中药药对抗心衰药理作用的研究进展

刘星雨, 孟鼎伦, 李舒弘, 郑春丽, 陆晨曦, 靳雅惠*

(延安大学延安医学院, 陕西 延安 716000)

摘要: 目前, 心力衰竭 (heart failure, HF) 已成为全球公共卫生领域的重大挑战, 其发病率与死亡率呈不断上升趋势。尽管现代医学采用的临床干预手段取得了一定成效, 但仍存在不良反应增多、病情反复及远期死亡率并未降低的情况。在此背景下, 基于传统中医药理论构建的药对配伍策略, 通过多成分协同与多靶点网络调控机制, 在心衰防治方面发挥重要作用。本文通过梳理近年来中药药对治疗心衰的相关文献, 整理了研究较为深入且具有代表性的药对16对, 它们主要通过减轻炎症反应、抗氧化应激、抗细胞凋亡、抑制心脏纤维化、调节神经内分泌紊乱及心肌微循环, 最终抑制或治疗心衰, 从而为临床制定个体化用药方案及新药开发拓展思路。

关键词: 心力衰竭; 药对; 药理机制; 信号通路; 靶点

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Research progress on anti-heart failure pharmacological effect of herb pair in traditional Chinese medicine

LIU Xing-yu, MENG Ding-lun, LI Shu-hong, ZHENG Chun-li, LU Chen-xi, JIN Ya-hui*

(*Yan'an Medical College, Yan'an University, Yan'an 716000, China*)

Abstract: Heart failure (HF) has become a major challenge in global public health, and its incidence and lethality are on the rise. While the effectiveness of clinical interventions in modern medicine, they are accompanied by rising adverse drug reactions, recurring diseases, and no reduction in long-term mortality. In this context, herb pairing methods informed by traditional Chinese medicine theories, through mechanisms of multi-component synergy and multi-target network regulation, have been vital in HF prevention and treatment. In this study, we have gathered and analyzed recent investigations on the pharmacological effects of traditional Chinese medicine for HF, resulting in a list of 16 notable and representative herb pairs. Their main functions include reducing inflammation, countering oxidative stress, preventing apoptosis, inhibiting cardiac fibrosis, regulating neuroendocrine disorders and myocardial microcirculation, and ultimately preventing or treating HF, thus broadening the scope of personalized clinical drug regimens and the development of new therapeutic agents.

Key words: heart failure; herb pair; pharmacological mechanism; signaling pathway; target

心力衰竭 (heart failure, HF), 简称心衰, 是一种由心脏结构或功能异常引发的临床综合征, 核心病理表现为心室充盈能力下降和 (或) 射血功能障碍, 多出现于心脏疾病的终末阶段[1], 具有发病率高、致死率高、治愈率低的特点, 严重影响患者的生活质量[2]。基于中国心血管疾病流行趋势预测, 我国现存心衰患者890万人, 其中多数心衰患者最终会发生心源性猝死[3]。临床多采用西药及手术等手段治疗心衰, 尽管取得了一定成效, 但长期用药容易导致不良反应增多和病情反复, 且部分患者远期的死亡率并未降低[4]。中医药以整体观念和辨证论治为基础来实现个体化治

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*通讯作者 E-mail: sxyajyh@126.com

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疗, 充分展现了多靶点、多维度及安全低毒的优势[5]。因此, 深入阐述目前中药用药现状, 是探索心衰有效防治手段的重要举措。

中医对“心衰”的描述最早可见于西晋时期的《脉经》。心衰的病位虽在心, 但与脾、肾、脑等多个脏腑存在关联[6-8], 故可纳入“心悸”、“水肿”等范畴。本病以气虚为本, 水饮停聚为标, 一则心失所养, 心神失摄; 再则心气不足, 水饮内停, 凌心射肺, 故而心衰发作[9,10]。在中医治疗心衰的过程中, 多种中药方剂发挥重要作用。其中, 药对作为方剂的最小特色单位, 具有紧扣病机、增效减毒等特点[11]。因此, 以药对为切入点开展抗心衰组方的作用及机制研究 (图 1), 是明确抗心衰中药用药规律及推动新药研发的有效途径。

本文总结了研究较深入且具有代表性的抗心衰药对 16 对, 主要分为“温阳益气”、“活血化瘀”、“健脾利水”、“益气养阴”及“调和阴阳”5 大类, 从而为心衰的诊治及新药研发提供理论依据。

1 温阳益气类 (warming Yang and invigorating Qi, WY-IQ)

《伤寒治例》记载: “气虚停饮, 阳气内弱, 心下空虚, 正气内动而悸也”。心衰的核心病机为心气虚衰、心肾阳虚, 因以温阳补气为主[12,13]。现代研究进一步揭示, 该病机与线粒体能量代谢障碍存在深度耦联, 心肌细胞线粒体 ATP 合成减少触发能量危机, 随后代偿性激活肾素−血管紧张素−醛固酮系统 (renin angiotensin aldosterone system, RAAS) , 通过血管收缩、水钠潴留等机制加重心脏负荷, 形成恶性循环[14]。相关研究表明, RAAS 在加剧心衰进程中具有双重作用, 一方面,

