

Recent Options for COVID-19 Treatment: Conventional Therapy, Herbal Medicine, and Stem Cell-Based Therapies

Maftuchah Rochmanti^{1*}, Bambang Haryo Tri Satya Wahyono², Rahmi Nugranigrum² and Mustofa³

1. Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, 60131
2. Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, 60131
3. Department of Pharmacology and Therapy, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281

Article Info

Submitted: 03-10-2023

Revised: 30-07-2024

Accepted: 16-09-2024

*Corresponding author
Maftuchah Rochmanti

Email:
maftuchah-r@fk.unair.ac.id

ABSTRACT

A range of pharmacological therapies have been explored for COVID-19 patients, yet substantial practical and clinical gaps persist. Current COVID-19 treatments remain largely pharmacologically driven and are primarily based on empirical data. Common therapeutic agents include histamine antagonists, antibiotics, antivirals, and monoclonal antibody therapies. However, the specific mechanisms of action and potential long-term side effects of these agents remain insufficiently understood. This narrative review examines the efficacy and safety profiles of promising novel therapeutic approaches for COVID-19, including herbal medicines and stem cell therapies, based on *in vitro*, *in vivo*, and clinical research. We utilized PubMed and ScienceDirect databases, applying search terms such as “COVID-19” AND “Herbal Medicine” OR “Stem Cell Therapy” OR “recent therapy” AND “efficacy” OR “safety” to identify relevant studies. This review presents clinical findings on the efficacy, safety, and indications of select recent therapies. Our results indicate that newer pharmacological therapies, herbal medicines, and stem cell therapy demonstrate high potential efficacy and safety for managing active COVID-19 infection and may also help prevent multi-organ damage post-infection. Further in-depth studies are required to assess additional therapeutic modalities that may serve as compelling candidates for future COVID-19 treatments.

Keywords: COVID-19, Herbal medicine, Pharmacology therapy, Stem cell therapy

INTRODUCTION

A novel coronavirus variant, COVID-19—formally known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)—was initially identified in Wuhan, China. COVID-19 shares a high degree of genetic homology (approximately 80%) with earlier SARS-CoV strains, which led to significant outbreaks and mortality during 2002-2003 (Li et al., 2020). Subsequent studies confirmed substantial human-to-human transmission (Zhang et al., 2020). Globally, COVID-19 has infected more than 3 billion individuals, accounting for approximately 44% of the world's population (Zhang, 2020).

Since the onset of the COVID-19 pandemic, a variety of pharmacological therapies have been developed and evaluated. The efficacy of multiple

drug classes—including antiviral agents, antibiotics, antimalarials, and immunomodulatory drugs—has undergone reassessment, with therapeutic effects varying across different viral strains. In addition to conventional therapies, researchers and clinicians have investigated herbal treatments as supportive or complementary therapies for COVID-19. Among these, Chinese herbal medicine (CHM) has been used in conjunction with modern antiviral agents to combat COVID-19 infections (Chien et al., 2022). The evolution of COVID-19 treatment strategies has also expanded to include non-pharmacological approaches, such as stem cell therapy. Numerous studies suggest that stem cell therapy can enhance survival rates and improve clinical outcomes in COVID-19 patients. However, a comprehensive

analysis of this approach remains lacking, with much of the current research limited to small patient samples and lacking adequate controls, complicating the derivation of definitive conclusions. Moreover, it is uncertain whether the observed effects in treatment groups can be attributed solely to stem cell administration, given that these therapies were often used concurrently with conventional treatments. Consequently, further research is necessary to thoroughly assess the efficacy and safety of stem cell therapy for COVID-19 (Choudhery & Harris, 2020).

This research will examine the progression of both standard and herbal treatments for COVID-19, offering a comparative analysis of their effectiveness. In addition, the potential of stem cells as an advanced therapeutic option for COVID-19 will be explored. This review aims to contribute valuable insights into the development of effective therapeutic strategies for COVID-19.

