科学通报 2022 年 第 67 卷 第 27 期: 3296 ~ 3310
评 述
《中国科学》杂志社
SCIENCE CHINA PRESS

“三药三方”治疗COVID-19的临床和药理研究进展

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2022-04-02 收稿, 2022-05-23 修回, 2022-05-26 接受, 2022-05-27 网络版发表
国家自然科学基金(82104431, 81973581)、组分中药国家重点实验室开放课题(CBCM2020201)、国家科技应急项目(2020YFC0841600)和国家重大科技专项(2018YFC1704502, 2020YFA0708004)资助

摘要 世界范围内爆发的新型冠状病毒肺炎(corona virus disease 2019, COVID-19)给全球人民的健康和财产带来了巨大的损失, 造成了数以百万计患者的死亡. “三药三方”是众多专家总结临床实践筛选出的能够有效防治COVID-19的中药方剂, 包括金花清感颗粒、连花清瘟胶囊(颗粒)、血必净注射液和清肺排毒汤、化湿败毒方、宣肺败毒方. “三药三方”不仅能缓解发热、咳嗽、疲劳、咯痰、腹泻等症状, 还可以缩短核酸转阴时间、阻止病情转重、改善CT影像特征、缓解肺部炎症、调节临床生化指标、减轻一系列并发症等. “三药三方”防治COVID-19的作用机制主要涉及抑制病毒入侵与复制、调节机体免疫和炎症以及多器官保护等. 本文综合介绍了“三药三方”在临床上治疗COVID-19的研究进展, 并对其潜在的作用机制进行了系统性梳理, 旨在为认识“三药三方”在治疗COVID-19发挥的积极作用提供理论依据和参考.

关键词 三药三方, 新型冠状病毒肺炎, 临床研究, 药理研究

新型冠状病毒肺炎(corona virus disease 2019, COVID-19)在全世界范围内进行蔓延, 给全球人民的健康和财产带来了巨大的损失, 世界卫生组织宣布其为国际公共卫生紧急事件[1]. 由严重急性呼吸综合征冠状病毒2(severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)引起的COVID-19潜伏期较长, 具有高度的传染性[2,3]. 截至2022年3月, 全球已超过四亿确诊病例, 死亡人数超过600万(https://www.who.int). COVID-19的发生和发展可分为3个阶段: SARS-CoV-2的侵袭和复制、免疫应答和细胞因子风暴、急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)和多器官功能障碍综合征(multiple organ dysfunction syndromes, MODS). 病毒毒性、血管内皮细胞损伤、细胞因子风暴、过度免疫和微血栓的串扰是COVID-19发病和恶化的重要因素[4]. 在这场突如其来的“战役”中, 中医药的介入不仅使疫情前期在临床上有药可用, 且通过临床研究发现, 其在COVID-19的各个阶段均有显著疗效, 如减轻患者的一系列临床症状、抑制疾病发展、改善肺功能、调节临床指标、有效缩短病程等[4~8]. 正所谓“大疫出良方”, 其中极具代表性的“三药三方”针对COVID-19患者的病症具有积极的治疗作用.

“三药三方”是众多专家经过筛选后推荐的能够有效防治COVID-19的中药, 即金花清感颗粒、连花清瘟胶囊(颗粒)、血必净注射液和清肺排毒汤、化湿败毒

引用格式: 高洁, 肖光旭, 樊官伟, 等. “三药三方”治疗COVID-19的临床和药理研究进展. 科学通报, 2022, 67: 3296–3310
Gao J, Xiao G X, Fan G W, et al. Clinical and pharmacological research progress of “three medicines and three formulae” for COVID-19 treatment (in Chinese). Chin Sci Bull, 2022, 67: 3296–3310, doi: 10.1360/TB-2022-0375

方、宣肺败毒方[9]. 临床实践表明, “三药三方”均可退热, 并且缓解胃肠道和消化系统的症状, 减轻一系列并发症[10]. 目前, 国家药品监督管理局已将治疗COVID-19纳入“三药”新的适应证[11]. 由于积极防控和救治, 我国COVID-19已得到有效的控制, 但全球形势依旧严峻. 因此, 本文介绍了“三药三方”在临床上治疗COVID-19的研究进展, 并对其可能的作用机制进行了系统的归纳. 旨在深入认识以“三药三方”为代表的中药在防治COVID-19中起到的积极作用, 为中医药的国际化起到促进作用.

1 中医理论探讨COVID-19的发病机制

中医擅于从整体的角度出发探讨疾病的发病机制, 包括疾病本身和人体内、外环境的影响. COVID-19本身属于中医“瘟疫”范畴, 具有很强的传染性和流行性. 张伯礼研究团队[4,12]将其病例特点归为“湿毒疫”, 基本病机表现为疫毒外侵、肺经受邪、正气亏虚, 病理性质为湿、热、毒、虚、瘀, 以化湿解毒、辟秽化浊为主要治则. 仝小林研究团队[13]将其病例特点归为“寒湿疫”, 其病机以寒湿伤阳为主线, 兼有化热、变燥、伤阴、致瘀、闭脱等变证, 以散寒除湿、避秽化浊、解毒通络为主要治则. 其共同病机为“疫戾”之气侵入而正气不足. 邪气从口鼻而入, 口鼻为脾肺之窍, 核心病位主要为脾肺, 脾胃影响饮食, 肺脏影响呼吸, 因此COVID-19患者出现咳嗽气短、呼吸不畅、厌食、腹泻等临床症状; 湿热毒邪入血致瘀, 故COVID-19患者大多产生心血管并发症. 临床研究表明, 年龄是影响COVID-19病情恶化的重要因素, 相比年轻人, 老年人的感染率和死亡率更高[14~16]. 《素问》云: “正气存内, 邪不可干; 邪之所凑, 其气必虚.” 阴阳气血营养脏腑均随年龄增长逐渐衰退, 因此老年人五脏渐虚, 正气不足, 正气虚故无力抗邪, 易感外邪而难于康复, 对老年患者应新老疾病兼顾、扶正祛邪、治疗关口前移. 在外部环境方面, 湿气盛易困阻脾胃且影响肺的宣发肃降, 易削弱机体正气致使邪气侵袭[17,18].

2 “三药三方”治疗COVID-19的临床证据

“三药三方”作为治疗COVID-19的推荐药物, 已被广泛用于临床. 通过对其组成进行归纳, 发现麻黄、生石膏、金银花、连翘、黄芩、苦杏仁等中药被多次使用, 大多具有清热、化湿、解毒的功效, 分别归肺、胃、心、肝或脾经等. 而COVID-19主要是病毒感染肺部, 引起免疫反应和炎症风暴, 且具有多器官损伤的特点, 这切合中医药因证施治的准则. “三药三方”的适用范围覆盖COVID-19的整个病程, 包括医学观察期及轻度、中度、重度和危重度的确诊期, 如图1. “三药三

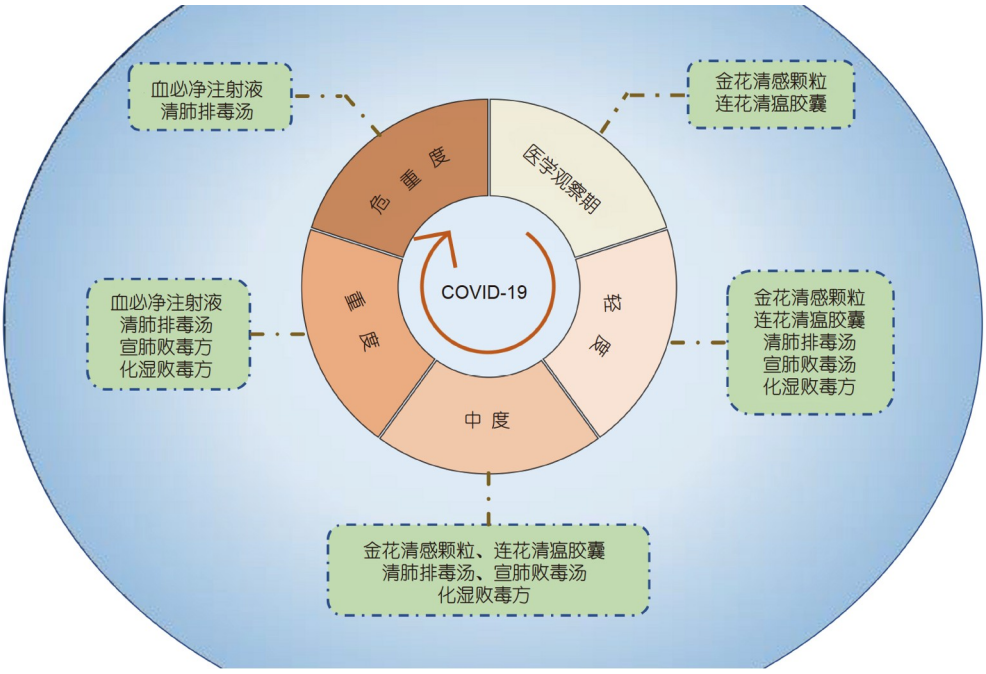

图 1 (网络版彩色)“三药三方”在COVID-19治疗不同阶段的应用
Figure 1 (Color online) The application of “three medicines and three formulae” for different stages of COVID-19 treatment

方”在临床治疗中一方面缓解发热、咳嗽、疲劳、咯痰、腹泻、食欲不振、胸闷气短和肌肉酸痛等临床症状; 另一方面, 加快了病毒清除率、缩短核酸转阴时间、促进肺部炎症吸收、改善胸部CT影像特征并提高临床治愈率等, 如表1.

