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中药治疗新冠病毒肺炎的科学基础

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摘要

新近暴发的新冠病毒肺炎（COVID-19）已成为危害全球健康的紧急事件。现有证据表明，新冠病毒（SARS-CoV-2）与其他冠状病毒（如SARS-CoV和MERS-CoV）的基因序列具有相似性。因此，针对现存冠状病毒的引发疾病的机制研究和在治疗SARS时所取得的经验和教训，可咨今天对抗新冠病毒引发疾病的参考。COVID-19患者的临床病理特征提示患者在病情进展过程中通常会经历五个发展阶段：大量病毒感染、免疫系统抑制、细胞因子风暴、多器官损伤及后期的肺纤维化样改变，严重者常导致死亡。早期阻断疾病进展是取得治疗成功的关键。但是，目前尚无针对COVID-19的特效药物或疫苗，世界卫生组织（WHO）正敦促尽快建立新型预防和治疗策略。传统中医药（TCM）对于疫病的防治的实践已经积累了几千年的有用经验，它通过整体调节机体功能发挥疗效。在此次疫情中，中医药作为替代治疗或与西药联合使用，在疫情防控中发挥了重要的作用。本文总结了此次抗疫过程中中国国家和省级机构推荐使用的中药复方和中成药的潜在用途和治疗机制，以期发现其治疗COVID-19的潜在科学内涵。同时，整合应用多种组学及转化医学技术开展基础与临床研究有望进一步证实中药复方的治疗机制。

1. 引言

自2019年12月以来，新冠病毒肺炎（COVID-19）在世界范围内迅速蔓延，敲响了国际卫生安全的警钟，成为了“国际关注的突发公共卫生事件”[1–4]。因病毒具有高度传染性，全球的感染病例及死亡病例持续上升。但针对COVID-19的有效药物或疫苗仍比较缺乏。在这种紧急情况下，大量的COVID-19中国患者在不同发病阶段接受了中医药（TCM）的治疗，效果显著[5]。尽管现有的基础和临床研究证据还不足以支撑解释其临床效果，但中医药的价值值得被进一步观察和验证。

严重急性呼吸综合征冠状病毒2（SARS-CoV-2）感染者的典型临床特征为发热、疲劳、咳嗽和急性肺炎，与人类严重急性呼吸综合征冠状病毒（SARS-CoV）引起的症状相似[4,6,7]，主要通过呼吸道和接触传播，具有高度传染性，且人群普遍易感。根据传统中医理论，COVID-19的发病原因是因为感染了疫气[5]，疫气为一种具有强传染性的外邪。《新型冠状病毒感染的肺炎诊疗方案》指出，COVID-19属于中医中的瘟疫，病位在肺，病机可概括为“湿、热、毒、血瘀”。中医药临床治疗可分为五个阶段：轻症期（寒湿或湿热蕴肺）、中度期（湿毒阻肺，寒湿困肺）、重症期（疫毒闭肺）、

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危重症期（内闭外脱）和恢复期（肺脾气虚，气阴两虚）。从西医角度来看，SARS-CoV-2的基因测序结果与蝙蝠中冠状病毒有高度相似性，且与SARS-CoV中大部分序列高度一致[8,9]。此外，COVID-19的病理特征也与SARS-CoV感染后表现相似，病毒通过S-蛋白与细胞表面ACE2受体结合后进入细胞[10–12]。在过往针对SARS-CoV和MERS-CoV的研究中已发现一些重要的药物治疗靶点，如刺突糖蛋白（S-protein）、血管紧张素转换酶2（ACE2）、跨膜丝氨酸蛋白酶2（TMPRSS2）、冠状病毒主蛋白酶（3CLpro）、RNA依赖的RNA聚合酶（RdRp）和木瓜样蛋白酶（PLpro）[13–16]等。

关于这种新型传染病，当前面对的主要挑战是对其发病机制和治疗方法认识很不足，且部分患者虽然表现轻微感染甚至无症状，但却具有高度传染性[17]。有些患者会迅速发展到严重/危重状态，但却没有有效的药物用于缓解病情。许多COVID-19患者还会经历五个阶段的病情进展，首先是遭受严重的病毒感染，免疫系统受到抑制；在由轻转重的过程中，患者还会出现细胞因子风暴，导致多器官损伤和功能障碍。如果宿主免疫反应强，疾病还会导致多器官损害和肺纤维化等复杂并发症[1,3,7,18–20]。