MATERIALS AND METHODS

This review was conducted by searching for the efficacy, safety indications, and recommendations for the use of recent pharmacological therapies, herbal medicine, and stem cell therapy for COVID-19 in two databases: PubMed (<https://pubmed.ncbi.nlm.nih.gov>) and ScienceDirect (<https://www.sciencedirect.com/>). The search utilized the following keywords: "COVID-19" AND "Herbal Medicine" OR "Stem Cell Therapy" OR "Recent Therapy" AND "Efficacy" OR "Safety."

The inclusion criteria for this review encompassed full-text literature and studies conducted within the last five years, specifically focusing on COVID-19 patients who received both standard and additional treatments. The types of studies included were *in silico* studies, experimental research (both *in vitro* and *in vivo*), and clinical trials. The exclusion criteria were limited to review articles that did not have an English version.

RESULTS AND DISCUSSION

Characteristics of viruses

COVID-19 is an RNA virus characterized by its envelope structure. Phylogenetically, the coronavirus responsible for COVID-19 belongs to the betacoronavirus group. A critical enzyme facilitating the virus's entry into host cells is the angiotensin-converting enzyme 2 (ACE2), which serves as a receptor (Zhou et al., 2020). In addition to ACE2, several receptor-binding domains are

essential for viral entry, including the transmembrane serine protease 2 (TMPRSS2) and the spike protein receptor-binding domain, as well as serum cell protease (Hoffmann et al., 2020).

The particle size of the coronavirus ranges from 60 to 140 nm (Zhu et al., 2020). The genome of 2019-nCoV, obtained from infected patients in Wuhan, was sequenced as part of an investigation into the outbreak's origins. Comparative genomic analysis revealed that several 2019-nCoV sequences were nearly identical to one another, showing greater genetic similarity to SARS-CoV than to the Middle East respiratory syndrome coronavirus (MERS-CoV). Subsequent research aimed to elucidate the origin of 2019-nCoV and its genetic relationship with other coronaviruses, confirming that it belongs to the betacoronavirus genus. Electron microscopy of 2019-nCoV filamentous particles revealed a spherical structure characterized by multiple polymorphisms, with diameters ranging from 60 to 140 nm. The spike protein, which is approximately 9 to 12 nm in size and present on the viral surface, imparts a distinctive crown-like appearance to the virus, thereby giving rise to its name (Zhu et al., 2020; Lu et al., 2020).

The pathogenesis of COVID-19 is closely linked to the virus's structural and genomic characteristics. Structural and non-structural proteins play crucial roles in viral entry. Key proteins involved in this process include four structural proteins: envelope protein (E), spike protein (S), nucleocapsid protein (N), and membrane protein (M). These proteins are encoded by messenger RNA (mRNA) components that do not participate in replication and transcription (Gennaro et al., 2020). Viral entry initiates with the spike protein (a glycoprotein located on the virus's surface), which binds to the host receptor, angiotensin-converting enzyme 2 (ACE2). Following this binding, the cellular protease transmembrane serine protease 2 (TMPRSS2) facilitates the virus's entry into host cells (Zhou et al., 2020).

Pathophysiology of COVID-19

SARS-CoV-2 attaches to nasal epithelial cells through its receptor, angiotensin-converting enzyme 2 (ACE2), and spreads via respiratory aerosols. The virus replicates and disseminates, infecting the hair cells of the respiratory tract and the upper respiratory system. This initial phase lasts several days, during which the immune response remains mild, and individuals may

remain asymptomatic. Despite the potential for a low viral load during this period, the infected person is still highly contagious, and a nasal swab test can detect the virus (Wan et al., 2020). As the infection progresses, symptoms such as fever, fatigue, and dry cough may emerge. Furthermore, approximately one-fifth of individuals with COVID-19 will advance to a more severe clinical state.

The initial stage of COVID-19 pathogenesis involves the entry of the virus into the host cell. The spike protein (S) facilitates the binding of the virus to host cells, allowing its entry, while the membrane (M), envelope (E), and nucleocapsid (N) proteins are essential for the assembly and release of viral particles (Xu et al., 2020). As noted previously, the angiotensin-converting enzyme 2 (ACE2) plays a crucial role in the successful attachment and penetration of the virus (Letko et al., 2020). This enzyme is expressed in various tissues, including the lungs, small intestine, kidneys, heart, thyroid, testes, and adipose tissue, indicating that the virus can directly infect a wide range of cells and organs, leading to symptoms in COVID-19-positive patients that extend beyond respiratory disorders (Li et al., 2020). Furthermore, although COVID-19 exhibits only a 72% amino acid sequence similarity to the first variant of SARS-CoV, it demonstrates a higher affinity for the ACE2 receptor than SARS-CoV itself (Chan et al., 2020; Chen et al., 2020).