2.1 金花清感颗粒

金花清感颗粒在甲型H1N1流感病毒流行时期研制成功, 主要由金银花、石膏、浙贝母、黄芩、牛蒡子、青蒿、知母、连翘、麻黄、苦杏仁、薄荷、甘草12味中药组成, 有疏风宣肺、清热解毒等功效; 主要化

表 1 “三药三方”治疗COVID-19的临床研究[a)]

Table 1 The clinical research of “three medicines and three formulae” for COVID-19 treatment

治疗方法	研究方法	患病程度	病例数(T/C)	临床效果	参考文献
金花清感颗粒+西药	RCT	轻度、中度	92/31	缓解发烧、咳嗽、疲劳、食欲不振和腹泻等症状	[19]
金花清感颗粒+西药	RCT	轻度	82/41	减轻发热、咳嗽、乏力、咳痰临床症状; 缓解患者焦虑情绪	[20]
金花清感颗粒+西药	RCS	中度、重度	44/36	加快病毒清除率、缩短核酸转阴时间; 加快肺部炎性渗出物吸收、减轻肺部炎症	[21]
连花清瘟胶囊	RCT	轻度至重度	72/72	改善发热、咳嗽、疲劳、肌肉酸痛、咳痰、鼻塞、呼吸困难、恶心呕吐等症状; 缩短发热持续时间	[22]
连花清瘟胶囊+西药	RCS	中度、重度	151/0	改善白细胞、淋巴细胞和中性粒细胞等血液指标	[23]
连花清瘟胶囊+藿香正气滴丸+西药	RCT	轻度至重度	189/94	缓解恶心、呕吐、肢体酸痛、发热、腹泻、疲劳、胸闷气短和咳嗽等症状; 降低抗感染药物使用率; 改善预后	[24]
连花清瘟胶囊+西药	RCS	中度	90/158	改善发热、厌食等症状; 减轻肺部炎症程度; 改善凝血血栓	[25]
连花清瘟胶囊+西药	荟萃分析	轻度、中度	142/142	显著缩短发热、疲劳、咳嗽的恢复时间; 提高胸部CT影像改善率; 提高临床治愈率	[26]
血必净注射液	RCT	重度	203/158	缓解肺炎恶化程度, 降低死亡率; 减少机械通气时间和ICU停留时间	[27]
血必净注射液	RCT	重度、危重度	11/0	改善肺炎程度; 缩短机械通气时间和ICU住院天数; 降低死亡率; 增强免疫功能	[28]
血必净注射液+西药	RCT	轻度、重度	42/16	缓解发热、咳嗽、咯痰、疲劳和腹泻等症状; 改善肺部CT影像结果; 缩短核酸转阴时间	[29]
血必净注射液+西药	RCT	重度	30/30	改善发热、咳嗽、气短和乏力等症状; 降低机械通气率和ICU住院时间	[30]
清肺排毒汤+西药	RCS	轻度至危重度	782/0	缩短病毒脱落期; 缩短住院时间; 加快恢复进程	[31]
清肺排毒汤	RCS	轻度至危重度	2568/6371	降低死亡率; 降低急性肝损伤和肺损伤的发生率	[32]
清肺排毒汤+西药	RCT	中度	70/70	改善发热、咳嗽、乏力、流涕和咽痛等临床症状; 促进肺部炎症吸收; 缩短住院天数	[33]
清肺排毒汤+西药	RCT	中度	37/26	改善炎症; 减轻多器官损伤程度	[34]
清肺排毒汤+西药	荟萃分析	轻度至危重度	未报道	缓解发热、咳嗽、咯痰、乏力、气短、咽痛、鼻塞和失眠多汗等症状; 缩短核酸转阴时间; 改善胸部CT影像特征; 改善临床指标	[35]
清肺排毒汤	RCS	轻度、中度	199/96	缓解咳痰、发热、咳嗽、乏力、头痛和腹泻等症状; 缩短核酸转阴时间; 改善胸部CT影像特征; 缩短住院时间	[36]
宣肺败毒方+西药	RCT	轻度至重度	22/20	明显缓解发热、咳嗽、乏力、食欲不振等临床症状; 提高免疫力; 增强抗炎效果	[37]
化湿败毒方+西药/中药注射液	非随机对照	轻度、中度	40/20	改善临床症状; 减少炎症反应	[38]
化湿败毒方+中药注射液	RCS	重度	23/32	增加病毒清除率、提高核酸转阴率; 改善肺部CT影像特征	[39]

a) RCT, 随机对照研究(randomized controlled trial); RCS, 回顾性队列研究(retrospective cohort study)

学成分为汉黄芩素、绿原酸、麻黄碱、山柰酚、木犀草素、连翘酯苷A、甘草苷、水杨酸和咖啡酸等[40]. 金花清感颗粒是预防和治疗COVID-19的推荐药物之一, 用于治疗处于医学观察期具有乏力伴发热症状的COVID-19患者[3]. 研究表明, 金花清感颗粒在解热和改善食欲方面具有优势, 可缓解发烧、疲劳和腹泻等症状, 还可以降低肺炎患者的血清C反应蛋白(C-reactive protein, CRP)和γ干扰素(interferon-γ, IFN-γ/IFNG)分泌水平[6,19]. 除此之外, 金花清感颗粒不仅显著减轻咳嗽和咯痰等症状, 并且还提高病毒清除率、有效缩短核酸转阴时间和加快肺部炎性渗出物的吸收[20,21].

2.2 连花清瘟胶囊

连花清瘟胶囊常被用于治疗病毒性流感[41~43]、急性肺损伤[44,45]等, 主要由连翘、金银花、石膏、板蓝根、苦杏仁、麻黄、广藿香、大黄、薄荷脑、绵马贯众、鱼腥草和甘草13味中药组成, 具有清瘟解毒、宣肺泄热等功效; 其主要化学成分为甘草查尔酮B、獐牙菜甙、大黄素、没食子酸乙酯、连翘苷、红景天甙、苦杏仁甙、左薄荷脑和广藿香醇等[46]. 连花清瘟胶囊用于治疗疾病发展早期乏力伴发热症状的COVID-19患者[3]. 研究表明, 连花清瘟胶囊可以显著缓解COVID-19患者发热、咳嗽、流鼻涕、呼吸困难、恶心、头痛、食欲不振等症状, 并且快速缩短这些症状的持续时间, 与其他抗病毒药物联合使用可增强治疗效果[22,47]. 利巴韦林、洛匹那韦/利托那韦、乌米诺韦和连花清瘟四联疗法被认为是重症新冠肺炎患者的首选治疗方法[23]. Xiao等人[24]对283名患者进行了临床试验, 发现连花清瘟胶囊联合藿香正气滴丸治疗对发烧、咳嗽、疲劳、胸闷、肢体疼痛等症状有疗效, 并且对改善预后效果也有一定优势. 此外, 连花清瘟胶囊对患者肺部炎症、患者胸部CT影像特征和微血管血栓等均具有显著的改善作用[25,26].

2.3 血必净注射液

血必净注射液由红花、赤芍、川芎、丹参和当归5种中药组成, 有化瘀通脉、溃散毒邪、菌毒并治等功效; 其主要化学成分为丹参素、洋川芎内酯Ⅰ、阿魏酸、芍药苷、羟基红花黄色素A等[48~50]. 前期研究表明, 血必净注射液常用于治疗脓毒症[51,52]、败血症[53]、农药所致的肺损伤[54~56]及凝血障碍[57]等. 血必净注射液是《新型冠状病毒肺炎诊疗方案(试行第九版)》中推荐治疗重型和危重型患者的中成药, 主治包括发烧、呼吸困难、心悸和烦躁不安等症状, 并在缓解患者病情、缩短患病进程、减少肺部炎症等方面发挥了良好的疗效[3,58]. 研究表明, 血必净注射液不仅可以改善肺损伤的严重程度, 还对改善患者氧合指数减少ICU的停留时间以及降低继发性死亡率有明显优势[27,28,59]. Guo等人[29]对42名COVID-19患者进行了研究, 结果表明, 血必净注射液观察组中白介素-6(interleukin 6, IL-6)、CRP的含量明显降低, 并且患者的发热、咳嗽和咯痰的症状有所改善. Luo等人[30]研究了血必净注射液对细胞因子风暴的作用, 发现血必净注射液能显著抑制重症COVID-19患者体内IL-6、IL-8、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)的分泌, 用血必净注射液进行治疗的患者体内淋巴细胞水平明显高于常规治疗组, 并且CRP水平显著降低.

2.4 清肺排毒汤

清肺排毒汤由麻黄、生石膏、杏仁、炙甘草、桂枝、白术、泽泻、猪苓、柴胡、黄芩、紫菀等21味中药组成, 有宣肺止咳、清热解毒、化湿祛邪的功效[60]; 其主要成分为黄芩苷、枸橼酸、麻黄碱、苦杏仁苷、次野鸢尾黄素、甘草甙和芦丁等[61]. 清肺排毒汤是在“伤寒论”四大经典方剂的基础上, 结合COVID-19的病机特点创新而成的, 适用于治疗COVID-19各个阶段的确诊患者[3,62]. 早期使用清肺排毒汤可以抑制疾病的恶化、缩短病毒脱落期、改善疾病指标, 并且在抢救的过程中也发挥着一定作用[9,31]. 前期研究发现, 清肺排毒汤可以显著降低患者的死亡率以及急性肝损伤和急性肾损伤的患病率[32]. 清肺排毒汤与西药联合使用具有更显著的治疗效果, 可以改善患者体内的CRP、肌酸激酶、乳酸脱氢酶等水平, 并且使患者体内循环的白细胞以及总淋巴细胞数量急剧增多, 从而进一步改善肺部炎症吸收, 减轻多器官的损伤, 加快缩短核酸转阴时间与症状恢复时间[33~35]. 但是, 也有研究表明, 与西药联用相比, 单独使用清肺排毒汤的治疗效果比较好, 单用该药可以促进患者核酸转阴率、改善胸部CT影像特征及排痰的症状、缩短住院时间[36].