鉴于SARS-CoV感染与COVID-19具有相似性，中药（CHM）在17年前治疗SARS-CoV感染的经验可为对抗COVID-19提供一些重要参考，尤其是在缺乏特效药的情况下，中药的使用应作为一种重要的替代疗法。中药复方已被中国广泛地应用于这场新冠肺炎的战斗中，其疗效和价值亦被《中华人民共和国新冠肺炎诊疗方案（第七版试行）》所认可和记载[5]。就中草药的治疗机制而言，它与传统西医既有相似之处，也有不同之处。它可通过直接干预病毒以及病毒与宿主在病毒细胞、分子靶点、宿主受体、信号通路、微生态等方面的相互作用，发挥直接抗病毒作用；同时，因其多成分、多通路、多靶点特点，亦可作用于人体的免疫系统产生整体效应，保护人体组织和器官，增强身体抵抗病毒的能力和免疫损伤[21,22]。事实上，越来越多的西医治疗不再依赖于单一药物，为了达到更好的综合疗效，西医也会依靠联合治疗和方法。例如，在COVID-19治疗中，建议同时使用抗病毒药物、IL-6抑制剂、干扰素-γ、免疫增强剂、氧疗和支持疗法进行治疗。西药和中药可在COVID-19患者的不同阶段，通过多个层次的途径和靶标达到协同、整合治疗效果（图1）。为此，本文总结了此次抗疫过程中中国国家和省级机构推荐使用的中药复方和中成药的潜在用途和治疗机制，以期发现其治疗COVID-19的潜在科学内涵。

2. COVID-19 的发病机制和中药的治疗机制

关于中药针对COVID-19的发病机制和治疗干预机制的总结如表1所示[23–56]。根据目前的网络药理学研究和一些体外实验，中药对COVID-19的作用机制是多组分、多靶点、多途径的。主要机制包括直接抗病毒作用、抗炎、免疫调节和保护靶器官作用等[54,55]。传统中药本身富含一系列复杂的具有药理活性的化合物，如多糖、类黄酮、皂苷、生物碱等。

2.1. 靶向 SARS-CoV-2 及其宿主受体 ACE-2 发挥抗病毒作用

SARS-CoV-2是一种包膜、单链、正链RNA β属冠状病毒。SARS-CoV-2表面的S蛋白通过识别ACE2受体诱导SARS-CoV-2附着和入侵宿主细胞[15]。入侵的病毒随后控制宿主细胞的基因复制，产生具有RdRp的新病毒RNA，并通过宿主核糖体合成糖蛋白，经病毒蛋白酶（3CLpro和PLpro）切割为非结构蛋白和结构蛋白（S蛋白），并组装新的病毒颗粒以释放、感染其他宿主细胞[56,57]。因此，ACE2受体、RdRp、Spike蛋白、3CLpro和PLpro对于SARS-CoV-2的侵袭和复制至关重要，可能是中药治疗COVID-19的潜在靶点[31,58]。COVID-19的病因是SARS-CoV-2经呼吸道传播感染肺部，引起肺炎，产生炎症因子；病毒在宿主细胞内复制释放，在血液中循环，与体内多个器官表面的ACE2结合，扰乱RAS信号通路的平衡，造成全身多个器官的损伤。该病毒还会引起身体的过度免疫反应，导致炎症风暴，从而导致病情恶化；肺部的炎症产生大量的分泌物阻塞气道，加剧了身体的缺氧。

中药是通过与ACE2受体和3CL pro结合，直接抑制病毒对宿主细胞的吸附和复制而产生治疗作用。Hao等[23]的综述中指出，中药可作为心血管疾病一级和二级预防的补充和替代方法，其心血管保护作用主要归因于其抗氧化、抗炎和抗细胞毒性作用[23,59]。心脏是一个富含ACE2受体的器官，我们推测中药对心脏的保护机制也与此有关。例如，热毒宁注射液用于重症COVID-19的治疗。这个针剂中含有丹参的成分，而丹参酮是中药中具有心血管保护作用的萜类化合物的典型代表。由此，我们推测热毒宁注射液中的丹参酮是治疗