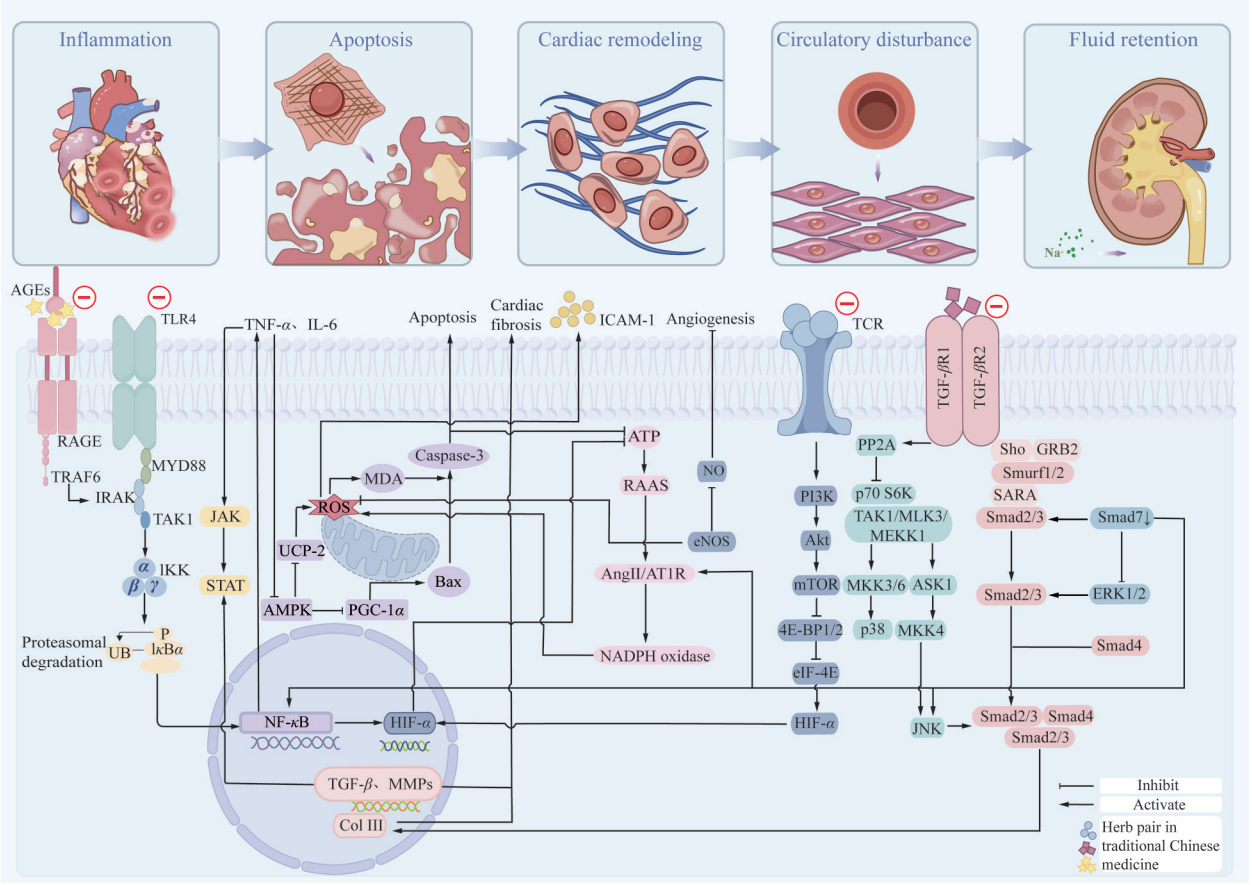


Figure 1 Pharmacological effect of herb pair in traditional Chinese medicine against heart failure. TRAF6: TNF receptor associated factor 6; IRAK: Interleukin-1 receptor associated kinase; TAK1: Transforming growth factor *β*-activated kinase 1; MYD88: Myeloid differentiation primary response 88; JAK: Janus kinase; UCP-2: Uncoupling protein 2; ROS: Reactive oxygen species; eNOS: Endothelial nitric oxide synthase; 4E-BP1: Eukaryotic translation initiation factor 4e-binding protein 1; eIF-4E: Eukaryotic translation initiation factor 4e; Caspase-3: Cysteine aspartic acid specific protease-3; HIF-1*α*: Hypoxia-inducible factor 1 alpha subunit; Col III: Collagen type III; NADPH oxidase: Nicotinamide adenine dinucleotide phosphate oxidase; GRB2: Growth factor receptor bound protein 2; ASK1: Apoptosis signal-regulating kinase 1; PP2A: Protein phosphatase 2a; p38: p38 mitogen-activated protein kinase; p70 S6K: p70 ribosomal protein S6 kinase; Smad: Drosophila mothers against decapentaplegic protein; JNK: c-Jun N-terminal kinase; MLK3/MEKK1: Mixed lineage kinase 3/mitogen-activated protein kinase/ERK kinase kinase 1; MKK: Mitogen-activated protein kinase kinase

RAAS可诱导肿瘤坏死因子α (tumor necrosis factor-alpha, TNF-α)、白细胞介素6 (interleukin-6, IL-6)等炎症介质的生成, 导致血管内皮和心肌细胞损伤[15]。另一方面, RAAS可促进心肌细胞凋亡及纤维化[16], 进一步推动心衰的发展。以下药对具有温阳益气功效, 在抗心衰方面发挥重要作用。