After successfully attaching to the host, the virus spreads, leading to its entry into the host cell. Like other coronaviruses, COVID-19 requires the priming or cleavage of the spike protein (S) by host cell proteases, specifically transmembrane serine proteases, to activate membrane fusion. This process is primarily facilitated by TMPRSS2, which can also be assisted by cathepsin B/L (Hoffmann et al., 2020). In addition, SARS-CoV-2 is believed to possess a furin-like cleavage site within the spike protein domain, situated between the S1 and S2 subunits, a characteristic that distinguishes it from other coronaviruses (Coutard et al., 2020). The infection of respiratory epithelial cells by SARS-CoV-2 induces damage and cell death through various mechanisms, including pyroptosis, similar to the effects observed with other cytopathic viruses (Chen et al., 2019).

When a virus induces cell death, it releases molecules known as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which are recognized by pattern recognition receptors on alveolar macrophages and endothelial cells. Toll-

like receptors (TLRs) detect PAMPs in the extracellular environment, leading to the activation of transcription factors that promote the production of proinflammatory cytokines. Conversely, the nucleotide-binding domain leucine-rich repeat-containing protein (NLR) recognizes DAMPs produced intracellularly, activates the inflammasome, and converts pro-interleukin-1 into its active form, interleukin-1 (IL-1). The circulation of IL-1 induces local inflammation without causing systemic effects (Schnappauf et al., 2019; Soy et al., 2020).

This mechanism further enhances the release of proinflammatory cytokines and chemokines, including type II interferon (IFN- γ), monocyte chemoattractant protein 1 (MCP-1), interferon gamma-induced protein 10 (IP-10), and interleukin-6 (IL-6). Additionally, it triggers the activation of macrophages and dendritic cells. The subsequent release of these cytokines and chemokines also activates T lymphocytes, which play a crucial role in targeting and destroying virus-infected lung alveolar cells (Tian et al., 2019; Tay et al., 2020; Xu et al., 2020).

Furthermore, an antibody neutralization mechanism is activated to clear the virus from the body. Consequently, the severity of COVID-19 is correlated with elevated levels of various interleukins (such as IL-6, IL-2, IL-7, and IL-10), IP-10, MCP-1, IFN- γ , macrophage inflammatory protein 1 (MIP-1), granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor (TNF), along with a mixture of T helper type 1 (Th1) and T helper type 2 (Th2) responses (Huang, 2020; Tay, 2020). While these inflammatory cells and mediators attempt to eliminate the virus, their efforts are often ineffective, leading to prolonged inflammation and damage to lung tissue. The subsequent apoptosis of lung tissue cells results in the release of new virus particles from type 1 and type 2 pneumocytes. The loss of these pneumocytes leads to extensive alveolar damage, ultimately culminating in acute respiratory distress syndrome (ARDS) due to persistent interference with inflammatory cell sequestration and viral replication (Xu et al., 2020). Numerous studies have linked increasing levels of circulating proinflammatory cytokines and chemokines to disease severity and mortality (Ye et al., 2020).

Effects on organs of COVID 19 infection

The onset of a systemic illness characterized by multi-organ failure or damage is one of the critical features associated with the severity of

COVID-19. In this context, extrapulmonary involvement arises as a direct consequence of uncontrolled inflammation.