2.5 宣肺败毒方

宣肺败毒方由生石膏、生薏苡仁、生麻黄、苦杏仁、马鞭草、干芦根、虎杖、广藿香、茅苍术、青蒿草、葶苈子、化橘红、生甘草13味中药组成, 其主要

成分为青蒿素、甘草酸、南葶苈内酯A、苦杏仁苷、大黄素等[63]. 宣肺败毒方是由张伯礼院士带领团队在武汉前线的临床救治过程中, 通过经典文献研究、临床经验和现代组分优化筛选总结出来的有效方剂, 用于治疗湿毒郁肺证, 临床表现为发热、咳嗽痰少、腹胀便秘、胸闷气促等[3,4]. 宣肺败毒方可以缓解轻、中度患者发热、咳嗽、食欲不振和疲劳等症状, 并防止病情进一步恶化[64]. 此外, 临床研究还发现, 宣肺败毒方不仅可以加速一系列典型症状的消失, 还可以促使白细胞和淋巴细胞的数量恢复正常, 改善炎症反应, 显著降低红细胞的沉降率[37,65].

2.6 化湿败毒方

化湿败毒方由生麻黄、杏仁、生石膏、藿香、厚朴、苍术、草果、茯苓、生大黄、生黄芪、法半夏、葶苈子、赤芍、甘草14味中药组成, 其主要成分为槲皮素、山柰酚、豆甾醇、黄芩苷、刺芒柄花素等[66]. 化湿败毒方是由黄璐琦院士为领队的援鄂抗疫中医医疗队研制, 临床实践发现其在治疗COVID-19上发挥出了良好的效果[47]. 该方主要治疗疫毒闭肺证的重型患者, 临床表现为发热面红、痰黄黏少、咳喘气促, 口干苦黏、便秘、恶心等[3]. 化湿败毒方不仅可以单独使用, 也可以联合西药或中药注射剂增强治疗COVID-19的疗效, 减少炎症反应, 显著缩短临床症状恢复时间[38]. 例如, 化湿败毒方与喜炎平注射液、血必净注射液和参麦注射液联合治疗, 可以显著降低CRP和血清铁蛋白的含量, 并且改善患者的肺部病变阴影的吸收和核酸转阴率[39].

3 “三药三方”治疗COVID-19的作用原理

药理研究表明, 中医药通过多成分、多靶点、多途径综合治疗COVID-19发病与发展. 因此, 我们将“三药三方”中用药频次较高的中药及其有效成分进行了整理, 并依据我们前期的文献分析研究[4]列举了与COVID-19相关的10个关键靶点: 血管紧张素转换酶2 (angiotensin-converting enzyme 2, ACE2)、IL6、TNF-α、3-胰凝乳样蛋白酶(3C-like protease, 3CLpro)、趋化因子2(chemokine 2, CCL2)、IL1B、木瓜样蛋白酶(papain-like protease, PLpro)、前列腺素内过氧化物合酶2 (prostaglandin-endoperoxide synthase 2, PTGS2)、转化生长因子β1(transforming growth factor beta 1, TGFB1)、血管内皮生长因子(vascular endothelial growth factor, VEGF), 并构建中药-成分-靶点关系网络, 见图2. “三药三方”防治COVID-19的潜在机制主要为: (1) 药物主要活性成分与ACE2、3CLpro、PLpro等

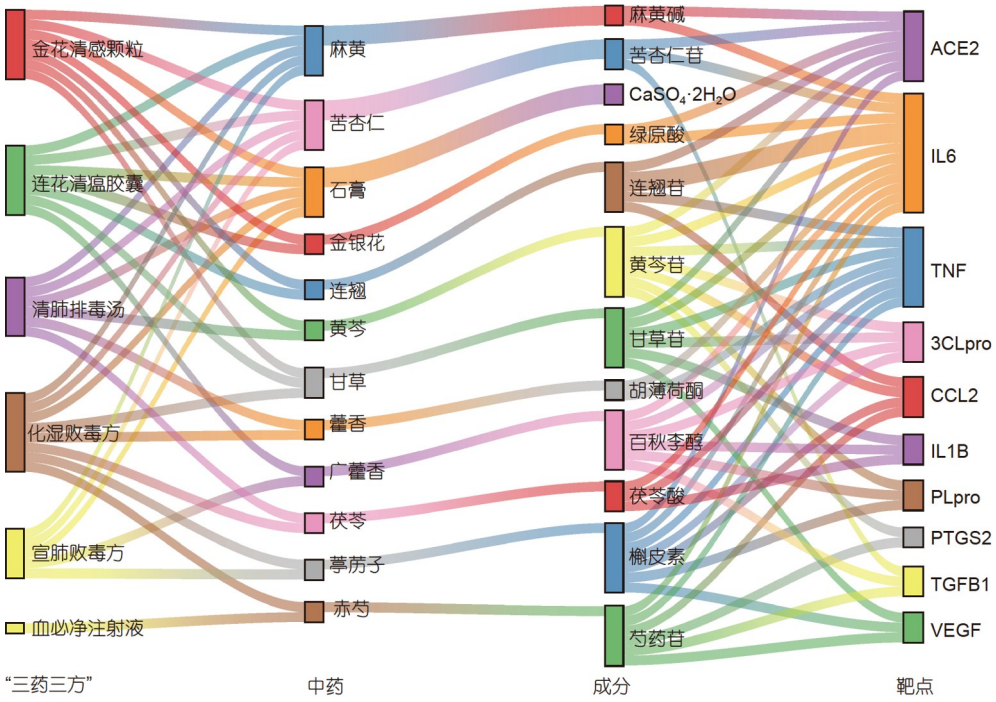

图 2 (网络版彩色)“三药三方”治疗COVID-19中药-成分-靶点网络
Figure 2 (Color online) The herb-ingredient-target network of “three medicines and three formulae” for COVID-19 treatment

受体结合阻止病毒的入侵与复制; (2) 通过抑制IL-6、TNF-1、IL-1、白介素-10(interleukin-10, IL-10)等炎性因子和趋化因子8(C-X-C motif chemokine ligand 8, CXCL8)、趋化因子10(C-X-C motif chemokine ligand 10, CXCL10)、CCL2等的分泌, 调节机体的免疫和炎症功能; (3) 调节白细胞、淋巴细胞、D-dimer和CRP等指标, 对器官进行保护. 我们对"三药三方"治疗COVID-19的作用原理进行了梳理和汇总, 如表2.

3.1 金花清感颗粒

金花清感颗粒一开始是作为治疗H1N1流感的临床药物, 后被广泛应用于各种流感病毒感染性疾病, 其具有抗病毒、抗炎、调节免疫等作用[6,67]. 研究表明, 金花清感颗粒可以降低血清中多种细胞因子的水平, 增强免疫功能, 主要与IL-6、IL-1β、CXCL8、CCL2、细胞间黏附分子-1(intercellular cell adhesion molecule-1, ICAM1)、IL-10、IFNG和IL-1A等靶点有关[6]. 龚普阳等人[68]通过分子对接评价了金花清感颗粒中芒柄花黄素、β-谷甾醇、脱水淫羊藿素等核心成分与3CLpro和ACE2的亲和作用, 并通过网络药理分析表明PTGS2、HSP90AA1、PTGS1等可能为关键作用靶点, 参与ATP结合、转录因子活化、细胞凋亡进程调控等. 该方也可以通过调控TNF、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)等多个信号通路, 减轻器官损伤、抑制病毒复制、激活抗病毒免疫力等, 这也可能是金花清感颗粒治疗COVID-19的作用机制[47,69].

3.2 连花清瘟胶囊

连花清瘟胶囊已被证明其有广谱抗病毒作用, 并且广泛应用于临床[96]. 现代药理研究表明, 连花清瘟胶囊具有抗病毒、抗炎、抗氧化、免疫调节等作用[58]. 据报道, 连花清瘟胶囊可以通过调节免疫来抑制病毒繁殖、干扰病毒和宿主反应、抑制细菌对呼吸道上皮细胞的黏附来发挥抗流感活性, 从而治疗一系列的流感病毒感染[97~99]. 在治疗COVID-19方面, 连花清瘟胶囊可以调节病毒生命周期, 显著抑制病毒复制, 调控机体免疫应答, 降低TNF-α、IL-6、MCP-1等促炎细胞因子的释放, 保护肺泡毛细血管屏障等[70~72]. 连花清瘟胶囊抑制病毒的感染及传播机制或许与连翘苷、连翘酯苷A和新绿原酸等活性成分通过影响ACE2与S蛋白之间的结合相关[73]. 网络药理学分析进一步揭示, 连花清瘟胶囊治疗COVID-19的机制可能是通过β-胡萝卜素、山萘酚、木犀草素和汉黄芩素等6种成分与丝氨酸/苏氨酸激酶1(AKT serine/threonine kinase 1, AKT1)结合来改善肺损伤、肺纤维化和病毒感染等[74], 并且连花清瘟胶囊治疗COVID-19也与其抑菌退热、调节免疫、止咳化痰等作用有关[75].

3.3 血必净注射液

血必净注射液主要用于治疗全身炎症反应综合征、多脏器功能衰竭以及脓毒症[58]. 已有研究表明, 血必净注射液具有抗炎、免疫调节、改善凝血、抗氧化等药理作用[53,100,101], 在防治COVID-19过程中其机制大多与调节炎症和免疫及抗病毒有关. 有研究表明, 血必净注射液可能通过调节IL-6、IL-8、TNF-α等炎性因子的分泌来减轻患者体内由病毒引起的细胞因子风暴, 或通过作用于AKT1调节TNF信号通路来影响炎症反应, 从而达到治疗COVID-19的效果[30,76,77]. 血必净注射液还可以影响病毒的增殖, 抑制新型冠状病毒诱导的促炎因子上调来发挥抗病毒效应[28]. 此外, 一些研究也通过了网络药理学方法对血必净注射液治疗COVID-19的可能机制进行了分析. 结果说明, 血必净注射液改善COVID-19带来的并发症可能与抑制过度炎症、病毒的入侵和复制、氧化应激和细胞凋亡有关, 其活性成分为槲皮素、羟基红花黄色素B、芦丁等[78,79]. 而另一项研究揭示, 甘油醛-3-磷酸脱氢酶(glyceraldehyde-3-phosphate dehydrogenase, GAPDH)、白蛋白(albumin, ALB)、TNF、表皮生长因子受体(epidermal growth factor receptor, EGFR)等或许是血必经注射液通过抗炎、抗凋亡以及减轻肺炎诱导的多器官损伤来治疗COVID-19的关键靶点[80].

