSH 是一种内源性抗氧化剂，临床研究发现，多烯磷脂酰胆碱联合还原型 GSH 治疗可有效改善 ALD 患者 AST、ALT、TBIL 和 γ-谷氨酰转移酶(γ-glutamyl transferase, GGT)水平[50]，多项临床研究显示，*Sal* 联合还原型 GSH 治疗 ALD 可发挥协同保肝作用，一项 60 例 ALD 患者的临床研究显示，给予 *Sal* 联合 GSH 干预可有效降低患者血清转氨酶及肝纤维化指标水平，疗效显著优于单一治疗[51]，临床试验(84 例 ALD 患者)结果显示，*Sal* 联合还原型 GSH 组有效率高达 95.24%[52]。另一项 126 例

ALD 患者的临床研究显示，*Sal* 联合 GSH 治疗有效率高达 90.48%，明显高于 GSH 单独给药组(76.19%)，可缓解失代偿期肝硬化患者的肝纤维化程度，具有协同疗效[53]。上述临床研究结果进一步肯定了还原型 GSH 和 *Sal* 联用在 ALD 治疗中的临床价值。

多烯磷脂酰胆碱(polyene phosphatidylcholine, PPC)是一种肝胆疾病辅助治疗药物，从大豆中提取的粗制磷脂物质精制而成的抗氧化药物可促进肝细胞再生，调节脂质代谢。一项 118 例 ALD 患者的临床报告发现，*Sal* 川芎嗪注射液联合多烯磷脂酰胆碱可降低酒精升高的肝脏 ALT、AST、TBIL 和 GGT 水平，提高 ALD 患者肠道有益菌两歧双歧杆菌(*Bifidobacterium bifidum*)水平，降低有害菌大肠埃希氏菌(*Escherichia coli*)、肠球菌(*Enterococcus*)丰度，以及血清脂蛋白(lipoprotein, LP)、脂质过氧化物(lipid peroxide, LPO)水平，缓解 ALD[54]。

3.3 *Sal* 联合其他药物缓解 ALD 的临床应用

硫普罗宁(tiopronin)是一种含巯基的保肝药物，具有抗氧化、抗炎和解毒等药理作用，可促进肝细胞代谢和修复再生，一项 86 例 ALD 患者的临床研究发现，其联合 *Sal* 注射液治疗效果优于 *Sal* 单药组，且未出现明显不良反应[55]。另一项临床报告显示，将 80 例 ALD 患者分为单药治疗组和联合治疗组，联合用药治疗组肝功能明显优于单独给药组[56]。一项 86 例 ALD 患者的临床报告发现，硫普罗宁联合 *Sal* 可改善 ALD 患者肝功能，降低肝脏纤维化水平，未出现明显不良反应，用药安全性较高[57]。

异甘草酸镁(magnesium isoglycyrrhizinate, MgIG)具有抗炎、抗氧化的保肝活性，有研究发现，其可改善酗酒引起的肝细胞氧化应激，调控中性粒细胞活性，缓解 ALD 肝损伤[58]。镁离子是多种酶的辅助因子，可抑制自由基生成酶的活性，减少自由基形成，降低线粒体内钙离子浓度，保护肝细胞膜的完整性，一项 76 例酒精性肝硬化患者的临床报告显示(2011−2013 年)，大剂量 *Sal* 联合硫酸镁(magnesium sulfate, $MgSO_4$)治疗 ALD 肝硬化的疗效明显，存在轻微毒副反应，少数患者出现轻微头疼，面色潮红等，可未经处理自行缓解，安全性较高[59]。

双环醇(bicyclol)是一类肝脏保护药物，可缓解药物、酒精等诱导的肝脏转氨酶水平升高，缓解肝脏炎症。临床上双环醇主要用于治疗慢性肝炎、药物性肝损伤等，一项临床研究发现，复方丹参滴丸与双环醇联合用药可抑制 70 例 ALD 患者 ALT、AST、GGT 与 ALP 异常升高，下调 TBIL 和肝纤维化指标，明显改善患者肝功能[60]。*Sal* 联合用药在 ALD 治疗中普遍呈现协同效应，但现有的 *Sal* 临床用药策略仍具有不同程度的临床不良反应，且作用机制尚未完全阐明。因此开发新的 *Sal* 联合用药新策略对改善 ALD 患者预后，提高疗效具有重要的临床意义。Sal 联合用药干预 ALD 的作用机制总结如表 2 所示。

4 微生态调节剂治疗 ALD 的研究进展

肠道菌群稳态参与调控 ALD 的发展进程，研究发现酒精暴露可显著抑制小鼠肠道微生物乙酰辅酶 A (acetyl coenzyme A, CoA)依赖的丁酸合成途径，降低产丁酸菌丰度，进而加剧肝脏脂肪变性、炎症反应及肝损伤，而丁酸前体药物三丁酸甘油酯(tributyrin, Tb)可逆转酒精所致的产丁酸菌丰度下降，改善肝脏病理损伤[61]。此外，核黄素也可通过调节小鼠肠道菌群结构，提升有益菌丰度，减轻肝脏炎症反应，进而改善 ALD 的病理进程[62]。虾青素是一种类胡萝卜素，可恢复有益菌嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)丰度，改善肠道菌群结构失衡，逆转酒精诱导的小鼠肝脏比重升高以及脂质代谢紊乱[63]。靶向肠道菌群是干预 ALD

表2 *Sal*联合用药干预ALD的作用机制汇总

Table 2 Summary of the mechanism of *Sal* combined medication in the treatment of alcoholic liver disease

Types	Drugs	Total target subjects	Results	References
Natural products	CG	152 ALD patients	It significantly improved serum AST and ALT levels, thereby ameliorating liver function in ALD patients when combined with *Sal*	[40-41]
	SIL	112 ALD patients	It can improve serum TBIL and hepatic fibrosis markers, with no significant adverse reactions in ALD patients when combined with *Sal*	[44]
	PN, DPE	ALD model	They can increase the expression level of PPARα mRNA and inhibit alcohol-induced hepatic steatosis when combined with *Sal*	[45]
	SC, PUE, SIL	ALD model	They can inhibit the TGF-β/Smad signaling pathway, a key pathway involved in hepatic fibrosis, thereby alleviating liver fibrosis when combined with *Sal*	[46]
	GLPS, PUE, AM	ALD model	They can inhibit hepatic oxidative stress, lipid accumulation and apoptosis in mice with acute ALD when combined with *Sal*	[47]
	MA, CP, AO, PUE, AM	ALD model	They can restore alcohol-suppressed hepatic levels of PPARα and MTP, thereby alleviating ALD when combined with *Sal*	[48-49]
Antioxidant	GSH	270 ALD patients	It can reduce the levels of serum transaminase and liver fibrosis indicators in patients (60 cases), when combined with *Sal*, and has other clinical effective rate 90.48% (126 cases) and 95.24% (84 cases) with a significant synergistic effect	[51-53]
	PPC	118 ALD patients	It increases the abundance of intestinal *Bifidobacterium bifidum*, reduces the serum levels of LP and LPO when combined with *Sal*	[54]
Hepatoprotective drugs	Tiopronin	246 ALD patients	Its combined therapy was more effective than monotherapy when combined with *Sal*	[55-57]
	Magnesium sulfate	76 ALD patients	The combination of high-dose Sal and magnesium sulfate has a significant therapeutic effect on ALD cirrhosis, with mild toxic side effects	[59]
	Bicyclol	70 ALD patients	It downregulated TBIL and fibrosis markers, leading to significant improvement in ALD liver function, when combined with *Sal*	[60]

的潜在调控靶点，也是 *Sal* 联合用药新策略研发的重要思路。

微生态调节剂是基于微生态学原理，通过调节宿主微生态平衡以改善健康状态的制剂，主要包含益生菌(probiotics)、益生元(prebiotics)、后生元(postbiotics)和合生元(synbiotics)等制剂，研究发现其可改善肠道功能屏障，调控肠-肝循环，对缓解 ALD 具有良好的生物学活性[64-66]。因此，益生菌、益生元、后生元和合生元等微生态调节剂是 *Sal* 联合用药治疗 ALD 的潜在干预策略。