Respiratory System Damage

SARS-CoV-2 is a respiratory illness transmitted via aerosols or microscopic droplets, which can lead to pneumonia-like symptoms with or without oxygen deprivation. This transmission raises concerns regarding the infection of the alveoli—specifically the gas exchange structures and the type I and type II lung epithelial cells. Type I lung cells resemble traditional epithelial cells, while type II lung cells are smaller, cuboidal in shape, and contain organelles known as "flat body" that secrete pulmonary surfactant. Without this surfactant, the alveoli would collapse upon exhalation. Leukocytes, endothelial cells, and epithelial cells collectively contribute to maintaining alveolar homeostasis, with alveolar macrophages and epithelial cells serving as critical components of the lung's defense barrier (Ali et al., 2020).

During type II pneumococcal infection, interferons and other interleukin genes associated with antiviral responses are expressed more frequently than genes responsible for surfactant production. This immune communication recruits additional cells from circulation, such as neutrophils, and activates resident immune cells in the alveoli, such as macrophages. Infected cells produce high viral loads and initiate a form of cell death known as "pyroptosis," releasing numerous inflammatory mediators. This cascade of events accelerates the death of type I lung cells, leading to the infiltration of plasma proteins and cellular debris, ultimately rupturing the alveolar barrier. As the immune response-damaged alveoli begin to fill with a mixture of plasma exudate, dead cells, virus particles, inflammatory cells, and fibrin, the interstitial space between the capillaries and the alveoli expands. Consequently, gas exchange is impaired, and acute respiratory distress syndrome (ARDS), a related respiratory dysfunction, may eventually develop (Alon et al., 2021).

Central Nerve System

Numerous case studies of COVID-19 have identified neurological symptoms associated with the infection. A study involving 214 patients diagnosed with COVID-19 revealed that neurological symptoms were present in 36.4% of the cohort, increasing to 45.5% among those with severe cases (Mao et al., 2020). Reported

symptoms include headache, vertigo, confusion, seizures, ataxia, ageusia (loss of taste), altered smell perception (hyposmia/anosmia), and Guillain-Barré syndrome. In addition, alterations in taste or smell have been observed in 80% of individuals with mild to moderate COVID-19 (Niazkar et al., 2020; Toscano et al., 2020; Lechien, 2020). According to Vaira et al. (2020), the pathophysiology underlying the loss of taste and smell is thought to involve the rapid degradation of taste particles by sialic acid and subsequent damage to the olfactory bulb and olfactory neuron function. Autopsy findings of SARS-CoV infection have demonstrated the presence of the virus in the cerebrospinal fluid (CSF) and clear indications of cerebral invasion (Baig et al., 2020).

Gastrointestinal, Liver, and Pancreatic Manifestations

It has been extensively documented that the liver and gastrointestinal (GI) system play significant roles in the development of COVID-19. Common gastrointestinal symptoms associated with COVID-19 in both adults and children include diarrhea, nausea, vomiting, and abdominal pain. These symptoms are believed to result from SARS-CoV-2 infection in enterocytes, leading to dysfunction in the ileum and colon. Evidence of this infection is supported by the extraction of viral RNA from GI epithelial cells, confirming that SARS-CoV-2 can infect the GI tract (Cha et al., 2020).

Cardiovascular Complications

Patients with severe COVID-19 can exhibit significant cardiovascular damage, as evidenced by several investigations that report notable increases in traditional biomarkers of heart disease and failure, such as cardiac troponin and brain natriuretic peptide (BNP). Elevated levels of cardiac troponin are associated with increased levels of inflammatory markers, including C-reactive protein (CRP), ferritin, and interleukin-6 (IL-6). Furthermore, research has linked myocarditis and cardiomyopathy to conditions of hypoxia and respiratory failure observed in these patients (Guo et al., 2020).

Kidney Damage and Failure

Kidney damage, presenting in forms ranging from proteinuria and mild elevations in blood creatinine to acute kidney injury (AKI) and renal failure, represents a significant complication associated with both COVID-19 and cardiovascular damage. Initial studies report an ARI incidence of approximately 3–15% during infection. Among COVID-19 patients, AKI has emerged as a

prognostic marker for survival, affecting 20–40% of ICU patients who subsequently require renal replacement therapy (Cheng et al., 2020; Zhou et al., 2020).