3.4 清肺排毒汤

清肺排毒汤在防治COVID-19中显示出良好的治疗效果和较好的安全性, 具有免疫调节、抗感染、抗炎、抗菌和抗病毒等药理作用. 感染COVID-19的患者已被证实其体内发生了肠道菌群的失调. 研究表明, 清肺排毒汤显著调节机体内源性代谢和肠道菌群的组成[81,82]. 网络药理分析揭示, 清肺排毒汤的重要靶标主要富集在IL-17、核因子κB(nuclear factor kappa-B, NF-κB)、TNF、MAPK、PTGS1等信号通路中, 推测该方抗COVID-19作用主要与炎症、神经保护、免疫调节、细胞凋亡以及减轻肺损伤等多种生物学功能有

表 2 “三药三方”治疗COVID-19的潜在作用机制

Table 2 The potential mechanisms of “three medicines and three formulae” for COVID-19 treatment

药方	验证方法	潜在机制	参考文献
金花清感颗粒	文献挖掘	增强免疫, 作用于IL-6、IL-1β、CXCL8、CCL2、ICAM1、IL-10、IFNG和IL-1A; 降低细胞因子的血清水平	[6]
	网络药理; 分子对接	抑制病毒复制; 减轻宿主炎症; 激活病毒免疫	[67]
	网络药理; 分子对接	调节细胞凋亡; 调节免疫与炎症	[68]
	网络药理	抑制炎症反应; 调节免疫; 减轻器官损伤	[69]
连花清瘟胶囊	感染Vero-E6细胞和Huh-7细胞; CPE; 斑块减少试验	抑制病毒复制; 减少促炎细胞因子TNF-α、IL-6、CCl-2/MCP-1和CXCL-10/IP-10的产生	[70]
	文献挖掘	干扰病毒生命周期; 调节宿主免疫反应; 抑制病毒转录和复制	[71]
	网络药理; 分子对接	保护肺泡毛细血管屏障; 抑制病毒复制; 抑制细胞因子风暴	[72]
	数据挖掘	大黄酸、连翘苷A、连翘苷I、新绿原酸及其异构体抑制ACE2的活性	[73]
	网络药理; 分子对接	β-胡萝卜素、山柰酚、木犀草素等核心成分结合AKT1减少肺部损伤, 消除病毒感染	[74]
	网络药理	调节肺部免疫、减少组织损伤; 广谱抗病毒; 阻止炎性因子释放	[75]
血必净注射液	感染Vero-E6细胞和Huh-7细胞; CPE; 斑块减少试验	阻断病毒增殖; 抑制SARS-CoV-2诱导的促炎细胞因子表达	[28]
	临床研究	抑制IL-6、IL-8、TNF-α的分泌	[30]
	临床研究; 网络药理	抑制促炎细胞因子IL-6、IL-8和TNF-α的分泌	[47,76]
	网络药理, 分子对接	作用于AKT1, 抑制炎症反应, 调节NOS活性与TNF信号通路	[77]
	网络药理; RNA测序	靶向CCL2、CXCL8、IFNB1、IL-1A、IL-1B、SERPINE1、FOS; 抑制氧化应激; 抑制炎症; 防止细胞凋亡	[78]
	网络药理; 分子对接	槲皮素、木犀草素、芹菜素等抑制过度炎症和细胞因子风暴; 羟基红花黄色素B、丹酚酸B、芦丁抑制病毒的侵袭和复制	[79]
	网络药理; 分子对接	抑制炎症; 抗免疫细胞凋亡; 减轻多器官损伤	[80]
清肺排毒汤	网络药理	与炎症、神经保护, 免疫调节, 细胞凋亡以及较少的肺损伤有关	[66]
	文献挖掘	调节肠道微生物群	[81]
	代谢组学; 肠道微生物组学	调节内源性代谢和肠道菌群组成	[82]
	网络药理; 分子对接	抗病毒; 抗炎; 调节代谢程序; 平衡免疫	[83,84]
	P450酶、羧酸酯酶抑制试验; 药代动力学	调节CYP3A底物药物的药代动力学, 防治药物互相作用	[85]
	网络药理; 建立肠炎、肠道特异性KLHL5缺陷的小鼠模型	通过下调USP14促进ATF2降解发挥抗炎作用	[86]
宣肺败毒方	网络药理	调节IL-6的分泌	[76]
宣肺败毒方、清肺排毒汤	感染A549细胞; LPS刺激THP-1细胞; RT-qPCR; ELISA; 免疫蛋白印迹; 品红细胞活性测定	抑制IL-6、TNF-α、CXCL10和MCP-1等炎性因子表达; 抑制NF-κB信号通路的激活; 钝化巨噬细胞吞噬活性	[87]

(续表2)

药方	验证方法	潜在机制	参考文献
宣肺败毒方	TGF-β1诱导的成纤维细胞活化模型和LPS/IL-4诱导的巨噬细胞炎症模型; 博莱霉素气管内滴注诱导小鼠肺纤维化模型	抑制IL-6/STAT3信号通路对巨噬细胞诱导的炎症和肺纤维化进行保护	[88]
	LPS诱导急性肺损伤、刺激RAW264.7巨噬细胞; 转录组学; 网络药理; 分子对接等	下调IL-6、TNF-α和IL-1β等促炎细胞因子的表达; PD-1/IL17A通路调节中性粒细胞和巨噬细胞的浸润	[89]
	网络药理; 分子对接	黄酮类和植物甾醇类活性成分与ACE2和3CLPro受体结合, 抑制病毒入侵及病毒复制; 调节IL-6、MAPK3、MAPK1、IL-1β、CCL2等靶点发挥抗炎、抗细胞因子风暴、抗氧化、调节机体免疫作用	[90]
	网络药理; 转录组学; 生物测定; 高分辨率质谱分析	虎杖苷、异甘草苷、麻黄碱、山柰酚、苍术内酯Ⅰ和毛蕊花苷等负调控炎症诱导的巨噬细胞活化, 减轻肺部炎症	[91]
	环磷酰胺诱导免疫抑制小鼠模型; 免疫器官指数计算; HE染色; ELISA; RT-PCR; 淋巴细胞增殖检测	提高免疫器官指数; 改善TNF-α、IFN-γ、IgG、IgM水平和脾组织中IL-2、IL-4、IL-6的表达; 增强淋巴细胞的增殖反应, 增加$CD4^+$、$CD8^+$ T细胞的数量	[92]
化湿败毒方	网络药理; 刺激RAW264.7细胞; UPLC-Q-TOF/MS验证; ELISA	降低IL-6和TNF-α的表达水平, 调节炎性细胞因子的产生	[76,93]
	网络药理; 分子对接	黄芩苷和槲皮素与ACE2结合, 降低ACE2活性	[39]
	网络药理; 分子对接	主要发挥作用的化学成分为槲皮素、木犀草素和山柰酚; 减少炎症损害; 缓解氧化应激; 改善肺损伤	[94]
	网络药理	干预"RAS通路-细胞因子风暴-重症危象"; 抑制病毒复制, 阻断病毒结合位点	[95]

关[62]. 另有研究表明, 清肺排毒汤的相关靶点主要作用于细菌和病毒反应、免疫平衡、信号传导等方面, 提示该方剂发挥治疗COVID-19作用的部分机制与抗病毒抗炎及调节代谢有关[83,84]. 清肺排毒汤能有效灭活细胞色素P450 3A(cytochrome P450 3A, CYP3A), 显著调节其底物的药代动力学, 从而避免潜在的药物相互作用风险, 达到提高治疗COVID-19的效果. 研究还发现, 清肺排毒汤抗COVID-19机制可能与其主要活性成分汉黄芩苷下调泛素化特异性蛋白酶14(ubiquitin-specific proteases14, USP14)的同时诱导激活转录因子2(activating transcription factor 2, ATF2)降解来减轻炎症相关[85,86]. 在最近的研究中, 清肺排毒汤和宣肺败毒方均已被证明具有较强的抗炎作用, 可抑制IL-6、TNF-α、CXCL10和MCP-1的过度表达、NF-κB通路的激活以及巨噬细胞的吞噬功能, 从而对COVID-19患者产生一定的疗效[87].

3.5 宣肺败毒方

宣肺败毒方中含有多种抗炎成分, 可以降低IL-6等炎性因子的含量和表达, 抑制NF-κB信号通路的激活, 从而发挥对COVID-19的治疗作用[76,87]. 研究表明, 宣肺败毒方不仅作用于IL-6/STAT3信号通路抑制成纤维细胞迁移和巨噬细胞极化, 改善巨噬细胞诱导的炎症和肺纤维化[88], 还可能下调IL-6、TNF-α和IL-1β的表达, 抑制PD-1/IL17A通路改善巨噬细胞和中性粒细胞的浸润治疗急性肺损伤[89]. 王汉等人[90]通过网络药理学分析对宣肺败毒方的潜在机制进行了探索, 推测宣肺败毒方可能是通过木犀草素、β-谷甾醇等主要活性成分与病毒受体结合来抑制病毒的复制与侵入, 并通过调节IL-6、MAPK3、MAPK1、IL-1β、CCL2、EGFR、诱导型一氧化氮合酶(nitric oxide synthase 2, NOS2)等核心靶点来发挥抗炎、抗氧化以及调节免疫的作用. 此外, 宣肺败毒方还可能负调控炎症诱导的巨噬细胞活化, 明显减轻肺部炎症, 这与其中的主要活性成分虎杖苷、异甘草苷、麻黄碱、山柰酚、苍术内酯Ⅰ和毛蕊花苷等有关[91]. 并且, 宣肺败毒方对免疫抑制具有积极的改善作用, 通过减少TNF-α、IFN-γ、

IgG、IgM、IL-2、IL-4、IL-6等水平的表达和免疫细胞的增值等, 调节免疫系统成分组成[92].