4.1 改善 ALD 的益生菌

益生菌是一类通过摄入足够数量对宿主健康产生有益作用的活性微生物，研究发现存在众多益生菌菌株可改善肠道功能屏障，通过调控“肠-肝轴”循环系统改善 ALD 肝损伤，例如嗜黏蛋白阿克曼氏菌、植物乳植杆菌(*Lactiplantibacillus plantarum*)、鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*)、双歧杆菌属(*Bifidobacterium*)、枯草芽孢杆菌(*Bacillus subtilis*)及屎肠球菌(*Enterococcus faecium*)、复合细菌制剂等益生菌及其制剂，对 ALD 肠道功能稳态均

具有重要的生物调控活性。

嗜黏蛋白阿克曼氏菌是一种肠道有益菌，研究发现 ALD 患者粪便阿克曼菌丰度数量减少与 ALD 疾病严重程度间接相关，而乙醇可抑制 ALD 小鼠肠道阿克曼菌相对丰度，口服阿克曼菌补充剂可缓解 ALD 小鼠肝脏中性粒细胞浸润、氧化应激损伤和肝脂肪变性，调控肠道 1 型常规树突状细胞(conventional type 1 dendritic cells, cDC1s)功能，改善肠道屏障功能，抑制细菌内毒素进入循环系统，缓解 ALD[67-69]。研究发现，在患有肝性脑病和认知功能障碍的人群粪便样本中阿克曼氏菌的丰度显著下调[70]。

植物乳植杆菌是一类属于乳酸菌家族中乳植杆菌属(*Lactiplantibacillus*)的常见益生菌。据报道，其可阻断 ALD 诱导的炎症相关因子 TNF-α、白细胞介素-1β (interleukin-1β, IL-1β)、IL-6、单核细胞趋化蛋白 1 (monocyte chemotactic protein 1, MCP1)、C-X-C 基序趋化因子配体 1 (C-X-C motif chemokine ligand 1, CXCL1)和 C-X-C 基序趋化因子配体 2 (C-X-C motif chemokine ligand 2, CXCL2)在结肠中的表达，通过表皮生长因子受体(epidermal growth factor receptor, EGFR)依赖性机制预防和减轻酒精引起的结肠上皮紧密连接破坏，改善肠道功能屏障，缓解肝损伤[71]。植物乳植杆菌 FB091 可减少 ALD 引起的肝细胞气球样扩张和炎症细胞浸润，减轻结肠组织结构损伤，降低 AST 水平，增加乙醇脱氢酶活性，促进酒精代谢，是 ALD 潜在的替代药物[72]。

鼠李糖乳酪杆菌是一类属于乳酸菌乳酪杆菌属(*Lacticaseibacillus*)的益生菌，临床试验显示，鼠李糖乳酪杆菌(*Lactobacillus rhamnosus*) R0011 和瑞士乳杆菌(*Lactobacillus helveticus*) R0052 可改善 ALD 肠道菌群组成，89 例 ALD 患者补充益生菌 7 d 后增加了类杆菌比例(*Bacteroides*, 147%)、减少了变形杆菌(*Proteobacteria*, 30%)和梭杆菌(*Fusobacterium*)的比例，同时降低脂多糖含量，改善肠道功能屏障，缓解 ALD 肝炎[73]。据报道，鼠李糖乳酪杆菌 CCFM1107、GG 和 NKU FL1-8 可降低血清 AST、ALT、TC、TG、TNF-α 和脂多糖水平，改善双歧杆菌等有益菌丰度，抑制肠道有害菌生长，激活 AMPKα1 缓解 ALD 损伤[74-76]。

双歧杆菌是一种革兰氏阳性厌氧菌，对改善肠道功能屏障具有重要的生物学活性，研究发现双歧杆菌四联活菌制剂可联合多烯磷脂酰胆碱改善 ALD 大鼠肝功能指标，抑制肝脏脂质积累和肝脂肪变性，减轻 ALD 肝脏炎症[77]。临床研究发现，*Sal* 川芎嗪注射剂联合多烯磷脂酰胆碱可增加 ALD 患者肠道有益菌双歧杆菌的相对丰度[54]，双歧杆菌三联活菌溶菌胶囊联合蒙脱石散(smectite powder)可有效治疗 ALD 患者 22 例(73.3%)，有效缓解 2 例(6.7%)，无效 6 例(20%)，治疗期间 1 例(3.3%)出现便秘，无严重不良反应，疗效较安全[78]。此外，假小链双歧杆菌(*Bifidobacterium pseudocatenulatum*)可减少致病性菌丰度，增加有益菌双歧杆菌和布劳特氏菌(*Blautia*)丰度，并可下调肝脏脂肪生成基因分化簇 36 (cluster of differentiation 36, Cd36)、脂肪酸合酶(fatty acid synthase, Fasn)、乙酰辅酶 A 羧化酶 α (acetyl-coa carboxylase α, Accα)、促炎细胞因子 Il-1β、趋化因子(C-C 基元)配体 2 [chemokine (C-C motif) ligand 2, CCL2]和 TNF-α 的表达，缓解 ALD 肝脂肪变性和炎症反应[79]。长双歧杆菌亚种 BL21 (*Bifidobacterium longum* subsp. *longum*) BL21 可改善 ALD 肝脏氧化应激、炎症反应和肝脂肪变性[80]。

枯草芽孢杆菌是一种革兰氏阳性需氧杆状细菌，而屎肠球菌是一种革兰氏阳性厌氧球菌，两者均是微生态调节剂中常用的益生菌菌株，一项针对 117 名 ALD 患者的临床研究表明，枯草芽孢杆菌及屎肠球菌混合制剂可改善 ALD 患者 AST、ALT、碱性磷酸酶、GGT 和 TBIL 的血清含量，抑制大肠埃希氏菌丰度，降低 TNF-α 和脂多糖水平，改善患者肠道功能屏障和肝功能指标[81]。

中国卫生部 2010 年 4 月发布了一种由 15 种可食用菌种制成的复合细菌制剂，包含动物双

歧杆菌乳亚种(*Bifidobacterium animalis* subsp. *lactis*) HN019、Bi-07，两歧双歧杆菌 Bb06，动物双歧杆菌(*Bifidobacterium animalis*) BB-12，长双歧杆菌(*Bifidobacterium longum*) R175、B94，鼠李糖乳酪杆菌 GG、R11，干酪乳酪杆菌(*Lacticaseibacillus casei*) LC11，瑞士乳杆菌(*Lactobacillus helveticus*) R52，类干酪乳酪杆菌(*Lacticaseibacillus paracasei*) Lpc-37，植物乳植杆菌 R1012，罗伊特氏黏液乳杆菌(*Limosilactobacillus reuteri*) HA188，嗜酸乳杆菌(*Lactobacillus acidophilus*) NCFM 和唾液链球菌嗜热亚种(*Streptococcus salivarius* subsp. *thermophilus*) St21，研究发现其可抑制肝脏 TLR4/NF-κB 信号通路，激活 AMPK-PPARα 信号通路，减轻肝脂肪变性与炎症反应，修复肠道屏障功能，改善酒精诱导的肝损伤[82]。

4.2 改善 ALD 的益生元

益生元是一类不能被人体消化吸收，但能被肠道有益菌选择性利用的物质。HRFP-II-a、HRFP-II-b 和 HRFP-II-c 是从沙棘果实中分离的 3 种果胶多糖，是缓解 ALD 潜在的益生元，研究发现 HRFP-II-a、HRFP-II-b 和 HRFP-II-c 可维持人肝细胞系 THLE-2 细胞完整性，抑制细胞炎症因子分泌，增强细胞抗氧化应激能力，减轻酒精诱导的细胞损伤；同时，HRFP-II可抑制 ALD 小鼠 AST、ALT、TG、TC 和 MDA 血清含量，升高 CAT、SOD 和 GSH 水平，降低增稠拟杆菌(*Bacteroides thickeningii*)与普通拟杆菌(*Bacteroides vulgatus*)的比例、增加肠道有益菌群丰度，并抑制有害菌生长，改善 ALD 肠道菌群稳态；此外，HRFP-II还可上调肠道闭锁小带蛋白 1 (zonula occludens 1, ZO-1)和闭合蛋白(Occludin)蛋白表达，修复 ALD 肠道黏膜屏障，调控肠-肝循环，改善 ALD 肝损伤[83]。壳寡糖(chitosan oligosaccharide)可促进双歧杆菌等多种有益菌生长，是一类具有食品开发潜力的益生元[84]。研究发现，壳寡糖可降低 ALD 肝脏代谢酶 CYP2E1 的表达，激活 Kelch 样 ECH 相关蛋白 1 (Kelch-like ECH-associated protein 1, Keap-1)/Nrf2/HO-1 通路，抑制 NF-κB 和 MAPK 通路，改善肝脂肪变性和炎症反应，缓解 ALD[85]。