Blood Clotting Changes

In severe COVID-19 infections, disseminated intravascular coagulation (DIC) and thrombotic events may arise, particularly within the pulmonary microvasculature, leading to pulmonary dysfunction. While the precise mechanisms remain unclear, the excessive release of proinflammatory cytokines is believed to play a critical role in coagulation activation. In this context, the cytokine storm induced by SARS-CoV-2 infection results in the release of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α). Additionally, SARS-CoV-2 infection leads to decreased levels of angiotensin-converting enzyme 2 (ACE2), resulting in elevated angiotensin II levels. Increased angiotensin II levels promote coagulation activation and inhibit the fibrinolytic system, contributing to a prothrombotic state associated with COVID-19. Notably, D-dimer, a byproduct of fibrin breakdown, is present in significantly higher concentrations in COVID-19 patients, particularly in severe cases. Elevated D-dimer levels are often observed early in the disease course and have been correlated with poorer prognoses; however, the underlying causes of these elevated D-dimer levels remain unclear (Rostami & Hasan, 2020; Yu et al., 2020; Lazzaroni et al., 2021).

Pharmacology Therapy Options.

As prevention has emerged as the most effective strategy against COVID-19, which has impacted the world for approximately three years, vaccination has been introduced as a critical intervention. Vaccination represents a pharmacological treatment approach aimed at improving individual health outcomes and alleviating the burden on healthcare systems (Chakraborty & Parve, 2020). In the management of COVID-19, antiviral and immunomodulatory agents are administered as part of the pharmacological treatment regimen, commonly referred to as conventional therapy

Antiviral

Antiviral medications interfere with the life cycle of the SARS-CoV-2 virus, effectively reducing viral load and inhibiting viral replication. This allows the immune system to better prepare to combat infections caused by the SARS-CoV-2 virus (Perazzolo et al., 2020). Classes of antiviral drugs utilized in the treatment of COVID-19 include

azithromycin, remdesivir, lopinavir/ritonavir, favipiravir, and ribavirin (Ali et al., 2020; Jean et al., 2020) (Table I).

Immunomodulators

Immunomodulatory drugs play a critical role in regulating the immune response. Numerous studies have demonstrated that SARS-CoV-2 infection can lead to progressive organ damage, particularly affecting the lungs. This damage is primarily attributed to an overactive immune response characterized by excessive levels of proinflammatory cytokines. Research indicates that such hyperinflammatory responses can trigger a cytokine storm, resulting in acute respiratory distress syndrome (ARDS), unchecked apoptosis, thrombosis, vascular leakage, and ultimately, mortality (Hertanto et al., 2021; Perazzolo et al., 2020). Various classes of immunomodulatory medications are employed in the management of COVID-19, particularly in cases exacerbated by cytokine storms. These include tocilizumab, baricitinib, interferon alpha-1a, statins, dexamethasone, famotidine, naproxen, colchicine, and melatonin (Rommasi et al., 2022) (Table II). By modulating cytokine levels, immunomodulators can help prevent the proinflammatory cytokine storms that lead to ARDS (Figure 1).

Herbal Medicine

Herbal medicines are industrially manufactured preparations that consist of pure, genuine, and naturally occurring active ingredients, unaltered by chemical processes. These products derive their therapeutic effects from various plant parts, including roots, rhizomes, stems, leaves, and flowers (Zheng & Navarro, 2015). The rising mortality rates, intersectoral impacts, and increased prevalence of comorbidities associated with COVID-19 have prompted researchers to seek potential drug candidates to combat this infection. For instance, antivirals such as remdesivir, ribavirin, and favipiravir—originally developed for influenza—have demonstrated positive effects against severe viral infections by inhibiting viral entry and replication (Kumar et al., 2021). However, the use of these antivirals is often accompanied by adverse side effects, including acute kidney injury, gastrointestinal disturbances, and fatigue (Izcovich et al., 2022). Other candidates, such as lopinavir, ritonavir, hydroxychloroquine, immunomodulators (Şimşek-Yavuz & Komsuoğlu, 2021; Soy et al., 2020), and interferon-beta, have not exhibited high efficacy and have failed to demonstrate beneficial effects on viral clearance and disease progression (Lauring & Malani, 2021).