3.6 化湿败毒方

化湿败毒方具有抗炎、抗病毒和调节免疫的药理作用[47]. 该方可降低IL-6、TNF-α在细胞中的表达水平, 并调节炎性细胞因子的产生[76,93]. 多项网络药理学分析表明, 化湿败毒方从多方面治疗COVID-19, 其作用机制可能与调控TNF、PI3K-Akt、MAPK、IL-17、AGE-RAGE等通路产生抗氧化、抗病毒和调节免疫与炎症等作用有关, 并且也与该方中主要活性成分黄芩素、甘草酚、槲皮素等与新型冠状病毒相关的ACE2、3CLpro相结合来发挥抗病毒作用有着密切的联系[66,94,95].

通过对“三药三方”治疗COVID-19临床和药理研究的系统梳理, 进一步绘制了“三药三方”治疗COVID-19不同疾病阶段的作用机制图, 如图3.

4 讨论和展望

在抗击COVID-19的临床实践中, 我国充分发挥了中西医结合的优势, 使患者的治愈率大大提升. 本文探讨了COVID-19的中医认识, 并总结了“三药三方”的临床研究进展及潜在的作用机制. “三药三方”能够缓解COVID-19患者的典型临床症状、加快病毒清除率、缓解肺部炎症、调节生化指标、减轻一系列并发症等; 其机制主要涉及抑制病毒入侵与复制、调节机体免疫和炎症以及多器官保护等, 希望本文能够为深入认识“三药三方”在治疗COVID-19中发挥的积极作用提供理论依据和参考. 虽然, 关于COVID-19的研究取得了一系列重要的研究进展, 但仍存在很多的局限性: 首先, “三药三方”治疗COVID-19缺乏更高水平的临床研究, 应总结和归纳更多高准确度、用药安全、设计严谨、大规模的随

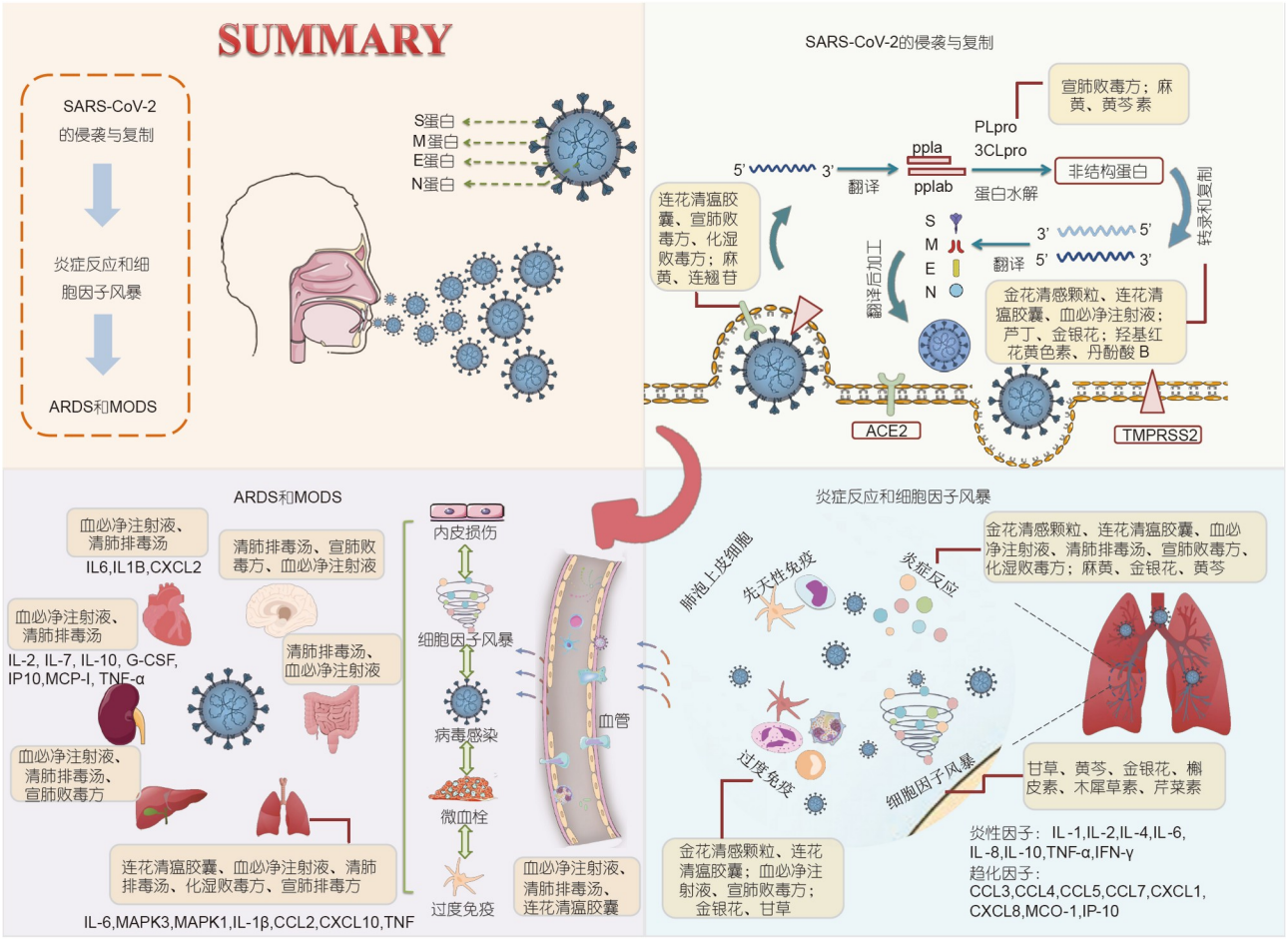

图 3 (网络版彩色)“三药三方”治疗COVID-19不同疾病阶段的潜在作用机制
Figure 3 (Color online) The potential mechanism of “three medicines and three formulae” for different stages of COVID-19 treatment

机对照试验, 提供更强大的临床证据. 其次, 临床和药理作用途径及作用机制还不是十分清楚, 病毒毒性、过度免疫、炎症风暴、内皮损伤、微血栓等多因素串扰可能是引起多器官损伤及急性呼吸窘迫综合征的关键诱因, 可围绕此方面进行更深入的理论和基础研究. 再者, 由于SARS-CoV-2具有高度的传染性和危险性, 对实验室条件及研究人员要求较高, 以病毒感染的体内动物模型为基础进行研究具有一定难度, 目前机制研究多以基于细胞模型和网络药理分析为主, 使得探究“三药三方”防治COVID-19的潜在机制存在一定的局限性. 因此, 在今后的研究中, 一方面应尽可能创造和构建病毒感染动物模型相关实验条件, 注重相关研究人员的培训, 或与具有相关资质的研究机构及实验室进行合作; 另一方面, 加强基于临床COVID-19数据, 包括转录组、基因组、蛋白组、表观组、代谢组等多组学的整合分析, 发现更多COVID-19的潜在作用途径和关键机制, 进一步完善基础研究的理论依据, 更有利于支持和应用于药物的研发及作用原理解析, 推进更符合临床预期作用机制的深入研究. 另外, 值得重视的是, 免疫力较低的儿童和具有基础疾病的老年人是患COVID-19的高危人群, 要分辨高危人群, 重视基础疾病变化, 多学科联合, 早发现、早预警、早研判、早干预, 也可以通过服用玉屏风散和桑菊饮等汤剂或焚烧艾蒿预防病毒感染[102]. COVID-19患者康复后仍可能存在一系列后遗症, 包括肺纤维化、耳鸣、呼吸困难、疲乏无力、肌肉酸痛和心悸等, 并且容易患上创伤后应激障碍、焦虑失眠和抑郁等心理疾病[103~105]. 多数人的相关症状经过积极康复基本可以逐渐消除, 对需要更长时间康复的患者可以给予中医药干预或通过体育锻炼, 比如打太极拳、八段锦, 还有食疗、心身调控等手段主动地促进康复[106].