表1 COVID-19的发病机制及中药的治疗机制概述

Disease	Pathogenesis	Chinese herbal formulas and active components	Targets and signaling pathways	Reference
Severe viral infection	Virus replication	Lianhua Qingwen formula, Wogonin (*Scutellariae Radix*), Baicalin (*Scutellariae Radix*), *L*-methylephedrin, *L*-ephedrine and *D*-pseudo-ephedrine (*Ephedrae Herba*), and patchouli alcohol (*Pogostemonis Herba*)	Inhibiting SARS-CoV-2, SARS-CoV, influenza A and B virus replication, inducing IFN-γ, modulating Toll-like receptors (TLRs), retinoic acid inducible gene-1 (RIG-1), adenosine monophosphate (AMP)-activated protein kinase (AMPK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), and extracellular signal-regulated kinases (ERK)/mitogen-activated protein kinase (MAPK) pathways	[23–27]
	Viral RNA synthesis	*Herba Houttuyniae*	Inhibiting SRAS-CoV RdRp	[28]
	Virus invasion	Qingfei Paidu decoction and Huoxiang Zhengqi oral liquid, patchouli alcohol, tussilagone (*Farfarae Flos*), ergosterol, asarinin (*Asari Radix et Rhizoma*), ephedrine hydrochloride (*Ephedrae Herba*), shionone (*Asteris Radix et Rhizoma*), quercetin, isorhamnetin (*Glycyrrhizae Radix et Rhizoma*), and irisolidone (*Herba Pogostemonis*)	Binding to ACE2 receptor	[29,30]
	Viral protein proteins and particle assembly	Houttuyniae Herba, Qingfei Paidu decoction and Huoxiang Zhengqi oral liquid, patchouli alcohol (*Pogostemonis Herba*), saikosaponin B (*Bupleuri Radix*), ergosterol (*Polyporus*), shionone (*Asteris Radix et Rhizoma*), 23-acetate alisol B (*Alismatis Rhizoma*), licorice glycoside E, kaempferol, (2*R*)-7-hydroxy-2-(4-hydroxyphenyl) chroman-4-ketone, quercetin, isorhamnetin (*Glycyrrhizae Radix et Rhizoma*), naringenin (*Citri Reticulatae Pericarpium*), robinin (*Platycodi Radix*) and irisolidone (*Herba Pogostemonis*), herbacetin (*Rhodiolae Crenulatae Radix et Rhizoma*), rhoifolin, apigenin, luteolin (*Citri Reticulatae Pericarpium*), quercetin, daidzein, and puerarin (*Puerariae Radix*)	Binding to 3CLpro and inhibiting the proteolytic activity of SARS-CoV 3CLpro	[28–31]
Inflammation and cytokine storm	Virus-infected alveolar cells release signals to recruit and activate immune cells, which secrete a variety of cytokines and chemokines and destroy the virus by releasing inflammatory mediators or phagocytosis. The excessive immune response initiates a "cytokine storm" that causes damage of lung tissue and exacerbation of pneumonia	Lianhua Qingwen capsule, *Lonicerae Japonicae Flos*, Platycodin D (*Platycodi Radix*), and *Moutan Cortex Radicis*	Suppressing pro-inflammatory cytokines production	[32–35]
		Lonicerae Japonicae Flos	Enhancing anti-inflammatory cytokines production	[33]
		Platycodin D (*Platycodi Radix*)	Suppressing apoptosis	[34]
		Platycodin D (*Platycodi Radix*) and *Moutan Cortex Radicis*	Strengthening antioxidant	[34,35]
		Platycodin D (*Platycodi Radix*) and *Moutan Cortex Radicis*	Protecting host against acute lung injury	[34,35]
		Polysaccharides of *Pinelliae Rhizoma*	Regulating IL-4 and IFN-γ	[36]

（续表）

Disease	Pathogenesis	Chinese herbal formulas and active components	Targets and signaling pathways	Reference
Prevention of pulmonary fluids and obstruction	Acute lung inflammation increases the permeability of lung endothelial and epithelial barriers, impairs alveolar fluids clearance mechanisms, causes edema, blocks airways, and leads to hypoxia	*Asteris Radix*, *Fritillaria cirrhosae Bulbus*, *Trichosanthis Fructus*, *Eriobotryae Japonicae Folium*, Polysaccharides of *Pinelliae Rhizoma*, and verticine	Dispelling phlegm and relieving cough, inhibiting mucus secretion in human airway epithelial cells	[36–39]
Multi-organ dysfunction	ACE2 receptor attack, immune destruction	*Astragalus* and *Angelica*, *Rheum* and its components, and triptolide	Boosting the immune system, relieving diuresis, anti-oxidation and inflammation	[40]
	Qi deficiency	*Radix Codonopsis* and *Panax ginseng*	Replenishing qi–yin deficiency, promoting organ and tissue regeneration and recovery	[21,40,41]
	Activation of the airway inflammatory pathway	Xiyanping injection (Andrographolide sulfonate)	Ameliorating airway inflammatory cell recruitment and inhibiting nuclear factor (NF)-κB and MAPK-mediated inflammatory responses	[42]
	Over-secretion of inflammatory cytokines	Xuebijing injection (*Carthamus tinctorius*, *Ligusticum wallichii*, and *Salvia miltiorrhiza*)	Suppressing inflammatory cytokine secretion	[43]
Lung fibrosis	Induction of lipogenesis	Naringenin	Inhibiting autophagy and suppressing lung inflammation and fibrosis	[44]
	Wnt signaling activation	Morusin	Alleviating mycoplasma pneumonia *via* the inhibition of Wnt/β-catenin and NF-κB signaling	[45]
	Transforming growth factor (TGF)-β and integrin activation	Yupingfeng formula (*Astragalus* and *Atractylodes macrocephala*)	Blocking fibroblast activation, collagen production, and extracellular matrix (ECM) degradation signaling pathway	[46]
	Tissue damage due to viral binding to ACE2	Tanshinone IIA	Attenuating bleomycin-induced pulmonary fibrosis via modulating ACE2	[47]
	p38 MAPK activation	Oxymatrine	Inhibiting phosphorylated p38 mitogen-activated protein kinase and blocking fibroblast activation and collagen production	[48]
	Activation of ECM	Honokiol	Inhibiting ECM and pro-inflammatory factors	[49,50]
	Induction of reactive oxygen Species and protein oxidation	Resveratrol and berberine	Acting as reactive oxygen species (ROS) scavenger, maintaining redox balance and preventing of protein oxidation	[51–53]