1.1 人参–黄芪 (*Ginseng radix et rhizoma-Astragali radix*, GR-AR) 人参补五脏虚损, 黄芪补气升阳, 二者配伍起源于东汉张仲景《伤寒杂病论》, 现可治疗心血管疾病, 具有抗氧化、抗凋亡、调节能量代谢等作用[17]。实验研究证实, 人参–黄芪可使H9c2心肌细胞缺氧/复氧损伤模型中CCAAT/增强子结合蛋白同源蛋白 (C/EBP homologous protein, CHOP)、caspase-12、Bax蛋白表达减少, sigma-1R、Bcl-2蛋白表达增多, 通过调控内质网应激抑制心肌细胞凋亡[17]。Yu等[18]应用人参–黄芪水煎剂 (人参15 g, 黄芪60 g)对16位心肌炎患者 (男10例, 女6例, 18～45岁)进行治疗。每日一剂, 连用28天后, 所有患者临床症状均有所改善, 其中, 治愈9例 (56.25%), 显效3例 (18.75%), 有效4例 (25%)。此外, Bian[19]利用人参健心胶囊对60位气虚血瘀型慢性心力衰竭 (chronic heart failure, CHF)患者的心功能进行评价, 结果显示, 中西药联合治疗的总有效率 (96.7%)优于卡托普利、琥珀酸、美托洛尔、氢氯噻嗪、地高辛联用的西药组总有效率 (73.3%), 这可能是由于人参健心胶囊以人参为君、黄芪为辅, 两药相须为用, 力大功专, 大补心气。

1.2 人参–附子 (*Ginseng radix et rhizoma-Aconiti lateralis radix praeparata*, GR-ALRP) 人参–附子药对始载于《圣济总录》参附汤, 方中人参大补元气、益气固脱; 附子回阳救逆、补火助阳。二者配伍温而兼润, 补而能固, 为气衰欲脱之要药[20]。低剂量附子在抗心衰方面具有良好的治疗潜力, 而高剂量往往会诱发室性快速心律失常, 甚至死亡[21], 这可能是因为附子中双酯型乌头类生物碱 (如乌头碱、新乌头碱)通过激活电压门控钠通道导致心律失常。当附子与人参配伍时, 人参皂苷Re、Rg1等成分可以调节离子通道途径, 抑制乌头碱引起的Cav1.2 (L-型钙通道α1C亚型)等mRNA表达, 降低细胞内Ca^{2+}浓度, 加速乌头碱代谢, 促进苯甲酰基乌头碱吸收, 从而减轻乌头碱引起的心肌毒性作用[22,23]。人参可加速附子乌头碱等毒性成分的代谢并增强其强心作用, 形成“气阳双补”协同效应[24,25]。环磷酸腺苷 (cyclic adenosine monophosphate, cAMP)信号通路在心肌细胞的生理病理过程中发挥关键作用, 当cAMP信号传导异常时, 可诱发CHF患者心肌重塑与肥厚, 加剧心衰进展, 而人参、附子均可通过调控cAMP信号通路, 改善心肌舒缩障碍[26]。Yang等[27]研究发现, 人参–附子在改善心肌梗死大鼠心脏损伤方面较单用附子呈现更显著的心脏保护效应。其机制可能与人参、附子协同下调心脏组织中微管相关蛋白1轻链3 (microtubule-associated protein 1 light chain 3, LC3) II/LC3-I的比值、Beclin-1的表达, 抑制腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK)信号激活, 同时上调自噬底物p62表达有关, 提示人参–附子可能通过抑制心肌过度自噬发挥协同治疗作用。此外, 人参–附子药对干预压力负荷诱导的CHF小鼠后, AMPK、过氧化物酶体增殖物激活受体γ共激活因子1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha, PGC-1α)及PPARα蛋白表达水平升高, 证实人参–附子可通过提高线粒体基础耗氧率和线粒体ATP合成量, 调节线粒体生物发生, 改善代谢重构, 维持心肌细胞能量代谢稳态[28]。据报道, 致炎性细胞因子的升高和心衰的严重程度成正比, 而人参–附子可有效提高血液中IL-10, 抑制IL-18、TNF-α, 因此, 该药对广泛应用于急性心衰及CHF的治疗[29]。

1.3 附子–黄芪 (*Aconiti lateralis radix praeparata-Astragali radix*, ALRP-AR) 附子–黄芪药对常见于《普济方》附子黄芪汤, 附子大辛大热, 可制约心肾阳衰, 黄芪甘温, 益气固表行水, 二者共补心、肾, 温阳益气, 常用于治疗心肾阳虚证心衰[24]。现代药理学证明, 黄芪甲苷通过调节Nrf2的活性, 加速附子生物碱的分布及消除过程, 这一作用不仅能改善心肌细胞的线粒体功能, 还能抑制心肌肥厚和纤维化, 从而有效保护心肌细胞, 最终抑制CHF的进程[24], 这一结果在Liu等[30]研究中也得以体现。此外, 附子–黄芪可通过线粒体途径调节细胞凋亡和膜电位, 平衡心肌细胞钙调节蛋白钙钠交换体1 (sodium-calcium exchanger 1, NCX1)和肌浆网Ca^{2+}-ATP酶2 (sarcoplasmic reticulum Ca^{2+}-ATPase 2, SERCA2)的表达, 起到保护心衰大鼠心肌细胞, 改善心功能的作用[31]。

1.4 附子–干姜 (*Aconiti lateralis radix praeparata-Zingiberis rhizome*, ALRP-ZR) 附子–干姜是《伤寒杂病论》中治疗心阳虚证的常用药对, 二者一走一守, 回阳救逆[24], 临床上可用于治疗射血分数保留型心力衰竭 (heart failure with preserved ejection fraction, HFpEF)[32]。Jin等[33]研究显示, 与常规西药组相比, 加用温阳益心汤 (附子、干姜等)治疗的阳虚血瘀水停证CHF疗效更加显著, 表现为显著降低循环系统中TNF-α、IL-6表达水平, 提升左室射血分数 (left ventricular ejection fraction, LVEF), 推测主要为附子–干姜在治疗