参考文献

1 Harapan H, Itoh N, Yufika A, et al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health, 2020, 13: 667–673
2 Guan W J, Ni Z Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med, 2020, 382: 1708–1720
3 General Office of National Health Commission of the People’s Republic of China, Office of National Administration of Traditional Chinese Medicine of the People’s Republic of China. Diagnosis and treatment of corona virus disease-19 (9th trial edition) (in Chinese). Chin Med, 2022, 17: 481–487 [中华人民共和国国家卫生健康委员会办公厅, 中华人民共和国国家中医药管理局办公室. 新型冠状病毒肺炎诊疗方案(试行第九版). 中国医药, 2022, 17: 481–487
4 Lyu M, Fan G, Xiao G, et al. Traditional Chinese medicine in COVID-19. Acta Pharm Sin B, 2021, 11: 3337–3363
5 Ren J L, Zhang A H, Wang X J. Traditional Chinese medicine for COVID-19 treatment. Pharmacol Res, 2020, 155: 104743
6 Ren W, Liang P, Ma Y, et al. Research progress of traditional Chinese medicine against COVID-19. Biomed Pharmacother, 2021, 137: 111310
7 Luo E, Zhang D, Luo H, et al. Treatment efficacy analysis of traditional Chinese medicine for novel coronavirus pneumonia (COVID-19): An empirical study from Wuhan, Hubei Province, China. Chin Med, 2020, 15: 34
8 Liu M, Gao Y, Yuan Y, et al. Efficacy and safety of integrated traditional Chinese and western medicine for corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. Pharmacol Res, 2020, 158: 104896
9 Yang Y Y, Dou X X, Wang F Y, et al. Discussion on traditional Chinese medicine theory of anti-COVID-19 “three drugs and three prescriptions” (in Chinese). J Tianjin Univ Tradit Chin Med, 2021, 38: 700–705 [杨玉莹, 窦晓鑫, 王方园, 等. 抗新型冠状病毒肺炎“三药三方”之中医理论探讨. 天津中医药大学学报, 2021, 38: 700–705]
10 Cai Y, Zeng M, Chen Y Z. Staged treatment analysis of the network pharmacology based traditional Chinese medicine compound “three Chinese patent medicines, three traditional Chinese medicine formula” in the treatment of COVID-19 (in Chinese). World Sci Technol/Mod Tradit Chin Med Mat Med, 2021, 23: 358–384 [蔡羽, 曾珉, 陈运中. 基于网络药理学中药复方“三药三方”治疗新冠肺炎的分期治疗分析. 世界科学技术-中医药现代化, 2021, 23: 358–384]
11 Zhang X Y, Liu S, Sun Y, et al. Strategy and thinking of the development and review policies of traditional Chinese medicine (TCM) new drugs taking “three Chinese patent medicines and three TCM prescriptions” as examples (in Chinese). Chin J New Drugs, 2020, 29: 1818–1821 [张晓雨, 刘硕, 孙杨, 等. 从“三药三方”谈中药新药审评理念、研发思路及策略. 中国新药杂志, 2020, 29: 1818–1821]
12 Huang M, Yang F W, Zhang L, et al. Experiences and strategies of traditional Chinese medicine in the treatment of coronavirus disease 2019: Academician Zhang Boli’s view on anti-epidemic in Wuhan (in Chinese). China Pharm Med Instrum, 2020, 61: 2117–2120 [黄明, 杨丰文, 张磊, 等. 中医药治疗新型冠状病毒肺炎的经验与策略——张伯礼院士武汉一线抗疫思考. 中医杂志, 2020, 61: 2117–2120]
13 Tong X L, Li X Y, Zhao L H, et al. Discussion on traditional Chinese medicine prevention and treatment strategies of coronavirus disease 2019 (COVID-19) from the perspective of “cold-dampness pestilence” (in Chinese). China Pharm Med Instrum, 2020, 61: 465–470, 553 [仝小林, 李修洋, 赵林华, 等. 从“寒湿疫”角度探讨新型冠状病毒肺炎的中医药防治策略. 中医杂志, 2020, 61: 465–470, 553]

14 Zazzara M B, Penfold R S, Roberts A L, et al. Probable delirium is a presenting symptom of COVID-19 in frail, older adults: A cohort study of 322 hospitalised and 535 community-based older adults. Age Ageing, 2021, 50: 40–48

15 Chen Y, Klein S L, Garibaldi B T, et al. Aging in COVID-19: Vulnerability, immunity and intervention. Ageing Res Rev, 2021, 65: 101205

16 O'Driscoll M, Dos Santos G R, Wang L, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature, 2021, 590: 140–145

17 Zheng Y, Jin D, Lin J, et al. Understanding COVID-19 in Wuhan from the perspective of cold-dampness: Clinical evidences and mechanisms. Front Med, 2021, 8: 617659

18 Li L C, Zhang Z H, Zhou W C, et al. Lianhua Qingwen prescription for coronavirus disease 2019 (COVID-19) treatment: Advances and prospects. Biomed Pharmacother, 2020, 130: 110641

19 An X D, Xu X, Xiao M Z, et al. Efficacy of Jinhua Qinggan granules combined with western medicine in the treatment of confirmed and suspected COVID-19: A randomized controlled trial. Front Med, 2021, 8: 728055

20 Duan C, Xia W G, Zheng C J, et al. Clinical observation on Jinhua Qinggan granule combined with conventional western medicine therapy in treating mild cases of coronavirus disease combined with conventional western medicine therapy in treating mild cases of coronavirus disease 2019 (in Chinese). J Tradit Chin Med, 2020, 61: 1473–1477 [段璨, 夏文广, 郑婵娟, 等. 金花清感颗粒联合西医常规治疗方案治疗轻型新型冠状病毒肺炎的临床观察. 中医杂志, 2020, 61: 1473–1477]

21 Liu Z, Li X, Gou C, et al. Effect of Jinhua Qinggan granules on novel coronavirus pneumonia in patients. J Tradit Chin Med, 2020, 40: 467–472

22 Zeng M, Li L, Wu Z. Traditional Chinese medicine Lianhua Qingwen treating corona virus disease 2019(COVID-19): Meta-analysis of randomized controlled trials. PLoS One, 2020, 15: e0238828

23 Li X, Yang Y, Liu L, et al. Effect of combination antiviral therapy on hematological profiles in 151 adults hospitalized with severe coronavirus disease 2019. Pharmacol Res, 2020, 160: 105036

24 Xiao M, Tian J, Zhou Y, et al. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: A randomized controlled trial. Pharmacol Res, 2020, 161: 105126

25 Shen P, Li J, Tu S, et al. Positive effects of Lianhuaqingwen granules in COVID-19 patients: A retrospective study of 248 cases. J Ethnopharmacol, 2021, 278: 114220

26 Hu K, Guan W J, Bi Y, et al. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. Phytomedicine, 2021, 85: 153242

27 Song Y, Yao C, Yao Y, et al. XueBiJing injection versus placebo for critically Ill patients with severe community-acquired pneumonia. Crit Care Med, 2019, 47: e735–e743

28 Ma Q, Qiu M, Zhou H, et al. The study on the treatment of Xuebijing injection (XBJ) in adults with severe or critical corona virus disease 2019 and the inhibitory effect of XBJ against SARS-CoV-2. Pharmacol Res, 2020, 160: 105073

29 Guo H, Zheng J, Huang G, et al. Xuebijing injection in the treatment of COVID-19: A retrospective case-control study. Ann Palliat Med, 2020, 9: 3235–3248

30 Luo Z, Chen W, Xiang M, et al. The preventive effect of Xuebijing injection against cytokine storm for severe patients with COVID-19: A prospective randomized controlled trial. Eur J Integrat Med, 2021, 42: 101305

31 Shi N, Liu B, Liang N, et al. Association between early treatment with Qingfei Paidu decoction and favorable clinical outcomes in patients with COVID-19: A retrospective multicenter cohort study. Pharmacol Res, 2020, 161: 105290

32 Zhang L, Zheng X, Bai X, et al. Association between use of Qingfei Paidu Tang and mortality in hospitalized patients with COVID-19: A national retrospective registry study. Phytomedicine, 2021, 85: 153531

33 Wang Y, Chen L, Zheng L, et al. Clinical effects of Qingfei Paidu decoction combined with conventional treatment on patients with coronavirus disease 2019 (in Chinese). Chin Tradit Pat Med, 2021, 43: 656–659 [王月, 陈立, 郑玲, 等. 清肺排毒汤联合常规治疗对新冠肺炎患者的临床疗效. 中成药, 2021, 43: 656–659]

34 Xin S, Cheng X, Zhu B, et al. Clinical retrospective study on the efficacy of Qingfei Paidu decoction combined with western medicine for COVID-19 treatment. Biomed Pharmacother, 2020, 129: 110500

35 Wang Q, Zhu H, Li M, et al. Efficacy and safety of Qingfei Paidu decoction for treating COVID-19: A systematic review and meta-analysis. Front Pharmacol, 2021, 12: 688857

36 Sun Y N, Lü W L, Li H, et al. Qingfei Paidu decoction for treatment of mild/moderate COVID-19 in 295 cases: A multi-centered (in Chinese). J Tradit Chin Med, 2021, 62: 599–603 [孙易娜, 吕文亮, 李昊, 等. 清肺排毒汤治疗轻型/普通型新型冠状病毒肺炎295例多中心临床研究. 中医杂志, 2021, 62: 599–603]

37 Xiong W Z, Wang G, Du J, et al. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: A pilot randomized clinical trial. Integrat Med Res, 2020, 9: 100489

38 Shi N, Guo L, Liu B, et al. Efficacy and safety of Chinese herbal medicine versus Lopinavir-Ritonavir in adult patients with coronavirus disease 2019: A non-randomized controlled trial. Phytomedicine, 2021, 81: 153367

39 Wang Y, Lu C, Li H, et al. Efficacy and safety assessment of severe COVID-19 patients with Chinese medicine: A retrospective case series study at early stage of the COVID-19 epidemic in Wuhan, China. J Ethnopharmacol, 2021, 277: 113888

40 Zeng Y Y, Chen Y T, He Y Y, et al. Identification of components *in vitro* and plasma of Jinhua Qinggan granules and preliminary pharmacokinetics analysis (in Chinese). Acta Pharm Sin, 2022, 57: 446–452 [曾垣烨, 陈嫣婷, 何盈盈, 等. 基于UPLC-QTOF/MS的中药金花清感颗粒体外及入血成分鉴定和初步药动学特征分析. 药学学报, 2022, 57: 446–452]

41 Gao D, Niu M, Wei S Z, et al. Identification of a pharmacological biomarker for the bioassay-based quality control of a thirteen-component TCM formula (Lianhua Qingwen) used in treating influenza a virus (H1N1) infection. Front Pharmacol, 2020, 11: 746

42 Wu L, Chen Y, Ma Y, et al. Clinical practice guideline on treating influenza in adult patients with Chinese patent medicines. Pharmacol Res, 2020, 160: 105101