4.3 改善 ALD 的后生元

后生元是一类益生菌经处理或代谢后产生的无生命活性成分，据报道，热灭活的强生乳杆菌(*Lactobacillus johnsonii*) HKLJ 可上调肠道溶菌酶(lysozyme)的表达，促进肠道细菌生成免疫调节物质，可激活核苷酸结合寡聚结构域 2 (nucleotide-binding oligomerization domain 2, NOD2)/白细胞介素 23 (interleukin 23, IL-23)/白细胞介素 22 (interleukin 22, IL-22)信号通路；上调抗菌肽的合成，抑制幽门螺杆菌(*Helicobacter pylori*)的相对丰度，改善肠道稳态，并激活肝脏 STAT3 通路调节“肠-肝轴”稳态，缓解 ALD[86]。类干酪乳酪杆菌坚韧亚种(*Lacticaseibacillus paracasei* subsp. *tolerans*) S-NB 中提取的荚膜多糖(capsular polysaccharide, CPS)和表面层蛋白(surface layer protein, SLP)可增加 ALD 肠道拟杆菌、双歧杆菌等益生菌丰度，抑制大肠埃希氏菌、布鲁氏菌属(*Brucella*)、柠檬酸杆菌属(*Citrobacter*)和梭杆菌属(*Fusobacterium*)等病原菌的生长，改善肠道功能屏障，缓解 ALD 肝损伤[87]。

4.4 改善 ALD 的合生元

合生元是一类改善宿主肠道菌群稳态的益生菌+益生元的协同组合制剂，例如凝结芽孢杆菌(*Bacillus coagulans*)联合果胶(pectin)、脆弱拟杆菌(*Bacteroides fragilis*)联合果胶、植物乳植杆菌联合儿茶素(epigallocatechin gallate, EGCG)等。凝结芽孢杆菌是一类可产孢和乳酸的功能益生菌，果胶是一类常见的益生元，凝结芽孢杆菌联合果胶可显著减少 ALD 肝脏炎症反应和脂质积累，降低促炎因子 TNF-α 和 IL-1β 的水平，促进肠道有益菌鼠杆状菌科(*Muribaculaceae*)的生长，增加短链脂肪酸的生成，促进肠道黏膜黏液分泌，增强肠道屏障功能，缓解 ALD 肝损伤[88]。脆弱拟杆菌 ATCC25285 是一类可产生短

链脂肪酸增强肠道屏障的益生菌，据报道其联合果胶可改善 ALD 肠道菌群组成，促进色氨酸代谢和增强肠道免疫功能，改善 ALD 肝损伤[89]。此外，植物乳植杆菌与 EGCG 联用可降低 ALD 大鼠模型酒精、内毒素和肝酶水平，抑制炎症相关因子 NF-κB、TNF-α、白细胞介素-12 (interleukin-12, IL-12)和信号分子 TLR4、分化簇 14 (cluster of differentiation 14, CD14)、髓样分化因子 2 (myeloid differentiation factor 2, MD2)、髓样分化初级反应蛋白 88 (myeloid differentiation primary response 88, MyD88)和环氧化酶 2 (cyclooxygenase 2, COX-2)的水平，是缓解 ALD 的重要策略[90]。

综上所述，益生菌、益生元、后生元和合生元等多种微生态调节剂可促进肠道双歧杆菌等有益菌生长，抑制大肠埃希氏菌等有害菌生长，并通过修复肠道功能屏障构成 ALD 防治的重要微生态干预体系，从而抑制 ALD 肝脏炎症、肝脂肪变性和氧化应激损伤，是 *Sal* 联合用药干预 ALD 的重要研发方向。微生态调节剂治疗 ALD 的作用机制总结如表 3 所示。

5 *Sal* 联合微生态调节剂改善 ALD 的研究进展

Sal 不仅对 ALD 具有良好的疗效[91]，还可改善肠道菌群稳态，调控多种疾病进程，例如肾衰竭[92]、高胆固醇血症[93]和 NAFLD[94]等。研究发现，丹酚酸 B 与葛根、水飞蓟联合用药可提高小鼠肠道阿克曼氏菌等有益菌丰度，并通过调控胆汁酸代谢缓解 NAFLD 肝损伤[95]。丹酚酸 A 可与益生菌干酪乳酪杆菌及嗜酸乳杆菌联合使用改善 NAFLD[96]，这些研究结果提示调控肠道菌群稳态是 *Sal* 联合用药干预 ALD 的潜在研究方向。益生菌是微生态调节剂的核心组成部分，临床研究发现复方丹参注射液联合枯草杆菌、肠球菌活菌胶囊对 NAFLD 患者的疗效(93%)明显高于单独用药组(83%)[97]，且枯草芽孢杆菌可改善 ALD 患者肠道功能屏障和肝功能[82]。丹参多糖(*Salvia miltiorrhiza* polysaccharide, SalP)可与植物乳植杆菌 X 或双歧杆菌 V 联合应用改善小鼠胰岛素抵抗，缓解 NAFLD 肝脂肪变性[98]。据报道，植物乳植杆菌 FB091 可减少 ALD 小鼠结肠组织损伤，缓解 ALD 肝损伤[72]。*Sal* 可联合多烯磷脂酰胆碱改善 ALD 肝功能，增加患者肠道双歧杆菌相对丰度[54]，并且双歧杆菌活菌溶菌胶囊可联合蒙脱石散有效治疗 ALD 患者 22 例(73.3%)[78]。此外，壳聚糖是一类益生元，可降低 ALD 小鼠血液中酒精和乙醛的含量[99]，与丹酚酸 B 联合用药可显著降低小鼠 AST、ALT、α-平滑肌动蛋白(α-smooth muscle actin, α-SMA)、I型胶原(collagen type I, COL I)和 IL-6 水平，并增加双歧杆菌等多种有益菌丰度，改善小鼠肝纤维化[100]。因此，微生态调节剂是 *Sal* 联合用药干预 ALD 的重要研发方向，具有良好的临床应用潜力。

表3 微生态调节剂治疗ALD的作用机制总结

Table 3 Summary of the mechanism of microecological regulators in the treatment of alcoholic liver disease

Ecological regulators	Types	Targets	Results	References
Akkermansia muciniphila	Probiotics	ALD model	It can regulate the intestinal functional barrier, inhibit bacterial endotoxins from entering the circulatory system, and alleviate ALD liver injury	[67-69]
Lactiplantibacillus plantarum	Probiotics	ALD model	It can regulate the EGFR-dependent mechanism prevents and alleviates alcohol-induced disruption of colonic epithelial tight junctions and liver injury	[71]

(待续)

(续表3)