阳虚血瘀水停证CHF中发挥抗炎作用。网络药理学研究表明, 附子−干姜通过抑制11β-羟基类固醇脱氢酶1型 (11β-hydroxysteroid dehydrogenase type 1, HSD11B1) 的活性, 促进血管新生, 并下调基质金属蛋白酶 (matrix metalloproteinases, MMPs) 表达, 维持心肌结构的完整性[34]。代谢组学进一步揭示, 附子−干姜抗心衰作用可能通过调节嘧啶代谢而维持心肌能量稳态, 调控色氨酸代谢以改善氧化应激状态[35]。综上, 附子−干姜在增强心肌收缩力、改善微循环等方面具有明显功效, 从而发挥抗心衰作用。

1.5 附子−桂枝 (*Aconiti lateralis radix praeparata-Cinnamomi ramulus*, ALRP-CR) 附子配伍桂枝常见于《伤寒论》桂枝附子汤, 二药相辅可温通肾阳以助心阳, 配伍后散寒止痛, 温阳宣痹[24]。附子−桂枝药对能下调血清TNF-α、IL-6、NO、丙二醛 (malondialdehyde, MDA) 的表达, 发挥抗炎镇痛作用[24]。据报道, 心衰患者的心功能恶化程度与血管紧张素II (angiotensin II, Ang II)、内皮素-1水平呈正相关[36]。而桂枝有效成分桂皮醛、桂皮油等能够抑制RAAS与内皮素系统过度激活, 发挥抗炎、保护心血管等作用[15]。此外, 心衰患者往往拥有较低的血清三碘甲状腺原氨酸 (triiodothyronine, T_3) 水平[37], 原因在于T_3水平与心衰严重程度呈负相关, 已成为预后不良的独立危险因素[38]。而附子−桂枝可上调T_3、四碘甲状腺原氨酸及促甲状腺激素水平, 温通肾阳以助心阳, 从而有利于心衰的治疗[6]。

2 活血化瘀类 (activating blood and removing stasis, AB-RS)

《黄帝内经》中有“血气不和, 百病乃变化而生”的中医理论, 并据此提出“疏其血气, 令其条达, 而致和平”的治疗法则, 强调了气血和谐对于维持人体健康的重要性[39]。现代医学领域, 颜德馨提出心衰关键在于心气阳虚、心血瘀阻[6]。Chen等[40]指出瘀血是CHF的主要病理产物, 也是导致心衰加重、缠绵难愈的主要原因。这些论述阐明了当心脏泵血功能低下时, 其推动和温煦功能的减退会导致心气 (阳) 亏虚, 进而产生血瘀的病理机制[20]。心脉瘀阻作为心衰的重要发病机制, 导致血运不畅, 影响新血生成, 久则无力荣养周身五脏, 引起心悸、胸闷、乏力等症, 故严世芸以“通”为法, 以温通心脉、活血养血、化瘀通络为切入口, 以期心脉通畅, 瘀去新生, 恢复心主血脉[11]。与此同时, Hu等[41]提出炎症因子通过损伤血管内皮、激活血小板促凝途径, 形成与中医血瘀证高度对应的血栓前状态, 这种病理过程与氧化应激形成正反馈环路, 共同加速心肌重构和心功能恶化过程。以下药对具有活血化瘀的功效, 在抗心衰方面发挥重要作用。

2.1 黄芪−水蛭 (*Astragali radix-Hirudo*, AR-H) 水蛭具有活血通脉、破瘀消癥的功效。针对心系顽疾, 应在辨证论治的基础上配伍水蛭, 以攻窜散结、祛瘀通络止痛, 但须注意其适用症, 如病久正虚, 或体质本虚, 当配伍适量黄芪以补益机体气机[42]。Su课题组[43]采用黄芪与水蛭配伍的策略以强化益气活血通络之效。现代药理研究证实, 水蛭提取物可显著降低乳酸脱氢酶、肌酸激酶、MDA含量, 抑制心肌细胞损伤标志物释放, 减轻氧自由基介导的脂质过氧化损伤, 进而改善心肌缺血, 维持心肌细胞能量代谢稳态[43]。黄芪−水蛭药对可抑制RAAS过度激活, 阻断AngII介导的转化生长因子β (transforming growth factor beta, TGF-β)/Smad通路, 从而减少心肌胶原沉积, 并降低血液黏度及微血栓风险, 协同改善冠脉微循环[44]。

2.2 红花−桃仁 (*Carthami flos-Persicae semen*, CF-PS) 红花−桃仁药对首载于《医宗金鉴》桃红四物汤, 红花行血和血, 桃仁破血逐瘀, 分别善祛上病与下病之瘀血, 是活血化瘀的经典药对[5]。以红花、桃仁为佐药的八味通络颗粒能有效降低射血分数中间值心衰患者的血流变指标, 延缓心衰病情[45]。桃红四物汤不仅能显著降低急性血瘀大鼠模型的全血黏度和血浆黏度[20], 还能上调低氧诱导的H9c2大鼠心肌细胞中Bcl-2的表达和LC3-II/LC3-I的比值, 下调Bax和p62的表达, 抑制心肌细胞凋亡, 促进细胞自噬, 从而保护心肌细胞[46]。据研究, 红花、桃仁配伍后, 抗凝、抗血小板聚集及促进血管内皮修复作用较单药疗效更为显著[5]。