COVID-19保护靶器官的有效成分。

此外，连花清瘟胶囊已被证明可以显著并剂量依赖性地抑制SARS-CoV-2感染的Vero E6细胞中SARS-CoV-2的复制（IC_{50}: 411.2 μg·mL^{-1}）[32]。鱼腥草水提物对SARS-CoV中的3CLpro和RdRp有明显的抑制作用[28]。通过网络药理学分析，清肺排毒汤和藿香正气口服液中包含：广藿香醇（广藿香）、柴胡皂苷B（柴胡）、麦角固醇（猪苓）、紫菀酮（紫菀）、乙酰泽泻醇B（泽泻）、甘草苷E、山奈酚、(2*R*)-7-hydroxy-2-(4-hydroxyphenyl) chroman-4-ketone、槲皮素、异鼠李素（甘草）、柚皮素（陈皮）、刺槐苷（桔梗）和尼泊尔莺尾素（广藿香），可以结合到3CLpro；广藿香醇、款冬酮（款冬）、麦角固醇、细辛素（细辛）、盐酸麻黄碱（麻黄）、紫菀酮、槲皮素、异鼠李素和鸢尾酮，可以结合到ACE2受体阻断SARS-

CoV-2病毒的入侵和复制[29,30]。此外，草质素（红景天）、野漆树苷、芹黄素、毛地黄黄酮（陈皮）、槲皮素、大豆苷、葛根素（葛根）和山奈酚亦被报道具有抑制SARS-CoV 3CLpro蛋白水解的活性[31]。有趣的是，许多用于治疗COVID-19的活性成分对流感病毒同样具有显著的抗病毒作用。例如，黄芩素通过调节AMPK通路，有效抑制了甲型流感病毒和乙型流感病毒在犬肾脏（MDCK）细胞和人肺上皮（A549）细胞中的复制[24]。黄芩苷（黄芩）在体内外表现出抗甲型流感病毒（H1N1）的活性，是主要的IFN-γ制备细胞中IFN-γ的有效诱导剂[25]。L-甲基麻黄碱、L-麻黄碱和D-伪麻黄碱(麻黄)可通过调节宿主的TLRs和RIG-1通路，在体外抑制甲型流感病毒复制，保护感染病毒的小鼠[26]。广藿香醇对不同流感病毒A株体外增殖有明显抑制作用，并可能通过细胞PI3K/Akt和ERK/MAPK信号通路吸附病毒后，直接灭活病毒颗粒，干扰病毒A感染的早期阶段，从而阻断流感病毒A感染[27]。