Ecological regulators	Types	Targets	Results	References
Lactiplantibacillus plantarum FB091	Probiotics	ALD model	It can reduce ballooning degeneration of liver cells and infiltration of inflammatory cells in ALD, alleviate the damage to the colonic tissue structure, promote alcohol metabolism, and relieve ALD liver injury	[72]
Lactobacillus rhamnosus R0011 and *Lactobacillus helveticus* R0052	Probiotics	89 ALD patients	They can reduce the levels of *Proteus*, *Fusobacterium*, and LPS, protect the intestinal barrier, and alleviate hepatitis	[73]
Lactobacillus rhamnosus CCFM1107	Probiotics	ALD model	It significantly inhibited the increase in the levels of serum aminotransferase, endotoxin, TG and TC, and ameliorated ALD liver injury	[74]
Lactobacillus rhamnosus NKU FL1-8	Probiotics	ALD model	It can decrease the levels of AST, ALT, MDA, SOD and GSH, relieve oxidative stress and decrease hepatic inflammation	[75]
Lactobacillus rhamnosus GG	Probiotics	ALD model	It ameliorates ALD liver injury through modulating antioxidant defenses	[76]
Bifidobacterium and PPC	Probiotics	ALD model	They can ameliorate liver function indicators in ALD rats, inhibit lipid accumulation and hepatic steatosis in ALD liver	[77]
Bifidobacterium and smectite powder	Probiotics	60 ALD patients	They can ameliorate ALD liver injury, without serious adverse reactions, and have the relatively safe therapeutic effect	[78]
Bifidobacterium pseudocatenulatum	Probiotics	ALD model	It can regulate the expression of Cd36, Fasn, Accα, Il-1β, CCL2 and TNF-α, and ameliorate ALD liver injury	[79]
Bifidobacterium longum subsp. *longum* BL21	Probiotics	ALD model	It reduced the ethanol-induced abnormal elevation of serum AST and ALT levels in ALD mice	[80]
Bacillus subtilis and *Enterococcus faecium*	Probiotics	117 ALD patients	They can regulate the expression of TNF-α, and alleviate ALD liver injury	[81]
Compound probiotic preparation	Probiotics	ALD model	It can alleviate hepatic inflammation, repair the intestinal barrier, reshape the intestinal flora, and alleviate ALD-induced injury	[82]
HRFP-II-a, HRFP-II-b, HRFP-II-c	Prebiotics	ALD model	They can protect ALD mice *via* antioxidant, anti-inflammatory, lipid metabolism regulation and intestinal flora improvement	[83]
Chitosan oligosaccharide	Prebiotics	ALD model	It can reduce the expression of the liver metabolic enzyme CYP2E1 in ALD, activate the Keap1/Nrf2/HO-1 pathway, inhibit the NF-κB and MAPK pathways, alleviate ALD oxidative damage, hepatic steatosis and inflammation	[85]
Lactobacillus johnsonii HKLJ	Postbiotics	ALD model	It can activate the nucleotide-binding NOD2/IL-23/IL-22 signaling pathway, improve intestinal homeostasis, activate the hepatic STAT3 pathway, and alleviate ALD	[86]
CPS and SLP	Postbiotics	ALD model	It can promote short-chain fatty acid production, improve the intestinal functional barrier, and alleviate ALD injury	[87]
Bacillus coagulans and pectin	Synbiotics	ALD model	It can enhance intestinal barrier function and alleviate ALD liver injury	[88]
Bacteroides fragilis ATCC25285 and pectin	Synbiotics	ALD model	It can promote tryptophan metabolism, enhance intestinal immune function and alleviate ALD liver injury	[89]
Lactiplantibacillus plantarum and EGCG	Synbiotics	ALD model	They can inhibit the level of NF-κB, TNF-α, IL-12, TLR4, CD14, MD2, MyD88, COX-2, and alleviate ALD	[90]

6 总结与展望

ALD 是全球高发的慢性肝病，发病机制复杂，临床缺乏高效低毒的特效方案，因此开发 ALD 新的干预策略已成为临床研究的核心需求。多项研究证实，*Sal* 及其活性单体可联合多种天然产物、抗氧化剂和其他保肝药物提高对 ALD 的疗效，但现有的 *Sal* 联合用药策略仍未能满足 ALD 的临床需求，开发 *Sal* 联合用药新策略是改善 ALD 临床局限性的重要研究思路。肠道菌群稳态对改善 ALD 具有重要的生物学功能，人源化菌群动物模型和临床研究发现，益生菌、益生元、后生元及合生元等多种微生态调节剂可调控肠道菌群稳态，增强肠道屏障功能，对缓解 ALD 具有重要的药用价值，是 *Sal* 联合用药干预 ALD 的重要研发方向，具有潜在的临床应用前景。聚焦微生态调节剂，开发高效低毒的 *Sal* 联合用药新策略，对优化 ALD 临床给药方案，提高疗效并改善患者预后具有重要的临床意义，也是未来临床转化的重要方向。*Sal* 联合用药治疗 ALD 的干预策略总结如图 1 所示。

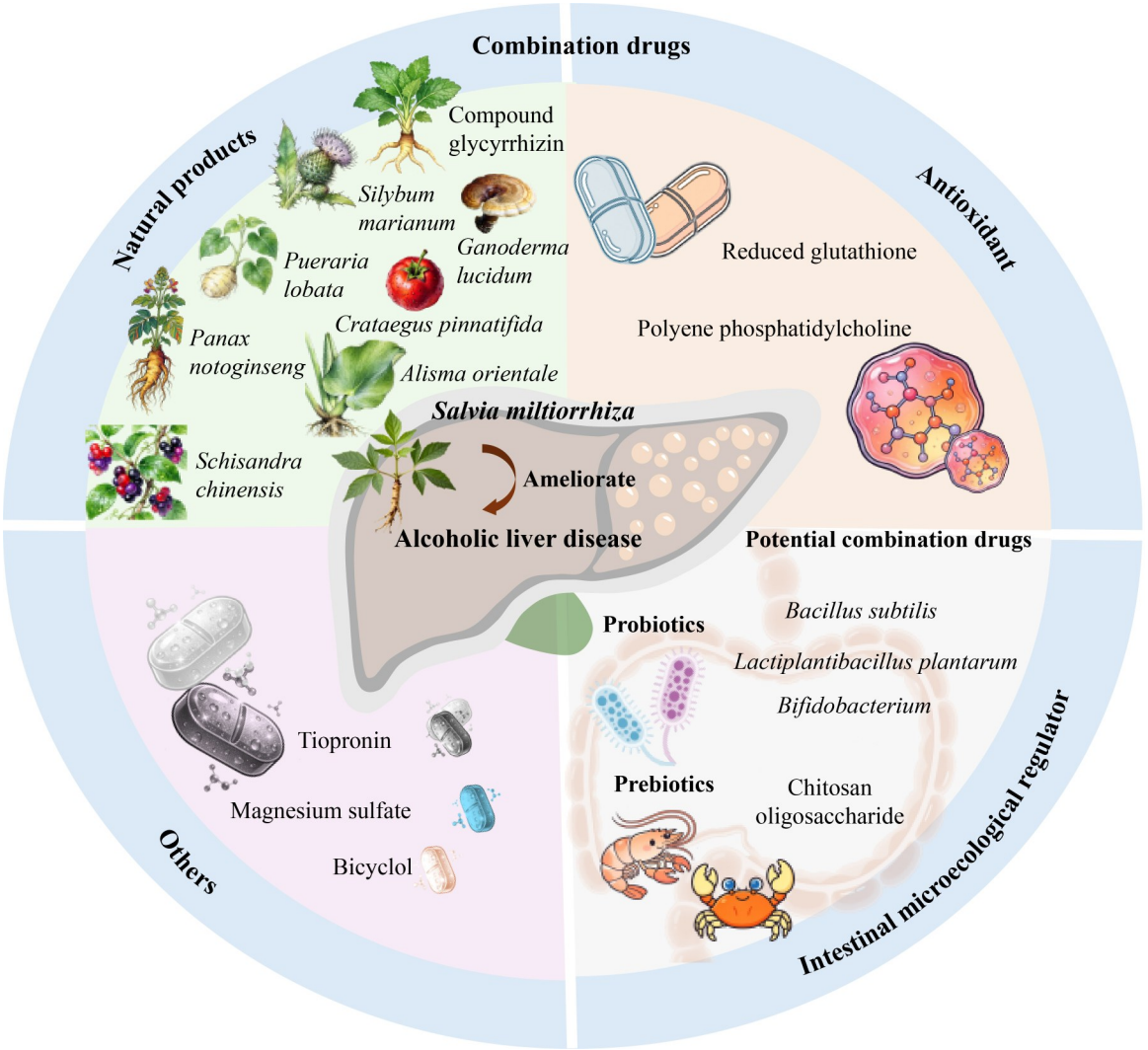


图1 *Sal*联合用药治疗ALD的干预策略图

Figure 1 Strategy diagram of *Sal* combined medication in the treatment of ALD.

作者贡献声明

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参考文献

[1] GBD 2023 Disease and Injury and Risk Factor Collaborators. Burden of 375 diseases and injuries, risk-attributable burden of 88 risk factors, and healthy life expectancy in 204 countries and territories, including 660 subnational locations, 1990−2023: a systematic analysis for the Global Burden of Disease Study 2023[J]. The Lancet, 2025, 406(10513): 1873-1922.

[2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA, 2024, 74(3): 229-263.

[3] Danpanichkul P, Pang YF, Suparan K, Saokhieo P, Jatupornpakdee P, Polpichai N, Attachaipanich T, Suenghataiphorn T, Ibrahim AF, Vichitkunakorn P, Chirapongsathorn S, Choudhury A, Kulkarni AV, Wijarnpreecha K, Kaewdech A, Liangpunsakul S. Burden of alcohol-related liver disease and alcohol use disorder in Asia[J]. United European Gastroenterology Journal, 2025, 13(8): 1456-1468.

[4] Jophlin LL, Singal AK, Bataller R, Wong RJ, Sauer BG, Terrault NA, Shah VH. ACG clinical guideline: alcohol-associated liver disease[J]. American Journal of Gastroenterology, 2024, 119(1): 30-54.