2.3 黄芪−当归 (*Astragali radix-Angelicae sinensis radix*, AR-ASR) 黄芪−当归药对益气生血, 甘温制燥, 最早记载于《陈素庵妇科补解·调经门》, 针对患者气虚血瘀症候具有一定疗效[43]。Li[47]关于姜丽红教授治疗CHF用药规律的研究指出, 338个处方中共包含210味中药, 黄芪出现频次302次, 位列第1位, 当归出现频次74次, 位列第14位, 二者共同出现频次等于当归出现频次, 该数据说明当归与黄芪配伍是治疗气虚血瘀性心衰的重要药对。Li[48]采用归芪护心汤治疗HFpEF, 发现中西药联合治疗组总有效率显著优于马来酸依那普利、富马酸比索洛尔、螺内酯联用的西药组总有效率, 说明归芪护心汤在改善患者临床症状方面发挥重要作用。黄芪−当归药对的益气作用主要表现为调节物质能量代谢及免疫功能, 活血作用表现为降低血液黏度, 该药对亦可通过抗氧化应激、抗炎、降血脂、降血糖、保护心功能、保护血管壁、干预血管生成、抗心脏纤维化等发挥益气活血作用, 在二者以3∶1 (总量36 g) 配伍时益气活血作用最为显著[49]。

2.4 川芎–当归 (*Chuanxiong rhizoma-Angelicae sinensis radix*, CR-ASR) 川芎–当归药对作为活血补血的经典配伍, 源自《太平惠民和剂局方》芎归汤。名老中医毕朝忠临床实践经验丰富, 灵活地将川芎–当归药对扩展至心血管疾病的治疗中[50]。Liu等[51]研究结果表明, 川芎–当归 (1∶1.5和1∶1) 在改善急性血瘀大鼠模型血流变学和凝血功能方面的效果最为显著。此外, 川芎–当归药对具有调节血液黏稠度、抗血栓形成、改善血液循环的作用。据报道, 川芎–当归提取物可能通过抑制丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 通路, 调控周期蛋白的表达, 从而抑制血管平滑肌增生[52]。

2.5 三七–扶芳藤 (*Notoginseng radix et rhizoma-Euonymi fortunei caulis*, NRR-EFC) 三七散瘀止血、消肿定痛, 扶芳藤益气血、舒筋活络、止血化瘀, 二者合用, 充分体现了心衰治疗中“化瘀通阳”的整合效应。据报道, 三七、扶芳藤具有抗氧化、抗血栓、心脏保护等多种药理作用, 对心血管系统产生良好的临床治疗效果[53]。此外, Zhao[54]对60例阳虚血瘀证CHF患者使用三七–扶芳藤药对联合西医常规治疗, 结果表明三七–扶芳藤可降低N末端B型利钠肽原 (N-terminal pro-B-type natriuretic peptide, NT-proBNP)、C反应蛋白、TNF-α等水平, 降低中医证候积分, 改善心功能, 提高患者生活质量。网络药理学研究发现, 三七–扶芳藤药对可通过晚期糖基化终末产物及其受体 (advanced glycation end products-receptor for advanced glycation end products, AGE-RAGE)、磷脂酰肌醇3-激酶/蛋白激酶B (phosphatidylinositol 3-kinase/protein kinase B, PI3K/AKT) 等多条通路, 发挥对CHF的治疗作用[55]。

3 健脾利水类 (strengthening spleen and promoting diuresis, SP-PD)

《金匮要略》言:“心水者, 其身重而少气, 不得卧, 烦而躁, 其人阴肿”[24]。中医理论认为“血瘀”、“水饮”是心衰的重要病机, 二者密切相关, 往往水病及血、血病及水[56]。“虚瘀水毒”理论揭示, 心肾阳虚为本, 推动无力遂水饮停聚; 脾虚失运为枢, 气血乏源则痰瘀互结; 终致毒损心络, 形成“本虚标实, 三焦水湿”的病理格局[57-59], 当以健脾祛湿利水法治之[60,61]。据报道, 心功能不全会引发血液高凝和微循环障碍, 进而导致液体潴留和代谢紊乱, 促使痰浊水饮内生, 最终加剧慢性炎症和免疫失衡, 形成恶性循环[62]。同时, 脾虚证候与线粒体能量代谢障碍之间存在显著相关性, 当脾失健运时, 心肌细胞线粒体结构肿胀、ATP酶活性下降, 心肌能量危机出现, 这与中医“脾不散精, 心失所养”的理念不谋而合[63]。由于心脾两脏在生理功能、解剖位置和经络络属关系的相关性, 决定了两脏在病理上的相互关联, 为从脾论治心衰提供了理论基础[64]。《素问·经脉别论》言“饮入于胃, 游溢精气, 上输于脾, 脾气散精, 上归于肺”, 可见肺为水液代谢的起点, 与脾存在密切关联。以下药对具有健脾利水的功效, 在抗心衰方面发挥作用。