43 Yang C, Wang Y, He J, et al. Lianhua-Qingwen displays antiviral and anti-inflammatory activity and synergistic effects with oseltamivir against influenza B virus infection in the mouse model. Evid Based Complement Altern Med, 2020, 2020: 3196375

44 Li Q, Yin J, Ran Q S, et al. Efficacy and mechanism of Lianhua Qingwen capsules (LHQW) on chemotaxis of macrophages in acute lung injury (ALI) animal model (in Chinese). China J Chin Mate Med, 2019, 44: 2317–2323 [李琦, 尹婕, 冉庆森, 等. 急性肺损伤模型中连花清瘟胶囊对巨噬细胞趋化能力的药效与机制研究. 中国中药杂志, 2019, 44: 2317–2323]

45 Yang R, Yang H, Wei J, et al. Mechanisms underlying the effects of Lianhua Qingwen on sepsis-induced acute lung injury: A network pharmacology approach. Front Pharmacol, 2021, 12: 717652

46 Fu S, Cheng R, Deng Z, et al. Qualitative analysis of chemical components in Lianhua Qingwen capsule by HPLC-Q Exactive-Orbitrap-MS coupled with GC-MS. J Pharm Anal, 2021, 11: 709–716

47 Huang K, Zhang P, Zhang Z, et al. Traditional Chinese medicine (TCM) in the treatment of COVID-19 and other viral infections: Efficacies and mechanisms. Pharmacol Ther, 2021, 225: 107843

48 Jiang M, Zhou M, Han Y, et al. Identification of NF-κB inhibitors in Xuebijing injection for sepsis treatment based on bioactivity-integrated UPLC-Q/TOF. J Ethnopharmacol, 2013, 147: 426–433

49 Huang H, Ji L, Song S, et al. Identification of the major constituents in Xuebijing injection by HPLC-ESI-MS. Phytochem Anal, 2011, 22: 330–338

50 Zuo L, Sun Z, Hu Y, et al. Rapid determination of 30 bioactive constituents in XueBiJing injection using ultra high performance liquid chromatography-high resolution hybrid quadrupole-orbitrap mass spectrometry coupled with principal component analysis. J Pharm Biomed Anal, 2017, 137: 220–228

51 Li C, Wang P, Li M, et al. The current evidence for the treatment of sepsis with Xuebijing injection: Bioactive constituents, findings of clinical studies and potential mechanisms. J Ethnopharmacol, 2021, 265: 113301

52 Shang T, Yu Q, Ren T, et al. Xuebijing injection maintains GRP78 expression to prevent candida albicans-induced epithelial death in the kidney. Front Pharmacol, 2019, 10: 1416

53 Li T, Qian Y, Miao Z, et al. Xuebijing injection alleviates Pam3CSK4-induced inflammatory response and protects mice from sepsis caused by methicillin-resistant staphylococcus aureus. Front Parmacol, 2020, 11: 104

54 Liu M, Su M, Zhang W, et al. Protective effect of Xuebijing injection on paraquat-induced pulmonary injury via down-regulating the expression of p38 MAPK in rats. BMC Complement Altern Med, 2014, 14: 498

55 Deng J, Huo D, Wu Q, et al. Xuebijing for paraquat poisoning. Cochrane Database Syst Rev, 2013, 7: Cd010109

56 He F, Wang J, Liu Y, et al. Xuebijing injection induces anti-inflammatory-like effects and downregulates the expression of TLR4 and NF-κB in lung injury caused by dichlorvos poisoning. Biomed Pharmacother, 2018, 106: 1404–1411

57 Hou S Y, Feng X H, Lin C L, et al. Efficacy of Xuebijing for coagulopathy in patients with sepsis. Saudi Med J, 2015, 36: 164–169

58 Zhuang W, Fan Z, Chu Y, et al. Chinese patent medicines in the treatment of coronavirus disease 2019 (COVID-19) in China. Front Pharmacol, 2020, 11: 1066

59 Guo J, Zhu J, Wang Q, et al. Comparative efficacy of seven kinds of Chinese medicine injections in acute lung injury and acute respiratory distress syndrome: A network Meta-analysis of randomized controlled trials. Front Pharmacol, 2021, 12: 627751

60 Wang K, Yan H Y, Wu S, et al. Inhibitory effect of Qing-Fei-Pai-Du decoction on coronavirus *in vitro* (in Chinese). Acta Pharm Sin, 2021, 56: 1400–1408 [王琨, 颜海燕, 吴硕, 等. 清肺排毒汤的体外抗冠状病毒作用研究. 药学学报, 2021, 56: 1400–1408]

61 Shen A, Zhou W, Xiong L, et al. Chemical profiling of Qingfei Paidu decoction by triplex off-line two-dimensional liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. J Sep Sci, 2022, 45: 1162–1169

62 Ren W, Ma Y, Wang R, et al. Research advance on Qingfei Paidu decoction in prescription principle, mechanism analysis and clinical application. Front Pharmacol, 2020, 11: 589714

63 Wang Y, Li X, Zhang J H, et al. Mechanism of Xuanfei Baidu Tang in treatment of COVID-19 based on network pharmacology (in Chinese). China J Chin Mater Med, 2020, 45: 2249–2256 [王毅, 李翔, 张俊华, 等. 基于网络药理学的宣肺败毒汤治疗新型冠状病毒肺炎机制研究. 中

国中药杂志, 2020, 45: 2249–2256]
64 Pan X, Dong L, Yang L, et al. Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China. Virus Res, 2020, 286: 198057
65 Li L, Wu Y, Wang J, et al. Potential treatment of COVID-19 with traditional Chinese medicine: What herbs can help win the battle with SARS-CoV-2? Engineering, 2021, doi: 10.1016/j.eng.2021.08.020
66 Tao Q, Du J, Li X, et al. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of Huashi Baidu formula in the treatment of COVID-19. Drug Dev Ind Pharm, 2020, 46: 1345–1353
67 Xiong W, Ran J Y, Xie X J, et al. Pharmacological effect and clinical application of Chinese patent medicine in novel coronavirus pneumonia (in Chinese). Her Med, 2020, 39: 465–476 [熊微, 冉京燕, 谢雪佳, 等. 治疗新型冠状病毒肺炎中成药的药理作用与临床应用. 医药导报, 2020, 39: 465–476]
68 Gong P Y, Guo Y J, Li X P, et al. Exploring active compounds of Jinhua Qinggan granules for prevention of COVID-19 based on network pharmacology and molecular docking (in Chinese). Chin Tradit Herb Drugs, 2020, 51: 1685–1693 [龚普阳, 郭瑜婕, 李晓朋, 等. 基于网络药理学与分子对接技术的金花清感颗粒防治新型冠状病毒肺炎的潜在药效物质研究. 中草药, 2020, 51: 1685–1693]
69 Lin J R, Zheng W W, Zeng G X, et al. Study on the network pharmacology of Jinhua Qinggan granules in the treatment of COVID-19 (in Chinese). J Chin Med Mater, 2020, 43: 2070–2076 [林嘉荣, 郑慰武, 曾贵兴, 等. 金花清感颗粒治疗新型冠状病毒肺炎网络药理学的研究. 中药材, 2020, 43: 2070–2076]
70 Li R F, Hou Y L, Huang J C, et al. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacol Res, 2020, 156: 104761
71 Shi M, Peng B, Li A, et al. Broad anti-viral capacities of Lian-Hua-Qing-Wen capsule and Jin-Hua-Qing-Gan granule and rational use against COVID-19 based on literature mining. Front Pharmacol, 2021, 12: 640782
72 Zhang X, Gao R, Zhou Z, et al. A network pharmacology based approach for predicting active ingredients and potential mechanism of Lianhuaqingwen capsule in treating COVID-19. Int J Med Sci, 2021, 18: 1866–1876
73 Chen X, Wu Y, Chen C, et al. Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 biochromatography screening. Acta Pharm Sin B, 2021, 11: 222–236
74 Xia Q D, Xun Y, Lu J L, et al. Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. Cell Prolif, 2020, 53: e12949
75 Wang L, Yang Z H, Zhang H R, et al. Study on the network pharmacology and preliminary evidence of Lianhua Qingwen in the treatment of novel coronavirus (2019-nCoV) pneumonia (in Chinese). J Chin Med Mater, 2020, 43: 772–778 [王林, 杨志华, 张浩然, 等. 连花清瘟治疗新型冠状病毒(2019-nCoV)肺炎网络药理学研究与初证. 中药材, 2020, 43: 772–778]
76 Niu W H, Wu F, Cao W Y, et al. Network pharmacology for the identification of phytochemicals in traditional Chinese medicine for COVID-19 that may regulate interleukin-6. Biosci Rep, 2021, 41: BSR20202583
77 Zhao T Y, Guan L Y. Identifying the molecular targets and mechanisms of xuebijing injection for the treatment of COVID-19 via network pharmacology and molecular docking. Bioengineered, 2021, 12: 2274–2287
78 He D D, Zhang X K, Zhu X Y, et al. Network pharmacology and RNA-sequencing reveal the molecular mechanism of Xuebijing injection on COVID-19-induced cardiac dysfunction. Comput Biol Med, 2021, 131: 104293
79 Xing Y, Hua Y R, Shang J, et al. Traditional Chinese medicine network pharmacology study on exploring the mechanism of Xuebijing Injection in the treatment of coronavirus disease 2019. Chin J Nat Med, 2020, 18: 941–951
80 Zheng W J, Yan Q, Ni Y S, et al. Examining the effector mechanisms of Xuebijing injection on COVID-19 based on network pharmacology. Bio Data Min, 2020, 13: 17
81 Zhang Q, Yue S, Wang W, et al. Potential role of gut microbiota in traditional Chinese medicine against COVID-19. Am J Chin Med, 2021, 49: 785–803
82 Wu G S, Zhong J, Zheng N N, et al. Investigation of modulating effect of Qingfei Paidu decoction on host metabolism and gut microbiome in rats (in Chinese). China J Chin Mater Med, 2020, 45: 3726–3739 [吴高松, 钟婧, 郑宁宁, 等. 清肺排毒汤对大鼠整体代谢及肠道菌群的调节作用研究. 中国中药杂志, 2020, 45: 3726–3739]
83 Chen J, Wang Y K, Gao Y, et al. Protection against COVID-19 injury by Qingfei Paidu decoction via anti-viral, anti-inflammatory activity and metabolic programming. Biomed Pharmacother, 2020, 129: 110281
84 Zhao J, Tian S S, Yang J, et al. Drugs investigating mechanism of Qing-Fei-Pai-Du-Tang for treatment of COVID-19 by network pharmacology (in Chinese). Chin Tradit Herb, 2020, 51: 829–835 [赵静, 田赛赛, 杨健, 等. 清肺排毒汤治疗新型冠状病毒肺炎机制的网络药理学探讨. 中草药, 2020, 51: 829–835]
85 Zhang F, Huang J, Liu W, et al. Inhibition of drug-metabolizing enzymes by Qingfei Paidu decoction: Implication of herb-drug interactions in COVID-19 pharmacotherapy. Food Chem Toxicol, 2021, 149: 111998