[5] Dawuti A, Sun SC, Wang RR, Gong DF, Liu RQ, Kong DW, Yuan TY, Zhou J, Lu Y, Wang SB, Du GH, Fang LH. Salvianolic acid A alleviates heart failure with preserved ejection fraction *via* regulating TLR/Myd88/TRAF/NF-κB and p38MAPK/CREB signaling pathways[J]. Biomedicine & Pharmacotherapy, 2023, 168: 115837.

[6] 武明东, 都广礼, 郑曙琴, 王镁. 丹参注射液对肝脏保护作用的临床研究[J]. 实用中医内科杂志, 2005, 19(1): 54.

[7] 王祖君, 李小丹. 还原型谷胱甘肽联合丹参注射液治疗酒精性肝病临床观察[J]. 现代中西医结合杂志, 2016, 25(12): 1304-1306.

[8] Li L, Xu S, Wang WY, Li X, Wang HT, Yang Q, Wang CY, Gu JN, Luo HF, Meng Q. Bruceine A alleviates alcoholic liver disease by inhibiting AIM2 inflammasome activation *via* activating FXR[J]. Phytomedicine, 2024, 130: 155693.

[9] Wang YK, Wang MQ, Liu CR, Hao M, Wang WJ, Li YP, Shi JJ, Jia XL, Zhang X, Dang SS. Global burden of liver cirrhosis 1990−2019 and 20 years forecast: results from the global burden of disease study 2019[J]. Annals of Medicine, 2024, 56: 2328521.

[10] Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG clinical guideline: alcoholic liver disease[J]. American Journal of Gastroenterology, 2018, 113(2): 175-194.

[11] Hofer BS, Tonon M, Buttler L, Camões Neves J, Herms Q, Pompili E, Ignat M, Métivier S, Rodrigues SG, Gutmann D, Donate J, Lai JC, Clemente-Sánchez A, Jiménez-Masip A, Cabello J, Bouzbib C, Karbannek H, Embacher J, Sorz-Nechay T, Parandian L, et al. Incidence and implications of abstinence-induced recompensation in alcohol-related cirrhosis[J]. Journal of Hepatology, 2026, 84(6): 1077-1088.

[12] Gawrieh S, Dasarathy S, Tu WZ, Kamath PS, Chalasani NP, McClain CJ, Bataller R, Szabo G, Tang Q, Radaeva S, Barton B, Nagy LE, Shah VH, Sanyal AJ, Mitchell MC, Chalasani N, Patidar KR, Vuppalanchi R, Samala N, Yoder L, et al. Randomized trial of anakinra plus zinc *vs*. prednisone for severe alcohol-associated hepatitis[J]. Journal of Hepatology, 2024, 80(5): 684-693.

[13] Wang YZ, Fahy C, Lu H. Liver-specific glucocorticoid action in alcoholic liver disease: study of glucocorticoid receptor knockout and knockin mice[J]. Liver Research, 2024, 8(2):91-104.

[14] Wan WM, Wei RM, Xu BL, Cao HK, Zhi YP, Guo FY, Liu HP, Li B, Wu JZ, Gao Y, Zhang KF. Qiwei Jinggan Ling regulates oxidative stress and lipid metabolism in alcoholic liver disease by activating AMPK[J]. Phytomedicine, 2024, 135: 156125.

[15] Hu MY, Chen Y, Deng F, Chang B, Luo JL, Dong LJ, Lu X, Zhang Y, Chen ZL, Zhou J. D-mannose regulates hepatocyte lipid metabolism *via* PI3K/Akt/mTOR signaling pathway and ameliorates hepatic steatosis in alcoholic liver disease[J]. Frontiers in Immunology, 2022, 13: 877650.

[16] Liu XW, Zhan ZB, Li ZH, Zhang Y, Qiao XY, Li XM, Liang XJ, Bai KH, Xia XF, Zeng FH, Gao Y, Weng J. RAB25/GCN1 signaling promotes endoplasmic reticulum stress to mediate alcohol-associated liver disease progression[J]. Clinical and Molecular Hepatology, 2026, 32(1): 200-220.

[17] Samuvel DJ, Li L, Krishnasamy Y, Gooz M, Takemoto K, Woster PM, Lemasters JJ, Zhong Z. Mitochondrial depolarization after acute ethanol treatment drives mitophagy in living mice[J]. Autophagy, 2022, 18(11): 2671-2685.

[18] Zhang JJ, Zhong JT, Wang WL, Wang SY, Guo X, Sun HM, Song J. Embelin improves alcoholic steatohepatitis in alcohol-associated liver disease *via* ATF6-mediated P2X7r-NLRP3 signaling pathway[J]. Phytomedicine, 2025, 140: 156638.

[19] Wang M, Wen X, Feng Z, Choubey M, Chen S, Pan R, Gong K, Tirumalasetty MB, Gao F, Liao C, Yin Z, Zhang S, He Y, Chen H, Cao Y, Miao QR, Hu W, Duan Y. ACSS2 protects against alcohol-induced hepatocyte ferroptosis through regulation of hepcidin expression[J]. Nature Communications, 2025, 16(1): 5491.