3.1 葶苈子–大枣 (*Descurainiae semen lepidii semen-Jujubae fructus*, DSLS-JF) 葶苈子–大枣药对出自《金匮要略》葶苈大枣泻肺汤, 方中葶苈子苦寒, 专于利水消肿, 大枣甘温补益。国医大师路志正教授常用葶苈大枣泻肺汤 (葶苈子15 g, 大枣5枚) 合真武汤加减治疗CHF[65], 周汝亮等[66]利用生脉散合葶苈大枣泻肺汤 (葶苈子12 g, 大枣12 g) 治疗气阴虚血瘀水停证心衰, 均取得显著疗效。其可能原因在于, 大枣甘温补益的功效可削弱葶苈子寒凉峻烈之性并协同增强其利水消肿之效, 二者配伍后可顾护脾胃、扶助正气, 在“补元”的基础上, 宣泄痰瘀水饮、补虚泄实、益气利水, 从而达到治疗CHF的效果[67,68]。Yuan等[69]研究表明, 葶苈大枣泻肺汤 (葶苈子15 g、大枣12枚) 不仅可以降低心衰大鼠的心肌羟脯氨酸和胶原蛋白含量, 调节血清MMPs水平, 还可通过提高血管紧张素转换酶2–Ang-(1-7)–Mas轴蛋白的表达水平改善心肌纤维化, 减缓心室重构, 发挥心肌保护作用。而在单味药作用机制方面, Li等[70]发现, 南葶苈子水提液可改善肺源性心脏病合并心衰大鼠的症状, 可能与上调肺组织水通道蛋白1 (aquaporin 1, AQP1) 的表达、稳定心肌细胞凋亡及自噬有关。此外, 大枣中高含量的cAMP可改善心肌缺氧、扩张冠脉、增强心肌收缩力、增加心输出量, 对CHF具有一定的疗效[71]。

3.2 泽泻–白术 (*Alismatis rhizome-Atractylodis macrocephalae rhizoma*, AR-AMR) 泽泻–白术来自《金匮要略》泽泻汤。白术重在健脾, 泽泻重在除湿, 二药相配共奏健脾除湿、消肿利尿之功效, 针对心衰“水瘀互结、浊毒内蕴”的病理特征, 泽泻–白术在CHF的治疗中充分展现了“利水降浊–调脂护脉”的协同效应[72-74]。Zhang课题组[75]常用泽泻汤加减, 治疗心衰水湿停聚之证。此外, 以泽泻–白术药对为主的加味泽泻汤下调Toll样受体4/核因子κ轻链增强子结合蛋白 (Toll-like receptor 4/nuclear factor-kappa B, TLR4/NF-κB) 信号通路相关蛋白表达, 改善炎症反应[76]。网络药理学发现, 泽泻–白术主要通过调控细胞外信号调节激酶1和2 (extracellular signal-regulated kinase 1/2, ERK1/2)、MAPK、PI3K、类固醇激素介导的信号通路, 发挥调控血脂的作用[76]。据报道, 泽泻汤 (泽泻、白术以5∶2配伍) 能抑制血管平滑肌细胞中MMP-9、MMP-2

的表达, 以改善血管功能[77]。

4 益气养阴类 (invigorating Qi and nourishing Yin, IQ-NY)

心藏神, 心阴虚乏, 则神志不安[78]。中医理论强调“心脑相通”, 心主血脉以奉脑髓, 脑统神明以调脏腑, 二者通过精气血的化生输布形成功能闭环[8,10], 当心衰发生时, “心脑共病”表现为心−脑轴失代偿[79]。据研究, 心衰时射血分数的降低, 会触发RAAS和交感神经过度激活, 进而引发儿茶酚胺风暴, 严重破坏血脑屏障完整性, 同时损伤脑血流自动调节功能, 使海马区神经元线粒体功能出现障碍, 还会诱发β淀粉样蛋白沉积, 加速认知功能衰退[9], 表现为失眠、焦虑及执行功能下降, 形成“心衰加重−脑损伤”交互的恶性循环模式[11]。心主神功能完整而寤寐得调, 以下药对能体用并举, 缓解心衰症状。

4.1 麦冬−五味子 (*Ophiopogonis radix-Schisandrae chinensis fructus*, OR-SCF) 麦冬甘寒养阴清心, 五味子酸温敛气固脱, 二者共奏益气复脉、宁心安神之效, 在心衰“气阴两虚−心神失养”的病机中展现出协同作用[80,81]。Nan[82]研究发现, 麦冬−五味子可显著降低LVEF、NT-proBNP水平。Shu[83]研究显示, 加味五味子汤 (五味子10 g、麦冬15 g) 治疗心律失常心气不足型患者总有效率 (92%) 显著高于盐酸胺碘酮片总有效率 (68%), 体现了麦冬、五味子协同提高心肌对缺氧的耐受性、扩张冠状动脉、改善心肌供血的作用。网络药理学进一步揭示了麦冬−五味子可能作用于AKT1、信号转导与转录激活因子3等关键靶点, 调控AGE-RAGE等通路, 减轻心衰患者心肌纤维化进程, 有效提升心肌细胞的存活率[84]。

4.2 酸枣仁−五味子 (*Ziziphi spinosae semen-Schisandrae chinensis fructus*, ZSS-SCF) Zhang课题组[85]常用酸枣仁−五味子养心肝之阴血, 除烦安神, 二者配伍的传统功效主要聚焦于镇静安神与补肾固本。据报道, 酸枣仁−五味子药对具有镇静催眠、抗焦虑、抗抑郁、抗氧化等药理作用[86], 临床可干预心脑血管疾病共病情绪障碍[87]。酸枣仁−五味子配伍比例不同, 功效主治亦不同, 使用较高频率的配伍比例有1∶1、2∶1和3∶1, 其中2∶1配伍比例通过下丘脑−垂体−肾上腺 (hypothalamic-pituitary-adrenal, HPA) 轴及脑源性神经营养因子/细胞外信号调节激酶/内源性大麻素系统 (brain-derived neurotrophic factor/extracellular signal-regulated kinase/endocannabinoid system, BDNF/ERK/ECS) 信号通路发挥显著抗焦虑作用[88]; 1∶1和3∶1配伍比例可能通过调节单胺类神经递质发挥明显的镇静催眠作用[89,90]。但酸枣仁−五味子药对中五味子酸敛最甚, 若实证用之, 有收敛邪气、闭门留寇之弊, 故实证患者当慎用[91]。