2.2. 抑制促炎细胞因子，阻断细胞因子风暴

越来越多的证据表明，COVID-19重症患者出现了细胞因子风暴。IL-1B、IL-1RA、IL-6、IL-7、IL-8、IL-9、IL-10、纤维母细胞生长因子（FGF）、粒细胞巨噬细胞集落刺激因子（GM-CSF）、干扰素-γ、粒细胞集落刺激因子（G-CSF）、干扰素-γ诱导蛋白（IP10）、单核细胞化学引诱物蛋白1（MCP1）、巨噬细胞炎性蛋白1α（MIP1A）、血小板衍生生长因子（PDGF）、肿瘤坏死因子（TNFα）、血管内皮生长因子（VEGF）的细胞因子水平显著增加[60,61]。在危重或死亡患者中，IL-6水平明显升高[2,62–64]。临床常通过采用多种抗炎治疗策略，如糖皮质激素、托珠单抗（重组人IL-6单克隆抗体）、巴瑞替尼（JAK抑制剂）、氯喹和羟氯喹等，可以减少发烧和肺炎恶化，促进肺炎分泌物吸收，以获取更多氧分，并改善肺部影像学表现，增加病毒转阴率[65]。强有力的证据表明，治疗COVID-19时，中药的活性成分可以抑制促炎细胞因子，从而缓解细胞因子风暴。Li等[32]研究表明，连花清瘟胶囊在mRNA水平水平上显著降低了SARS-CoV-2感染的Huh-7细胞中TNF-α、IL-6、CCL-2/MCP-1和CXCL-10/IP-10的水平，且具有浓度依赖效应。金银花乙醇提取物可提高细胞核中Sp1的结合活性，增强IL-10的表达；且可降低脂多糖（LPS）诱导小鼠急性肺炎症模型中核NF-κB结合活性，从而抑制TNF-α、IL-1β、IL-6的表达[33]。桔梗D（桔梗）可通过抑制凋亡（降低Caspase-3和Bax的表达）和炎症（降低TNF-α、IL-6和NF-κB）以及增强抗氧化作用[降低髓过氧化物酶（MPO）的活性和改善超氧化物歧化酶的活性]，改善被LPS或博来霉素诱导的急性肺损伤[34]。牡丹皮提取物还可通过降低IL-1β、MIP-2、IL-6和MOP的活性，改善LPS诱导的大鼠急性肺损伤[35]。半夏多糖通过调节NCI-H29 2细胞（人气道上皮细胞）中IL-4和IFN-h的水平及抑制黏液分泌，明显抑制脂多糖诱导的气道炎症[36]。槲皮素、山奈酚、木犀草素、异鼠李素、黄芩素、柚皮苷、汉黄芩素可能是中草药抑制炎症介质、调节免疫、清除自由基治疗COVID-19的主要活性成分。这些成分可通过调节花生四烯酸、HIF-1、Ras和NF-κB信号通路靶向抑制IL-17，或通过COX-2、CASP3、IL-6、MAPK1、MAPK14、MAPK8和REAL信号通路靶向抑制TNF发挥作用。

2.3. 抑制肺部炎症以减少肺上皮分泌并预防肺阻塞

尽管大多数COVID-19患者以发热、疲劳和干咳为主，且预后良好[61]，但部分重症患者可出现呼吸困难和低氧血症，并迅速发展为急性呼吸窘迫综合征（acute respiratory distress syndrome, ARDS）[63]，而必须使用呼吸机。ARDS的病理生理复杂，涉及急性肺部炎症，会增加肺内皮和上皮屏障的通透性，削弱肺泡液清除机制，引起水肿并阻塞气道，从而导致缺氧[66]；而推荐的中药及其活性成分不仅可以抑制肺部炎症，减缓细胞因子风暴，还可以减少肺上皮的分泌，从而预防肺梗阻。如千余年来中药中紫菀、川贝母、瓜蒌、枇杷叶等提取物用于祛痰止咳，其活性成分贝母碱具有明显的祛痰、止咳、抗炎作用[37–39]。且中药可减少肺泡细胞和血管上皮细胞的渗出，减轻气道分泌物阻塞，抗纤维化。这可能是其改善新冠病毒肺炎患者缺氧症状的原因；也是中西医结合患者治疗组中，COVID-19轻症患者转重症和危重症的概率较低的原因。

2.4. 保护肺及多器官不受损害

据报道，合并有其他疾病或老年COVID-19患者死亡率较高，因其发生多器官功能衰竭、进展为危重状态的可能性较大。多器官衰竭是SARS-CoV-2感染致死的主要原因之一，因为SARS-CoV-2不仅可以攻击肺组织，还可影响许多重要的人体器官，如心脏、肾脏、睾丸、肝脏、结肠和脑等[1,13,16,17,19,67]。这些器官均表达高水平的ACE2，因此成为SARS-CoV-2攻击的关

键目标[14]。大多数COVID-19的住院患者在胸部计算机断层扫描中表现出典型的毛玻璃样影和双侧斑片状影[40,68]。当病毒感染心脏和肾脏时，它会与ACE2结合并导致心脏骤停和肾功能衰竭，这是大多数患者死亡的原因，包括那些在重症监护室（ICU）接受治疗的重症患者。因此，在早期减少病毒摄入，减轻症状，预防疾病进展至关重要。中药的早期应用已被证实可保护重要器官并预防轻症患者向重症转变。例如，黄芪、当归、大黄及其成分（大黄素、大黄酸等）通过改变Th17细胞和Th17/调节性T细胞比例来调节免疫系统，缓解利尿、抗氧化和抗炎，从而治疗慢性肾脏疾病[44]。党参和人参可以促进细胞自噬和葡萄糖代谢途径治疗危重症患者的气虚症状[21,22,69]。喜炎平注射剂与活性成分穿心莲内酯磺酸盐可以改善气道炎症细胞聚集并抑制NF-κB和MAPK调节的炎症反应[42]。血必净注射液（红花、川芎、丹参）抑制炎症细胞因子分泌，并起到补气的作用[43]。虽然这些CHM并不直接以ACE2为靶点，但它们能够全面缓解患者的综合征，增加患者的舒适度，并防止疾病的进一步发展[70]。