[20] Cresci GA, Glueck B, McMullen MR, Xin W, Allende D, Nagy LE. Prophylactic tributyrin treatment mitigates chronic-binge ethanol-induced intestinal barrier and liver injury[J]. Journal of Gastroenterology and Hepatology, 2017, 32(9): 1587-1597.
[21] Cohen JI, Roychowdhury S, DiBello PM, Jacobsen DW, Nagy LE. Exogenous thioredoxin prevents ethanol-induced oxidative damage and apoptosis in mouse liver[J]. Hepatology, 2009, 49(5):1709-1717.
[22] Maccioni L, Gao B, Leclercq S, Pirlot B, Horsmans Y, De Timary P, Leclercq I, Fouts D, Schnabl B, Stärkel P. Intestinal permeability, microbial translocation, changes in duodenal and fecal microbiota, and their associations with alcoholic liver disease progression in humans[J]. Gut Microbes, 2020, 12(1): 1782157.
[23] Gao YT, Zhang P, Wei YM, Ye CL, Mao DQ, Xia DS, Luo Y. *Porphyromonas gingivalis* exacerbates alcoholic liver disease by altering gut microbiota composition and host immune response in mice[J]. Journal of Clinical Periodontology, 2023, 50(9): 1253-1263.
[24] Ma HY, Yamamoto G, Xu J, Liu X, Karin D, Kim JY, Alexandrov LB, Koyama Y, Nishio T, Benner C, Heinz S, Rosenthal SB, Liang S, Sun M, Karin G, Zhao P, Brodt P, Mckillop IH, Quehenberger O, Dennis E, et al. IL-17 signaling in steatotic hepatocytes and macrophages promotes hepatocellular carcinoma in alcohol-related liver disease[J]. Journal of Hepatology, 2020, 72(5): 946-959.
[25] Zhang DQ, Tong X, Nelson BB, Jin E, Sit J, Charney N, Yang MC, Omary MB, Yin L. The hepatic BMAL1/AKT/lipogenesis axis protects against alcoholic liver disease in mice *via* promoting PPARα pathway[J]. Hepatology, 2018, 68(3): 883-896.
[26] Han J, Lee C, Jeong H, Jeon S, Lee M, Lee H, Choi YH, Jung Y. Tumor necrosis factor-inducible gene 6 protein and its derived peptide ameliorate liver fibrosis by repressing CD44 activation in mice with alcohol-related liver disease[J]. Journal of Biomedical Science, 2024, 31(1): 54
[27] Lu YW, Chen YM, Hu WX, Wang M, Wen XD, Yang J. Inhibition of ACSS2 attenuates alcoholic liver steatosis *via* epigenetically regulating *de novo* lipogenesis[J]. Liver International, 2023, 43(8): 1729-1740.
[28] 吕明, 王泰一, 田晓轩, 石鑫慧, 樊官伟, 张砚, 朱彦. 网络药理学分析揭示的常用活血化瘀中药抗炎-抗血栓作用[J]. 药学学报, 2015, 50(9): 1135-1141.
Lü M, Wang TY, Tian XX, Shi XH, Fan GW, Zhang Y, Zhu Y. Interaction of anti-thrombotic and anti-inflammatory activities of commonly used traditional Chinese medicine for promoting blood circulation and removing blood stasis revealed by network pharmacology analysis[J]. Yao Xue Xue Bao, 2015, 50(9): 1135-1141 (in Chinese).
[29] Jiang WY, Jeon BH, Kim YC, Lee SH, Sohn DH, Seo GS. PF2401-SF, standardized fraction of *Salvia miltiorrhiza* shows anti-inflammatory activity in macrophages and acute arthritis *in vivo*[J]. International Immunopharmacology, 2013, 16(2): 160-164.
[30] Yue SQ, Hu B, Wang ZP, Yue ZG, Wang F, Zhao Y, Yang ZF, Shen M. *Salvia miltiorrhiza* compounds protect the liver from acute injury by regulation of p38 and NFκB signaling in Kupffer cells[J]. Pharmaceutical Biology, 2014, 52(10): 1278-1285.
[31] Ding L, Wo LK, Du ZY, Tang LH, Song ZY, Dou XB. Danshen protects against early-stage alcoholic liver disease in mice *via* inducing PPARα activation and subsequent 4-HNE degradation[J]. PLoS One, 2017, 12(10): e0186357.
[32] 熊宗斌, 吴萍, 黄云峰, 张力, 黄艳君, 袁萍, 叶笃筠. 丹参改善小鼠慢性酒精性肝损伤机制的研究[J]. 中国中西医结合杂志, 2005, 25(5): 425-428.
Xiong ZB, Wu P, Huang YF, Zhang L, Huang YJ, Yuan P, Ye DY. Protective mechanisms of radix salviae miltiorrhizae against chronic alcoholic liver injury in mice[J]. Zhongguo Zhong XI Yi Jie He Za Zhi, 2005, 25(5): 425-428 (in Chinese).
[33] Shi X, Zhao Y, Ding CC, Wang ZC, Ji AL, Li ZL, Feng DC, Li Y, Gao DY, Zhou JJ, Tian XF, Yao JH. Salvianolic acid A alleviates chronic ethanol-induced liver injury *via* promotion of β-catenin nuclear accumulation by restoring Sirt1 in rats[J]. Toxicology and Applied Pharmacology, 2018, 350: 21-31.
[34] Shi X, Sun RM, Zhao Y, Fu R, Wang RW, Zhao HY, Wang ZC, Tang F, Zhang N, Tian XF, Yao JH. Promotion of autophagosome-lysosome fusion *via* salvianolic acid A-mediated Sirt1 up-regulation ameliorates alcoholic liver disease[J]. RSC Advances, 2018, 8(36): 20411-20422.
[35] Zhang N, Hu Y, Ding CC, Zeng WJ, Shan W, Fan H, Zhao Y, Shi X, Gao LL, Xu T, Wang RW, Gao DY, Yao JH. Salvianolic acid B protects against chronic alcoholic liver injury *via* Sirt1-mediated inhibition of CRP and ChREBP in rats[J]. Toxicology Letters, 2017, 267: 1-10.
[36] Yin HQ, Choi YJ, Kim YC, Sohn DH, Ryu SY, Lee BH. *Salvia miltiorrhiza* Bunge and its active component cryptotanshinone protects primary cultured rat hepatocytes from acute ethanol-induced cytotoxicity and fatty infiltration[J]. Food and Chemical Toxicology, 2009, 47(1): 98-103.
[37] Nagappan A, Kim JH, Jung DY, Jung MH. Cryptotanshinone from the *Salvia miltiorrhiza* bunge attenuates ethanol-induced liver injury by activation of AMPK/Sirt1 and Nrf2 signaling pathways[J]. International Journal of Molecular Sciences, 2020, 21(1): 265.
[38] Yin HQ, Kim YS, Choi YJ, Kim YC, Sohn DH, Ryu SY, Lee BH. Effects of tanshinone IIA on the hepatotoxicity and gene expression involved in alcoholic liver disease[J]. Archives of Pharmacal Research, 2008, 31(5): 659-665.
[39] Lin XP, Yin XG, Li B, Liu YH, Li M. Therapeutic effect of reduced glutathione combined with compound glycyrrhizin on acute liver injury in children and its effect on inflammatory cytokines: a retrospective study[J]. Medicine, 2025, 104(28): e43350.
[40] 苏雁. 酒精性肝病应用复方甘草酸苷与丹参联合治疗的效果分析[J]. 按摩与康复医学, 2017, 8(11): 38-40.
Su Y. Analysis of the effect of combination therapy of

compound glycyrrhizin and *Salvia miltiorrhiza* on alcoholic liver disease[J]. Chinese Manipulation & Rehabilitation Medicine, 2017, 8(11): 38-40 (in Chinese).

[41] 袁索红, 周红兵, 刘杨. 丹参冻干针剂联合复方甘草酸苷(美能)治疗酒精性肝病临床分析[J]. 中国医药导报, 2011, 8(4): 68-69.
Yuan SH, Zhou HB, Liu Y. Clinical analysis of the function of *Salvia miltiorrhiza* combined with Compound Glycyrrhizin Injection (Stronger Neo-Minophagen C) in the treatment of alcoholic liver disease[J]. China Medical Herald, 2011, 8(4): 68-69 (in Chinese).

[42] Feng RB, Chen JH, Liu CH, Xia FB, Xiao ZY, Zhang XG, Wan JB. A combination of *Pueraria lobata* and *Silybum marianum* protects against alcoholic liver disease in mice[J]. Phytomedicine, 2019, 58: 152824.

[43] Li BY, Xi Y, Liu YP, Wang D, Wang C, Chen CG, Fang XH, Li ZX, Chen YM. Effects of *Silybum marianum*, *Pueraria lobata*, combined with *Salvia miltiorrhiza* tablets on non-alcoholic fatty liver disease in adults: a triple-blind, randomized, placebo-controlled clinical trial[J]. Clinical Nutrition ESPEN, 2024, 63: 2-12.

[44] 吴伟梯, 陈晓烨, 邵辉, 汤永志, 张剑波, 陈华忠. 复方丹参滴丸联合水飞蓟宾胶囊治疗酒精性肝病56例[C]//第二十四次全国中西医结合肝病学术会议论文集. 沈阳, 2015: 107-108.

[45] Horie Y, Kikuchi M, Yamagishi Y, Umeda R, Ebinuma H, Saito H, Kato S, Ishii H, Hibi T, Han JY. Effect of a herbal medicine on fatty liver in rats fed ethanol chronically[J]. Nihon Arukoru Yakubutsu Igakkai Zasshi, 2009, 44(6): 636-648.

[46] Li XM, Liu YJ, Yue WY, Tan YF, Wang H, Zhang LS, Chen JY. A compound of Chinese herbs protects against alcoholic liver fibrosis in rats *via* the TGF-*β*1/Smad signaling pathway[J]. Evidence-Based Complementary and Alternative Medicine, 2019, 2019: 9121347.

[47] Yang XN, Wang L, Cui XJ, Zhang J, Liang Y, Luo ZJ, Zhou BX, Jiang Z, Yang RYH, Wu Y, Wei KH, Du MB, Qin SS, Dai C, Zhao GL. Proteomics and network pharmacology of Ganshu Nuodan capsules in the prevention of alcoholic liver disease[J]. Frontiers in Endocrinology, 2023, 14: 1229777.

[48] Kwon HJ. Amelioration effects of traditional Chinese medicine on alcohol-induced fatty liver[J]. World Journal of Gastroenterology, 2005, 11(35): 5512.

[49] Kwon HJ, Hyun SH, Choung SY. Traditional Chinese Medicine improves dysfunction of peroxisome proliferator-activated receptor α and microsomal triglyceride transfer protein on abnormalities in lipid metabolism in ethanol-fed rats[J]. BioFactors, 2005, 23(3): 163-176.

[50] 张新民. 多烯磷脂酰胆碱联合还原型谷胱甘肽在酒精性肝病治疗中的应用效果分析[J]. 慢性病学杂志, 2018, 19(1): 81-83.

[51] 陈冬梅, 田琰. 复方丹参联合还原型谷胱甘肽治疗酒精性肝病的临床疗效观察[C]//2008年贵州省医学会消化及内镜学分会学术大会论文集. 贵阳, 2008: 204-205.

[52] 李红广. 还原型谷胱甘肽联合丹参注射液治疗酒精性肝病的临床应用[J]. 临床医学研究与实践, 2016, 1(15): 55.