5 调和阴阳类 (harmonizing Yin and Yang, HY-HY)

《素问·阴阳应象大论》曰: “阳化气, 阴成形”, 正常人体阴阳平衡, 而在心衰状态下, 阳化气不足、阴成形太过[92], 表现为失眠、心悸等症, 作用机制与线粒体功能障碍、炎症因子积聚、心肌细胞过度自噬密切相关[93,94]。针对这一病理过程, 中医提出“扶正祛邪, 调和阴阳”的理念, 通过调节上述病理机制以达到治疗心衰的目的。以下药对具有调和阴阳的功效, 在抗心衰方面发挥重要作用。

5.1 黄芪−葶苈子 (*Astragali radix-Descurainiae semen lepidii semen*, AR-DSLS) 黄芪为君药, 具有补益心气、固本培元之功; 葶苈子为臣药, 具有泻肺利水、祛痰饮瘀毒之效[1]。网络药理学研究发现, 黄芪−葶苈子药对可改善线粒体功能并抑制细胞凋亡, 在心衰治疗中发挥作用[95]。Li等[96]实验结果表明, 黄芪−葶苈子药对不仅能够上调线粒体融合蛋白1 (mitofusin 1, Mfn1)、线粒体融合蛋白2 (mitofusin 2, Mfn2) 和视神经萎缩蛋白1 (optic atrophy 1, OPA1) 的表达水平, 抑制裂变蛋白1 (fission 1, Fis1) 和动力相关蛋白1 (dynamin-related protein 1, Drp1) 的活性, 还能减轻心衰时心肌细胞线粒体嵴断裂、肌节缺失等结构改变, 调节心肌组织线粒体动力学, 从而发挥抗心衰作用[28]。自噬是细胞内溶酶体介导的参与蛋白和细胞器降解的高度保守机制, 但其过度激活是导致心衰的重要原因之一[10]。Wang等[10]研究表明, 黄芪−葶苈子药对水煎液可通过抑制AMPK/mTOR介导的自噬途径降低LC3-II/LC3-I比值, 上调p62表达, 改善大鼠的心功能。综上, 黄芪−葶苈子通过抗自噬、调节线粒体功能等, 在心衰中发挥积极作用。

5.2 酸枣仁−柏子仁 (*Ziziphi spinosae semen-Platycladi semen*, ZSS-PS) 酸枣仁−柏子仁药对具有补益心脾、调和阴阳、协同增效的作用, 临床上已被证实是治疗冠心病合并失眠及心房颤动的重要药物组合[97,98]。Wang[97]关于杨丽华教授在治疗冠心病合并失眠的研究中, 酸枣仁用量通常为10～90 g, 最多可达200 g。据报道, 酸枣仁油不仅可以促进细胞外Ca^{2+}内流发挥强心及抗心衰作用, 还能够提高超氧化物歧化酶 (superoxide dismutase, SOD)、谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px) 活性发挥抗氧化作用, 有助于保护心脏免受氧化应激损伤[99]。研究表明, 酸枣仁总皂苷JuA通过抑制大鼠心肌细胞的L型钙通道电流 (L-type calcium channel current, Ica-L) 发挥抗心律失常的作用, 同时阐明了柏子仁霜、柏子仁油及柏

子仁总萜类成分能促进小鼠入睡并延长睡眠时间[100]。此外, 酸枣仁–柏子仁药对中的酸枣仁生物碱、柏子仁总皂苷等多种活性成分[86,101], 在改善心血管疾病伴随的睡眠障碍中发挥协同作用。

上述16个药对在心衰防治中展现出多维潜力, 同时使临床遣方用药更具针对性。基于此, 本文初步梳理了这16个药对在方剂中的应用情况 (表1)[5,6,9-11,14-35,42-55,65-68,72-74,78,80-90,95-112]。

6 总结与展望

近年来, 心衰的发病率呈持续增长趋势, 对患者构成严重威胁。相较于西药单靶点治疗模式, 药对配伍既保留了中医辨证论治的精髓, 又充分阐释了现代药理作用的科学内涵, 在改善血液循环障碍、纠正能量代谢失衡等关键病理环节展现出独特优势, 对心衰的防治起重要作用。该综述系统梳理的16对抗心衰药对中, "温阳益气"(5对) 与"活血化瘀" (5对) 类占比突出, 印证了中医"阳微阴弦"的核心病机理论——心气心阳虚损为本、血瘀水停为标的"虚–瘀–水"三者交织的动态病理过程。值得注意的是, "健脾利水" (2对)、"益气养阴" (2对) 及"调和阴阳" (2对) 类药对虽数量较少, 却体现了中医"标本兼治"的诊疗原则, 其配伍规律与作用机制亟待深度解析。