2.5. 预防肺纤维化

基于过去治疗SARS-CoV感染的经验和COVID-19的近期报道，尽管COVID-19的死亡率不高，许多患者将遭受肺功能长期损害。重症患者通常发生急性病毒感染、严重炎症、肺泡上皮细胞（AEC）损伤、成纤维细胞激活、胶原蛋白生成、ECM降解抑制，而最终产生肺纤维化，导致肺损伤和肺组织瘢痕形成[71,72]。长期的肺损伤和肺活量降低将影响患者出院后的日常活动和生活质量。因此，有效预防肺纤维化和康复护理也是我们面临的重大挑战；而中药可能有助于缓解甚至逆转这种肺纤维化情况[44,45,73]。因此，在康复阶段中药亦是必不可少的，应推广使用。此外，尽管部分患者已经无病毒负荷，且呼吸综合征得到缓解，达到了出院标准，但根据中医诊断，患者通常仍处于气阴两虚的状态。

当SARS-CoV2侵入呼吸道和肺部时，宿主免疫防御反应和炎症可激活上皮细胞的细胞增殖导致组织再生。MUC5b、TGF-β、p38 MAPK、整合素信号传导、Wnt信号传导途径在感染和发炎的情况下，大部分会被激活[46,47,74–79]，也会引起活性氧（ROS）的感应。它将打开细胞周期调控基因，从而导致肺成纤维细胞增殖。ROS还会诱导蛋白氧化，而蛋白氧化与细胞损伤相关的炎症反应有关，最终导致肺纤维化和阻塞[48,71,72,74]。此外，细胞衰老、线粒体功能障碍和蛋白稳态失调也是肺纤维化的病因之一[71,72]。药物通过抑制上述因素可产生一定的预防肺纤维化作用，尤其在疾病的早期。

先前的研究表明，一些药用植物、中药以及它们的活性成分可以缓解多种肺炎导致的肺纤维化，如包括SARS-CoV。因此，我们建议尽早应用中药治疗COVID-19，来阻断这些通路和肺纤维化。玉屏风由黄芪、白术组成的草药配方，它对TGF-β细胞增殖刺激信号有抑制作用，阻碍成纤维细胞的活化和胶原蛋白的产生[49]。此外，有报道称柚皮苷通过降低ROS抑制自噬，从而抑制肺炎症和纤维化[65]，桑根皮素通过抑制Wnt/β连环蛋白和NF-κB信号减轻肺炎支原体[75]。丹参酮IIA通过抑制病毒结合调节ACE2，减弱博莱霉素诱导的肺纤维化[50]，氧化苦参碱抑制磷酸化的p38丝裂原活化蛋白激酶细胞增殖信号[51]。

即使在患者出院后，仍可能存在中医气阴虚证这种情况，亦可能有抑郁症或其他需要进一步接受治疗的不适。人参、黄芪是临床上常用的中草药，在预防实验性肺纤维化等方面表现出明显的效果[21,22,69,70]。据报道，厚朴酚还能抑制细胞外基质和促炎因子，减轻肺纤维化[52,53]。此外，从中药中提取的一些化合物可作为ROS清除剂，如白藜芦醇、小檗碱等可能靶向氧化还原失衡来减轻肺部炎症和纤维化[80–82]。

综上所述，通过聚焦于COVID-19的发病机制，确认了其治疗靶点和潜在的治疗策略；抗病毒药物、IL-6抑制剂、IFN-γ、免疫增强剂、氧疗和支持疗法均被推荐用于治疗COVID-19患者（图1）。在COVID-19患者不同阶段，中医可通过多维的通路和靶点实现治疗效果。

3. 展望

在当前这种情况紧急且缺乏有效治疗药物的情况下，我们应在合适的安全用药指导和监测下，采取中西药物结合方法治疗COVID-19患者。唯有将中医药传统经验与现代创新研究成果相结合，才能共同抗击这场全球性的抗病毒战争。中医通过对患者的临床表现、辨证分型及个性化特征进行整合分析得到合适的中药复方。除此之外，在确定组方的过程中，中医还需对中药材的