[53] 杨小花, 吴时胜, 刘斌, 梅冬雪, 徐晓平, 王娜, 张国顺. 还原型谷胱甘肽联合丹参注射液治疗酒精性肝病失代偿期肝硬化患者的临床观察[J]. 中国中医急症, 2017, 26(4): 671-673.
Yang XH, Wu SS, Liu B, Mei DX, Xu XP, Wang N, Zhang GS. Clinical effect analysis of reduced glutathione with salviae in treatment of decompensated cirrhotic patients with alcoholic liver disease[J]. Journal of Emergency in Traditional Chinese Medicine, 2017, 26(4): 671-673 (in Chinese).

[54] 王林霞, 倪美鑫, 黄向华. 丹参川芎嗪注射液联合多烯磷脂酰胆碱治疗酒精性肝病的疗效分析[J]. 现代消化及介入诊疗, 2021, 26(9): 1136-1139.

[55] 高谦. 硫普罗宁联合丹参注射液治疗酒精性肝病的临床效果分析[J]. 中外女性健康研究, 2016, 2016(10): 184-190.

[56] 杨汉泽. 硫普罗宁联合丹参注射液治疗酒精性肝病的临床效果分析[J]. 医药前沿, 2016, 6(23): 58-58, 59.
Yang HZ. Clinical effect analysis of tiopronin combined with Danshen injection in treating alcoholic liver disease[J]. Yiayao Qianyan, 2016, 6(23): 58-58, 59 (in Chinese).

[57] 刘静. 丹参注射液联合硫普罗宁对酒精性肝病患者肝功能及肝纤维化指标的影响[J]. 中国医学工程, 2018, 26(3): 101-103.
Liu J. Effect of *Salvia miltiorrhiza* injection combined with tiopronin on liver function and hepatic fibrosis indexes in patients with alcoholic liver disease[J]. China Medical Engineering, 2018, 26(3): 101-103 (in Chinese).

[58] Wang Y, Zhang ZZ, Wang X, Qi D, Qu AJ, Wang GQ. Amelioration of ethanol-induced hepatitis by magnesium isoglycyrrhizinate through inhibition of neutrophil cell infiltration and oxidative damage[J]. Mediators of Inflammation, 2017, 2017: 3526903.

[59] 戴丽岩, 谢德武. 大剂量丹参联合硫酸镁治疗酒精性肝硬化临床观察[J]. 中国冶金工业医学杂志, 2014, 31(3): 299-300.

[60] 高日金, 吴富, 暴军玲. 复方丹参滴丸联合双环醇治疗酒精性肝病临床效果观察[J]. 基层医学论坛, 2014, 18(2): 139-141.
Gao RJ, Wu F, Bao JL. Effect of compound Danshen dripping pill plus bicyclol on alcoholic liver disease[J]. The Medical Forum, 2014, 18(2): 139-141 (in Chinese).

[61] Singhal R, Donde H, Ghare S, Stocke K, Zhang J, Vadhanam M, Reddy S, Gobejishvili L, Chilton P, Joshi-Barve S, Feng WK, McClain C, Hoffman K, Petrosino J, Vital M, Barve S. Decrease in acetyl-CoA pathway utilizing butyrate-producing bacteria is a key pathogenic feature of alcohol-induced functional gut microbial dysbiosis and development of liver disease in mice[J]. Gut Microbes, 2021, 13: 1946367.

[62] Shen XY, Shi CP, Xu JC, Zhi FN, Luo KP, Di YZ, Li WH, Ma WJ, Jiang YN, Sun H. Intestinal microbiota homeostasis analysis in riboflavin-treated alcoholic liver disease[J]. Communications Biology, 2024, 7: 1030.

[63] Liu HL, Liu MH, Fu XQ, Zhang ZQ, Zhu LY, Zheng X,

Liu JS. Astaxanthin prevents alcoholic fatty liver disease by modulating mouse gut microbiota[J]. Nutrients, 2018, 10(9): 1298.
[64] Koga H, Tamiya Y, Mitsuyama K, Ishibashi M, Matsumoto S, Imaoka A, Hara T, Nakano M, Ooeda K, Umezaki Y, Sata M. Probiotics promote rapid-turnover protein production by restoring gut flora in patients with alcoholic liver cirrhosis[J]. Hepatology International, 2013, 7(2): 767-774.
[65] Ding QC, Cao FW, Lai SL, Zhuge H, Chang KX, Valencak TG, Liu JX, Li ST, Ren DX. *Lactobacillus plantarum* ZY08 relieves chronic alcohol-induced hepatic steatosis and liver injury in mice *via* restoring intestinal flora homeostasis[J]. Food Research International, 2022, 157: 111259.
[66] Liu MZ, Jiang XX, Zeng XQ, Guo YX, Zhang T, Fan XK, Xu J, Wu Z, Pan DD. A protective mechanism of heat inactivation to enhance *Levilactobacillus brevis* PDD-2 against alcohol-induced chronic liver disease based on proteomic analysis[J]. Food & Function, 2024, 15(16): 8356-8369.
[67] Grander C, Adolph TE, Wieser V, Lowe P, Wrzosek L, Gyongyosi B, Ward DV, Grabherr F, Gerner RR, Pfister A, Enrich B, Ciocan D, Macheiner S, Mayr L, Drach M, Moser P, Moschen AR, Perlemuter G, Szabo G, Cassard AM, et al. Recovery of ethanol-induced *Akkermansia muciniphila* depletion ameliorates alcoholic liver disease[J]. Gut, 2018, 67(5): 891-901.
[68] Hao LY, Zhong W, Woo J, Wei XY, Ma H, Dong HB, Guo W, Sun XG, Yue RC, Zhao JC, Zhang QB, Zhou ZX. Conventional type 1 dendritic cells protect against gut barrier disruption *via* maintaining *Akkermansia muciniphila* in alcoholic steatohepatitis[J]. Hepatology, 2023, 78(3): 896-910.
[69] Grander C, Grabherr F, Spadoni I, Enrich B, Oberhuber G, Rescigno M, Tilg H. The role of gut vascular barrier in experimental alcoholic liver disease and *A. muciniphila* supplementation[J]. Gut Microbes, 2020, 12(1): 1851986.
[70] Kang EJ, Cha MG, Kwon GH, Han SH, Yoon SJ, Lee SK, Ahn ME, Won SM, Ahn EH, Suk KT. *Akkermansia muciniphila* improve cognitive dysfunction by regulating BDNF and serotonin pathway in gut-liver-brain axis[J]. Microbiome, 2024, 12: 181.
[71] Shukla PK, Meena AS, Manda B, Gomes-Solecki M, Dietrich P, Dragatsis I, Rao R. *Lactobacillus plantarum* prevents and mitigates alcohol-induced disruption of colonic epithelial tight junctions, endotoxemia, and liver damage by an EGF receptor-dependent mechanism[J]. The FASEB Journal, 2018, 32(11): 6274-6292.
[72] Lee SJ, Yang J, Keum GB, Kwak J, Doo H, Choi S, Park DG, Kim CH, Kim HB, Lee JH. Therapeutic potential of *Lactiplantibacillus plantarum* FB091 in alleviating alcohol-induced liver disease through gut-liver axis[J]. Journal of Microbiology and Biotechnology, 2024, 34(10): 2100-2111.
[73] Gupta H, Kim SH, Kim SK, Han SH, Kwon HC, Suk KT. Beneficial shifts in gut microbiota by *Lacticaseibacillus rhamnosus* R0011 and *Lactobacillus helveticus* R0052 in alcoholic hepatitis[J]. Microorganisms, 2022, 10(7): 1474.
[74] Tian FW, Chi FF, Wang G, Liu XM, Zhang QX, Chen YQ, Zhang H, Chen W. *Lactobacillus rhamnosus* CCFM1107 treatment ameliorates alcohol-induced liver injury in a mouse model of chronic alcohol feeding[J]. Journal of Microbiology, 2015, 53(12): 856-863.
[75] Liu HW, Fan DC, Wang J, Wang Y, Li A, Wu SH, Zhang BW, Liu JM, Wang S. *Lactobacillus rhamnosus* NKU FL1-8 isolated from infant feces ameliorates the alcoholic liver damage by regulating the gut microbiota and intestinal barrier in C57BL/6J mice[J]. Nutrients, 2024, 16(13): 2139.
[76] Salazar C, Barreto M, Adriasola-Carrasco AA, Carvajal F, Lerma-Cabrera JM, Ruiz LM. *Lactobacillus rhamnosus* GG modulates mitochondrial function and antioxidant responses in an ethanol-exposed *in vivo* model: evidence of HIGD2A-dependent OXPHOS remodeling in the liver[J]. Antioxidants, 2025, 14(6): 627.
[77] 李凯, 马振华, 段春兰, 卢艳, 呼达古拉. 多烯磷脂酰胆碱联合双歧杆菌四联活菌对酒精性肝病大鼠模型的疗效分析[J]. 中国处方药, 2025, 23(4): 15-18.
Li K, Ma ZH, Duan CL, Lu Y, Hu D. Therapeutic efficacy analysis of polyene phosphatidylcholine combined with *Bifidobacterium* quadruple live bacteria on alcoholic liver disease rat model[J]. Journal of China Prescription Drug, 2025, 23(4): 15-18 (in Chinese).
[78] 朱晓红, 王全楚, 董晓锋, 刘建琴. 蒙脱石散、双歧杆菌三联活菌联合参苓白术散治疗酒精性肝病的临床观察[J]. 中西医结合肝病杂志, 2018, 28(3): 178-180.
[79] Li YT, Yang LY, Xu H, Bian XY, Shi D, Wu WR, Li LJ. Restoration of ethanol-induced *Bifidobacterium pseudocatenulatum* depletion ameliorates alcohol-associated liver disease[J]. npj Biofilms and Microbiomes, 2026, 12: 47.
[80] Dong Y, Wu ZY, Gai ZH, Han M. *Bifidobacterium longum* subsp. *longum* BL21 ameliorates alcoholic liver disease in mice through enhancement of the hepatic antioxidant capacity and modulation of the gut microbiota[J]. Journal of Applied Microbiology, 2023, 134(11): lxad251.
[81] Han SH, Suk KT, Kim DJ, Kim MY, Baik SK, Kim YD, Cheon GJ, Choi DH, Ham YL, Shin DH, Kim EJ. Effects of probiotics (cultured *Lactobacillus subtilis*/*Streptococcus faecium*) in the treatment of alcoholic hepatitis: randomized-controlled multicenter study[J]. European Journal of Gastroenterology & Hepatology, 2015, 27(11): 1300-1306.
[82] Liu HX, Kang X, Yang XD, Yang H, Kuang XY, Ren P, Yan H, Shen XR, Kang YB, Li L, Wang XH, Guo LZ, Tong MW, Fan WP. Compound probiotic ameliorates acute alcoholic liver disease in mice by modulating gut microbiota and maintaining intestinal barrier[J]. Probiotics and Antimicrobial Proteins, 2023, 15(1): 185-201.
[83] Zhang XP, Yang B, Yi YX, Nie ML, Yang BX, Song NN, Abuduwaili A, Mansur S, Rozi P, Wali A, Yili A. Structural characterization of Seabuckthorn polysaccharides and protective effects on acute alcoholic