86 Xu X, Xia J, Zhao S, et al. Qing-Fei-Pai-Du decoction and wogonoside exert anti-inflammatory action through down-regulating USP14 to promote the degradation of activating transcription factor 2. FASEB J, 2021, 35: e21870

87 Li Y, Li B, Wang P, et al. Traditional Chinese medicine, Qingfei Paidu decoction and Xuanfei Baidu decoction, inhibited cytokine production via NF-κB signaling pathway in macrophages: Implications for coronavirus disease 2019 (COVID-19) therapy. Front Pharmacol, 2021, 12: 722126

88 Wang Y, Sang X, Shao R, et al. Xuanfei Baidu decoction protects against macrophages induced inflammation and pulmonary fibrosis via inhibiting IL-6/STAT3 signaling pathway. J Ethnopharmacol, 2022, 283: 114701

89 Wang Y, Wang X, Li Y, et al. Xuanfei Baidu decoction reduces acute lung injury by regulating infiltration of neutrophils and macrophages via PD-1/IL17A pathway. Pharmacol Res, 2022, 176: 106083

90 Wang H, Song H X, Wang D F, et al. Potential mechanism of Xuanfei Baidu formula intreating new coronavirus pneumonia based on network pharmacology and molecular docking (in Chinese). J Hainan Med Univ, 2020, 26: 1361–1372 [王汉, 宋红新, 王敦方, 等. 基于网络药理学和分子对接探讨宣肺败毒方治疗新型冠状病毒肺炎的潜在作用机制. 海南医学院学报, 2020, 26: 1361–1372]

91 Zhao L, Liu H, Wang Y, et al. Multimodal identification by transcriptomics and multiscale bioassays of active components in Xuanfeibaidu formula to suppress macrophage-mediated immune response. Engineering, 2021, doi: 10.1016/j.eng.2021.09.007

92 Yan H, Lu J, Wang J, et al. Prevention of cyclophosphamide-induced immunosuppression in mice with traditional Chinese medicine Xuanfei Baidu decoction. Front Pharmacol, 2021, 12: 730567

93 Wei W L, Wu S F, Li H J, et al. Chemical profiling of Huashi Baidu prescription, an effective anti-COVID-19 TCM formula, by UPLC-Q-TOF/MS. Chin J Nat Med, 2021, 19: 473–480

94 Xie Y Z, Zhong C T, Ji S L, et al. Study of molecular mechanism of Huashibaidu decoction on COVID-19 based on network pharmacology and molecular docking technology (in Chinese). Pharmacol Clin Chin Mater Med, 2020, 36: 28–35 [谢铱子, 钟彩婷, 纪树亮, 等. 基于网络药理学及分子对接技术探讨化湿败毒方治疗新型冠状病毒肺炎的分子机制. 中药药理与临床, 2020, 36: 28–35]

95 Sun X, Tao J L, Xu S J, et al. The molecular mechanism of treating COVID-19 with Huashi Baidu formula based on network pharmacology (in Chinese). J Chin Med Mater, 2020, 43: 2047–2052 [孙逊, 陶嘉磊, 许少菊, 等. 基于网络药理学探究化湿败毒方治疗新型冠状病毒肺炎的分子机制. 中药材, 2020, 43: 2047–2052]

96 Shen X, Yin F. The mechanisms and clinical application of traditional Chinese medicine Lianhua-Qingwen capsule. Biomed Pharmacother, 2021, 142: 111998

97 Zhang Z J, Morris-Natschke S L, Cheng Y Y, et al. Development of anti-influenza agents from natural products. Med Res Rev, 2020, 40: 2290–2338

98 Ding Y, Zeng L, Li R, et al. The Chinese prescription Lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. BMC Complement Altern Med, 2017, 17: 130

99 Du Q, Huang W, Zhao J, et al. Lianhuaqingwen capsule inhibits influenza-induced bacterial adhesion to respiratory epithelial cells through down-regulation of cell adhesion molecules. J Ethnopharmacol, 2021, 280: 114128

100 Liu J, Wang Z, Lin J, et al. Xuebijing injection in septic rats mitigates kidney injury, reduces cortical microcirculatory disorders, and suppresses activation of local inflammation. J Ethnopharmacol, 2021, 276: 114199

101 Jin H, Chen Y, Ding C, et al. Microcirculatory disorders and protective role of Xuebijing in severe heat stroke. Sci Rep, 2018, 8: 4553

102 Zhao Z, Li Y, Zhou L, et al. Prevention and treatment of COVID-19 using traditional Chinese medicine: A review. Phytomedicine, 2021, 85: 153308

103 Yelin D, Wirtheim E, Vetter P, et al. Long-term consequences of COVID-19: Research needs. Lancet Infect Dis, 2020, 20: 1115–1117

104 An X, Duan L, Zhang Y H, et al. The three syndromes and six Chinese patent medicine study during the recovery phase of COVID-19. Chin Med, 2021, 16: 44

105 Ma K, Wang X, Feng S, et al. From the perspective of traditional Chinese medicine: Treatment of mental disorders in COVID-19 survivors. Biomed Pharmacother, 2020, 132: 110810

106 Zhao Z N. Zhang Boli: The combination of Chinese and western medicine, Chinese and western medicine, to help patients with severe disease control reverse disease and reduce the death rate (in Chinese). Wenhui Daily, 2022-04-26 [赵征南. 张伯礼: 中西医结合、中西药并用, 帮重症患者控制病情逆转病情降低病亡率. 文汇报, 2022-04-26]

Summary for “‘三药三方’治疗COVID-19的临床和药理研究进展”

Clinical and pharmacological research progress of “three medicines and three formulae” for COVID-19 treatment

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The COVID-19 outbreak has resulted in extensive human casualties and serious economic losses worldwide. The main pathogenesis of COVID-19 is viral lung infection, which causes excessive immune response and cytokine storm, leading to acute respiratory distress syndrome and multiple organ dysfunction syndrome. Due to China’s long history of battling plagues, traditional Chinese medicine (TCM) has formulated herbal recipes and developed theories on infectious diseases. During the fight against COVID-19, “three medicines and three formulae”, including Jinhua Qinggan granules, Lianhua Qingwen capsules, Xuebijing injection, Qingfei Paidu decoction, Huashi Baidu decoction, and Xuanfei Baidu decoction, were recommended by leading TCM experts and academicians. These remedies were adopted in the national guidelines for the prevention and treatment of COVID-19. Guided by the TCM theory of heat removal, humidity reduction and detoxification, the scope of the “three medicines and three formulae” approach covers the entire course of a COVID-19 infection, including the phase of pre-symptomatic medical observation and the different diagnostic stages (mild, moderate, severe, and critical) of the disease. This study reviewed progress in clinical research as well as the mechanisms of action, concerning “three medicines and three formulae” for COVID-19. Clinical evidence suggests that the “three medicines and three formulae” are effective in preventing and treating COVID-19 by alleviating typical symptoms such as fever, coughing, fatigue, phlegm and diarrhea, shortening nucleic acid-negative conversion time, improving computed tomography images feature, inhibiting lung inflammation, normalizing clinical biomarkers, and reducing COVID-19-related complications. The pharmacological mechanisms of the “three medicines and three formulae” mainly include: binding with ACE2, 3CLpro, PLpro, and TMPRSS2 to inhibit virus invasion and replication; reducing the production and secretion of pro-inflammatory factors (such as IL-6, TNF-α, IL-1, IL-10, CXCL8, CXCL10, and CCL2) to regulate immune function; and decreasing clinical indicators (such as IL-6, CRP, and D-dimer) associated with the crosstalk of viral toxicity, endothelial damage, cytokine storm, excessive immune response, and microthrombosis to protect multiple organs against damage. In the future, it is necessary to collect further clinical evidence of the “three medicines and three formulae” for COVID-19 by conducting high-quality, large-scale randomized controlled trials. Trials targeting different Chinese medicine syndromes in specific patient populations are particularly desirable. Big data collection and analysis of the efficacy and safety of the “three medicines and three formulae” for COVID-19 can be facilitated by artificial intelligence and deep learning. In addition, the active components of these treatments, in various combinations with one another, should be identified, and their respective underlying mechanisms of action should be assessed using advanced technologies, such as multi-omics integration and human induced pluripotent stem cell-derived disease models. Moreover, more attention should be paid to the COVID-19 patients of post-infection, with common syndromes such as fatigue or muscle weakness, sleep deprivation, and anxiety or depression especially for low-immunity children and elderly with chronic diseases. TCM has many advantages and should be actively explored for patients with unmet medical needs.

three medicines and three formulae, COVID-19, clinical research, pharmacological research

doi: 10.1360/TB-2022-0375