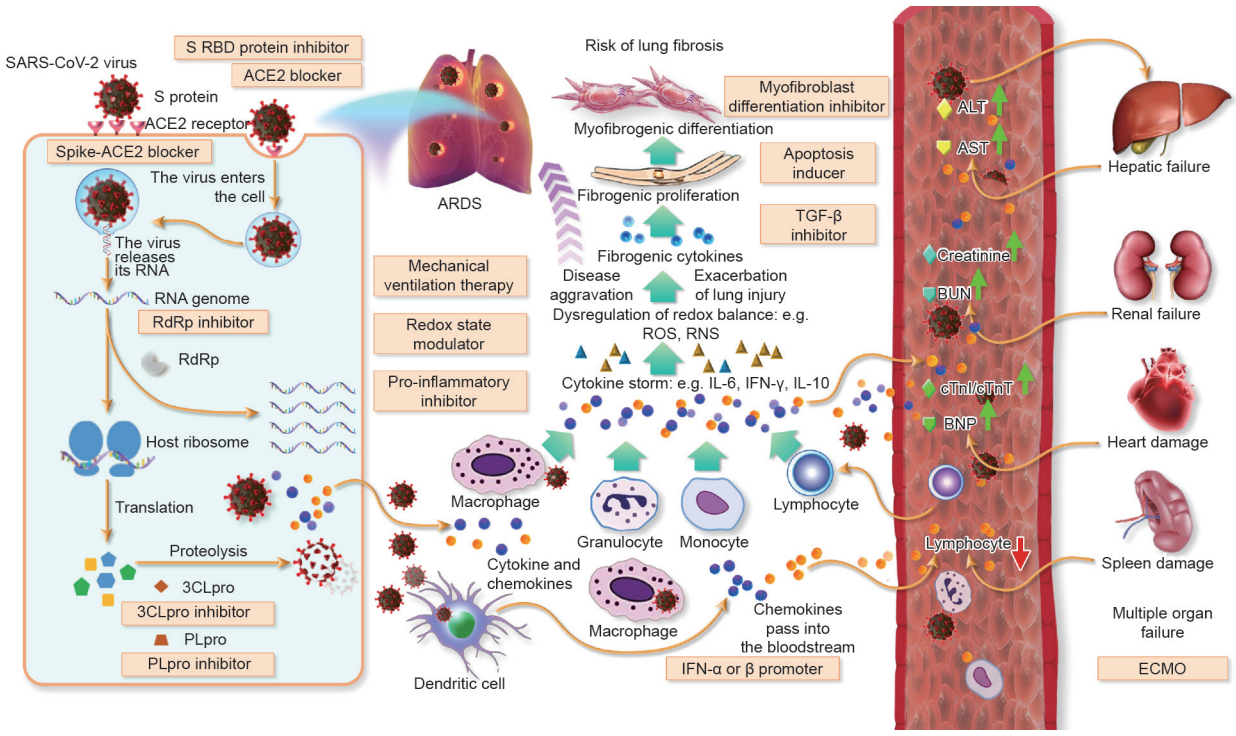

图1. COVID-19的治疗靶点和潜在治疗策略。SARS-CoV-2通过与跨膜酶ACE2的相互作用感染气道上皮细胞。阻断该病毒与人ACE2蛋白结合可能是治疗感染病毒患者的有效手段。一旦SARS-CoV-2进入细胞，被感染的细胞就会死亡并释放病毒颗粒以及细胞内组分，从而触发炎症反应。抗病毒剂，如RNA聚合酶抑制剂和蛋白酶抑制剂，是潜在的治疗策略。随后，促炎性细胞因子的激增和氧化还原平衡的失调导致水肿并损害毛细血管和肺组织，甚至导致急性呼吸窘迫综合征（ARDS）；肺损伤的恶化也增加了肺纤维化的风险。在疾病的细胞因子风暴期，推荐使用抑制促炎性细胞因子的药物，如托珠单抗（IL-6抑制剂），并且可以使用氧化还原状态的调节剂来恢复氧化还原平衡。当其他器官（如肝、肾、心脏和脾脏）充满炎性细胞因子和趋化因子时，继而发生器官衰竭，并造成致命后果。在此阶段，体外膜氧合（ECMO）在治疗严重COVID-19中起作用。RBD：受体结合结构域；TGF：转化生长因子；ROS：活性氧；RNS：活性氮；ALT：丙氨酸转氨酶；AST：天冬氨酸转氨酶；BUN：血尿素氮；BNP：B型利钠肽；cTnI：心肌肌钙蛋白I；cTnT：心肌肌钙蛋白T。

安全给予高度的重视，通过文献数据和实验结果去确认药物的安全性。

根据张伯礼教授、仝小林教授等临床专家治疗武汉新冠肺炎患者的经验，中药复方应尽早开始使用，以期达到多维治疗效果，减缓或预防疾病的进展。中医可以根据实际需要选择不同中药处方来治疗不同阶段的患者，以期获得最佳的治疗效果。中医药的救治应实行“全覆盖”和“全过程”的临床用药与质量保障体系。