liver disease[J]. International Journal of Biological Macromolecules, 2026, 338: 149752.
[84] Liu W, Li XQ, Zhao ZL, Pi XE, Meng YY, Fei DB, Liu DQ, Wang X. Effect of chitooligosaccharides on human gut microbiota and antiglycation[J]. Carbohydrate Polymers, 2020, 242: 116413.
[85] Liu YL, Sun JW, Yan QH, Wen BJ, Bai Y, Che QS, Cao H, Guo J, Su ZQ. Chitosan oligosaccharides prevent alcohol-induced liver disease by attenuating inflammation and oxidative stress[J]. Marine Drugs, 2025, 23(3): 134.
[86] Yin RP, Wang T, Sun JZ, Dai HQ, Zhang YT, Liu NN, Liu HW. Postbiotics from *Lactobacillus johnsonii* activates gut innate immunity to mitigate alcohol-associated liver disease[J]. Advanced Science, 2025, 12(2): 2405781.
[87] Xiao LY, Zhang CL, Zhang XL, Zhao XG, Chaeipeima Mahsa G, Ma K, Ji F, Azarpazhooh E, Ajami M, Rui X, Li W. Effects of *Lacticaseibacillus paracasei* SNB-derived postbiotic components on intestinal barrier dysfunction and composition of gut microbiota[J]. Food Research International, 2024, 175: 113773.
[88] Liu ZZ, Liu T, Fan YR, Jiang ZY. *Bacillus coagulans*-pectin synbiotic modulates gut microbiota composition and attenuates ethanol-induced alcoholic liver disease in mice[J]. Microorganisms, 2025, 13(9): 1986.
[89] Wang QQ, Li YT, Lv LX, Jiang HY, Yan R, Wang ST, Lu YM, Wu ZJ, Shen J, Jiang SM, Lv JW, Li SJ, Zhuge AX, Li LJ. Identification of a protective *Bacteroides* strain of alcoholic liver disease and its synergistic effect with pectin[J]. Applied Microbiology and Biotechnology, 2022, 106(9/10): 3735-3749.
[90] Rishi P, Arora S, Kaur UJ, Chopra K, Kaur IP. Better management of alcohol liver disease using a 'microstructured synbox' system comprising *L. plantarum* and EGCG[J]. PLoS One, 2017, 12(1): e0168459.
[91] Li M, Lu Y, Hu Y, Zhai X, Xu W, Jing H, Tian X, Lin Y, Gao D, Yao J. Salvianolic acid B protects against acute ethanol-induced liver injury through Sirt1-mediated deacetylation of p53 in rats[J]. Toxicology Letters, 2014, 228(2): 67-74.
[92] Cai HD, Su SL, Li YH, Zhu ZH, Guo JM, Zhu Y, Guo S, Qian DW, Duan JN. Danshen can interact with intestinal bacteria from normal and chronic renal failure rats[J]. Biomedicine & Pharmacotherapy, 2019, 109: 1758-1771.
[93] Meng XY, Chen Y, Zhao BX, Liu QP, Zhao LQ, Zheng XK, Feng WS. Salvianolic acid B attenuates hypercholesterolemia *via* modulating the gut microbiota and bile acid metabolism[J]. European Journal of Pharmacology, 2025, 999: 177701.
[94] Li LX, Lan XT, Peng X, Shi S, Zhao YL, Liu WT, Luo QH, Jia LL, Feng B, Chen ZL, Zou YF, Huang C. Polysaccharide from salviae miltiorrhizae radix et rhizoma attenuates the progress of obesity-induced non-alcoholic fatty liver disease through modulating intestinal microbiota-related gut-liver axis[J]. International Journal of Molecular Sciences, 2022, 23(18): 10620.
[95] Wang X, Jin YF, Di C, Zeng YP, Zhou YQ, Chen Y, Pan ZJ, Li ZX, Ling WH. Supplementation of silymarin alone or in combination with salvianolic acids B and puerarin regulates gut microbiota and its metabolism to improve high-fat diet-induced NAFLD in mice[J]. Nutrients, 2024, 16(8): 1169.
[96] Hassan A, Rijo P, Abuamara TMM, Ali Lashin LS, Kamar SA, Bangay G, Al-Sawahli MM, Fouad MK, Zoair MA, Abdalrhman TI, Elebeedy D, Ibrahim IA, Mohamed AF, Abd El Maksoud AI. Synergistic differential DNA demethylation activity of *Danshensu* (*Salvia miltiorrhiza*) associated with different probiotics in nonalcoholic fatty liver disease[J]. Biomedicines, 2024, 12(2): 279.
[97] 刘士俊, 张会敏, 贾爱平, 鲁晓峰. 枯草杆菌肠球菌二联活菌胶囊联合复方丹参注射液治疗非酒精性脂肪肝的疗效观察[J]. 临床合理用药杂志, 2014, 7(28): 32-33.
[98] Wang W, Xu AL, Li ZC, Li Y, Xu SF, Sang HC, Zhi F. Combination of probiotics and *Salvia miltiorrhiza* polysaccharide alleviates hepatic steatosis *via* gut microbiota modulation and insulin resistance improvement in high fat-induced NAFLD mice[J]. Diabetes & Metabolism Journal, 2020, 44(2): 336-348.
[99] Cho SY, Yun JW, Park PJ, Sohn JH, Seo DB, Lim KM, Kim WG, Lee SJ. Effects of chitooligosaccharide lactate salt on activity of acetaldehyde dehydrogenase[J]. Journal of Medicinal Food, 2010, 13(5):1061-1068.
[100] Yao ZW, Du MS, Wang YL, Zhu H, Shu L, You X, Wang J. Pharmacodynamic study of chitosan in combination with salvianolic acid B in the treatment of $CC1_4$-induced liver fibrosis in mice[J]. Clinical and Experimental Pharmacology and Physiology, 2024, 51(1): 17-29.