尽管中药药对在临床应用中展现出显著优势, 但目前仍存在需完善之处。一方面, 部分新兴药对在心衰研究中的作用机制仍有待深化, 如泽兰–益母草。另一方面, 古今中医对心衰的诊治虽形成了许多上述效如桴鼓的经验药对, 但其药理机制尚不十分清楚。未来应充分结合网络药理学、多组学等手段, 开展分子机制方面的深入探索, 推动形成中西医优势互补的心衰防治新范式。

Table 1 Primary therapeutic effects of Chinese medicinal "herb pair" and their anti-heart failure prescription. GR-AR: *Ginseng radix et rhizoma-Astragali radix*; GR-ALRP: *Ginseng radix et rhizoma-Aconiti lateralis radix praeparata*; ALRP-AR: *Aconiti lateralis radix praeparata-Astragali radix*; ALRP-ZR: *Aconiti lateralis radix praeparata-Zingiberis rhizome*; ALRP-CR: *Aconiti lateralis radix praeparata-Cinnamomi ramulus*; AR-H: *Astragali radix-Hirudo*; CF-PS: *Carthami flos-Persicae semen*; AR-ASR: *Astragali radix-Angelicae sinensis radix*; CR-ASR: *Chuanxiong rhizoma-Angelicae sinensis radix*; NRR-EFC: *Notoginseng radix et rhizoma-Euonymi fortunei caulis*; DSLS-JF: *Descurainiae semen lepidii semen-Jujubae fructus*; OR-SCF: *Ophiopogonis radix-Schisandrae chinensis fructus*; AR-AMR: *Alismatis rhizome-Atractylodis macrocephalae rhizome*; ZSS-SCF: *Ziziphi spinosae semen-Schisandrae chinensis fructus*; AR-DSLS: *Astragali radix-Descurainiae semen lepidii semen*; ZSS-PS: *Ziziphi spinosae semen-Platycladi semen*

Herb pair	Effect	Anti-heart failure prescription	Ref.
GR-AR	Anti-apoptosis	Shenqi Tang, Yangxin Tang, Baoyuan Tang, Xinkang Chongji, Shenqi Dingji Tang	[17-20,102]
GR-ALRP	Anti-inflammatory; anti-apoptosis; inhibition of cardiac fibrosis	Shenfu Zhusheye, Nuanxin Fang, Shenfu Tang, Shenfu Yixin Ke Li	[14,16,20-29,31]
ALRP-AR	Protection of cardiomyocytes; inhibition of cardiac fibrosis	Qi Fu Shenmai Xinshuai Tang, Fu Zi Huang Qi Tang, Qiangxinning Jianji, Qiangxin Huoli Tang	[24,30,31,103]
ALRP-ZR	Anti-inflammatory; inhibition of cardiac fibrosis	Si Ni Tang, Po Ge Jiu Xin Tang, Gan Jiang Fu Zi Tang, Zhen Wu Tang	[20,24,32-35,103]
ALRP-CR	Anti-inflammatory; anti-apoptosis	Gui Zhi Fu Zi Tang, Wen Yang Hua Yin Fang	[6,15,24]
AR-H	Improvement of coronary microcirculation	Jian Pi Bu Shen Fang, Zhi Long Huo Xue Tong Yu Jiao Nang	[11,42,44,104]
CF-PS	Improvement of myocardial microcirculation	Xue Fu Zhu Yu Tang, Tao Hong Si Wu Tang, Tao Ren Hong Hua Jian, Ba Wei Tong Luo Ke Li	[5,43,45,46]
AR-ASR	Improvement of hemodynamics	Dang Gui Bu Xue Tang, Gui Qi Hu Xin Tang, Bu Yang Huan Wu Tang	[47-49,105]
CR-ASR	Anti-thrombotic; improvement of blood rheology	Xiong Gui Tang, Xue Fu Zhu Yu Tang, Tao Hong Si Wu Tang	[43,50-52,106]
NRR-EFC	Anti-thrombotic; improvement of cardiac function	Fu Fang Teng Yi Xin Fang, Zhuang Tong Yin	[53-55,107-109]
DSLS-JF	Diuretic	Ting Li Da Zao Xie Fei Tang, Wen Yang Li Shui Jian	[65-68,103,110]
AR-AMR	Diuretic	Ze Xie Tang, Yi Xin Hua Zhuo Fang, Wen Yang Hua Yin Fang	[9,15,72-74]
OR-SCF	Protection of myocardium; improvement of sleep	Shen Song Yang Xin Jiao Nang, Yi Xin Shu, Xin Yin Pian, Yi Qi Yang Xin Tang, Shen Mai San, Tian Wang Bu Xin Dan	[20,78,80-84,101,111]
ZSS-SCF	Protection of myocardium; improvement of mood disorders	Shen Ling Yang Xin Tang, Suan Zao An Shen Cheng Fang Zhi Ji, Zao Ren An Shen Ke Li, Shi Wei Wen Dan Tang, An Mei Dan, Tian Wang Bu Xin Dan	[78,85-90,101,112]
AR-DSLS	Improve mitochondrial function; anti-autophagy	Qi Li Shen Yu Yi Xin Fang, Qi Li Qiang Xin Jiao Nang, Fu Xin Tang, Li Xin Chong Ji, Shen Gui Yi Xin Tang	[9,10,28,95,96]
ZSS-PS	Strengthen cardiac function; improve sleep quality	Yang Xin Tang, Shen Ling Yang Xin Tang, Bai Zi Yang Xin Wan, Suan Zao Ren Tang, Tian Wang Bu Xin Dan	[78,86,97-101,111]

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