同时，我们亦需将重点放在SARS和COVID-19的比较研究上；这两种疾病在药物处方上的“异”和“同”需很好地去阐明。根据国家药品监督管理局现行的规定，尽管SARS和COVID-19两种疾病的病毒基因组序列具有相似性，但已批准的处方药物存在很大差异，因此尚未在全球范围内达成COVID-19治疗药物的统一意见。目前，中药复方的随机对照临床试验研究结果仍明显不足；这些通过临床观察得出的“疗效明显”的主张引起了学术界和公众的质疑，限制了中医药在全球范围内的广泛使用。因此，我们更应进一步开展高质量的临床试验来证实特定处方或化合物的临床疗效。同时，运用多学科的先进技术对传统医学和现代科学进行深入研究以发现复方的药效物质基础。通过传统复方配伍机制结合客观临床证据和充实的实验室数据，明确复方化学组成、疗效及作用机制，方可为复方的有效性提供坚实的证据（图2）。

4. 结语

综上所述，中医药对COVID-19的临床治疗价值已得到了文献和临床经验的支持。在中国，COVID-19患者在不同阶段采用中药复方单独使用或与西药联合应用均收效良好。但由于COVID-19是一种新型传染病，其发病机制和治疗可能与以往发生的其他大流行疾病存在不同，有效的药物和治疗仍面临较大挑战。我们相信，中医药是人类抵御包括疫情在内各种疾病的宝贵财富，多学科创新技术将促进中医药发展，帮助我们发现其科学内涵。我们真诚希望，可以与世界各国临床医生和科学家携手共进，共同抗击新冠肺炎疫情。

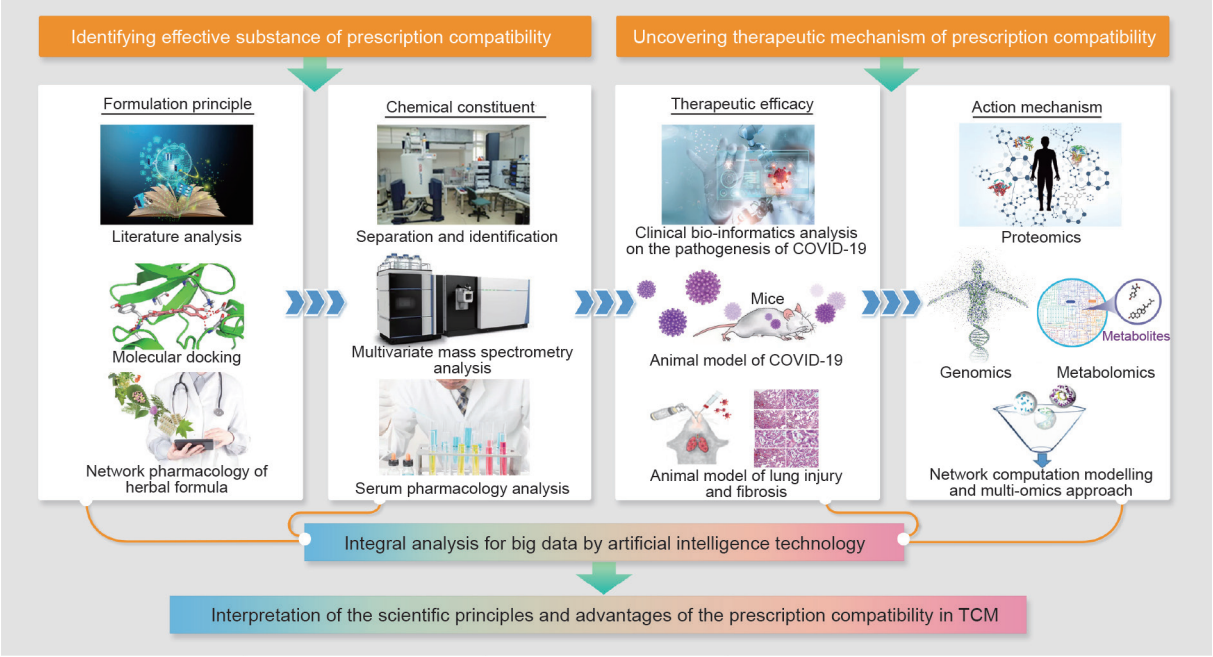

图2. 整合多元创新技术阐明中药复方的科学内涵。可以应用网络药理学和多元质谱分析等多元创新技术来识别中药复方的组方原理和化学成分，从而识别有效物质和配伍机制。 另外，为了揭示复方的治疗机制，建议采用多组学方法来确定中药复方用于治疗复杂疾病的多个目标。 通过人工智能技术对大数据进行整体分析，将更好地阐明中药复方的科学原理和优势。

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Compliance with ethics guidelines

Elaine Lai-Han Leung, Hu-Dan Pan, Yu-Feng Huang, Xing-Xing Fan, Wan-Ying Wang, Fang He, Jun Cai, Hua Zhou, and Liang Liu declare that they have no conflict of interest or financial conflicts to disclose.

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