Table I. The mechanism and side effects of administering antiviral in COVID-19

Drug	Work mechanism	Dose	Contraindications	Toxicity
Hydroxychloroquine (HCQ)	Disrupts the entry and exit of viruses from cells and inhibits viral protein synthesis.	400 mg b.i.d x 2, then 400mg q day for four days orally	Hypersensitivity to HCQ or cause impairment in the visual field.	Narrow therapeutic index; may cause QT interval prolongation, arrhythmias, bone marrow suppression, seizures, retinopathy, and myopathy.
Azithromycin (AZM)	Inhibits bacterial protein synthesis and exhibits some antiviral effects.	500 mg x 1, then 250 mg x 4 (5 days), orally	Myasthenia gravis; hypokalemia; hypomagnesemia; risk of Torsade de Pointes.	Prolonged QT interval.
Remdesivir	Adenosine analogue that induces early termination of viral synthesis by integrating into the virus genome.	200 mg x 1, followed by 100 mg x 9 (total of 10 doses), Intravenously (IV)	None specified.	Increased transaminase levels; potential for kidney injury.
Lopinavir (LPV)/ritonavir (RTV)	HIV protease inhibitor that inhibits HIV-1 maturation and infectivity; similar mechanism for SARS-CoV-2.	400/100 mg b.i.d x 10 days, orally	None specified.	GI intolerance, nausea, vomiting, pancreatitis, hepatotoxicity, cardiac conduction abnormalities
Favipiravir	Inhibits RNA-dependent polymerase (RdRp) of viral RNA causing chain termination.	RNA Dosage varies; adjustment necessary for renal and liver impairment, orally.	None specified.	Neutropenia, hyperuricemia, increased transaminase levels, diarrhea,
Ribavirin	Guanosine nucleoside analogue that inhibits RNA polymerase; induces chain breaker; resulting in defective viral progeny, referred to as "glitch catastrophes."	400 mg TID (>50 ml/min), acting as a 400 mg BID (50-30 ml/min), 200 mg daily patients (<30 ml/min) x 10 days, Orally	Pregnant women; men with pregnant partners;	anemia; teratogenic effects.

Table II. The mechanism and side effects of administering immunomodulators in COVID-19 (Rommasi et al., 2022)

Medicine name	Category	Mechanism of action of the drug	Side effects
Tocilizumab	IL-6 blocker from the humanized monoclonal antibody family	Binds to mIL-6R and soluble IL-6 receptor (SIL-6R) and blocks IL-6 from attaching to them, preventing an inflammatory response	Headache, hypertension, hepatotoxicity, injection-related reactions.
Baricitinib	Janus kinase 1/2 inhibitor family	Interferes with the downstream janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway and inhibits the synthesis of inflammatory factors (CRP, IL-6, erythrocyte sedimentation rate (ESR), and others)	Blurred vision, infection, cytopenia, nausea, thrombosis and shingles.
Interferon I-β1a	Immunomodulatory drugs	Increases cluster of differentiation (CD) 73 concentration in pulmonary capillaries, converting prothrombin and proinflammatory compounds into anti-inflammatory molecules	Headache, tense muscles, weakness.
Atorvastatin (as a member of the statins)	Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors of lipid-lowering drugs	Inhibits the production of isoprenoid and regulatory genes of inflammatory pathways	Headache, dizziness, feeling nauseous.
Dexamethasone	Corticosteroid immunomodulatory drugs	Acts as an anti-inflammatory corticosteroids and immunosuppressants	Psychosis, mood swings, cognitive dysfunction, and behavioural disorders.
Famotidine	Histamine-2 receptor antagonists	Prevents cytokine storms by blocking the production of histamine H2 and inflammatory factors	Headache, thrombocytopenia and dry mouth
Naproxen	Nonsteroidal anti-inflammatory drug	Inhibits cyclooxygenase (COX)-1 and COX-2 enzymes and reduces the synthesis of inflammatory molecules.	Headache, drowsiness, dizziness, and rash.
Colchicine	Anti-uric acid agent	Immunomodulates by anti-fibrotic and anti-inflammatory effects, inhibiting nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing (NLRP3)	Diarrhea, nausea, cramps, abdominal pain and vomiting.

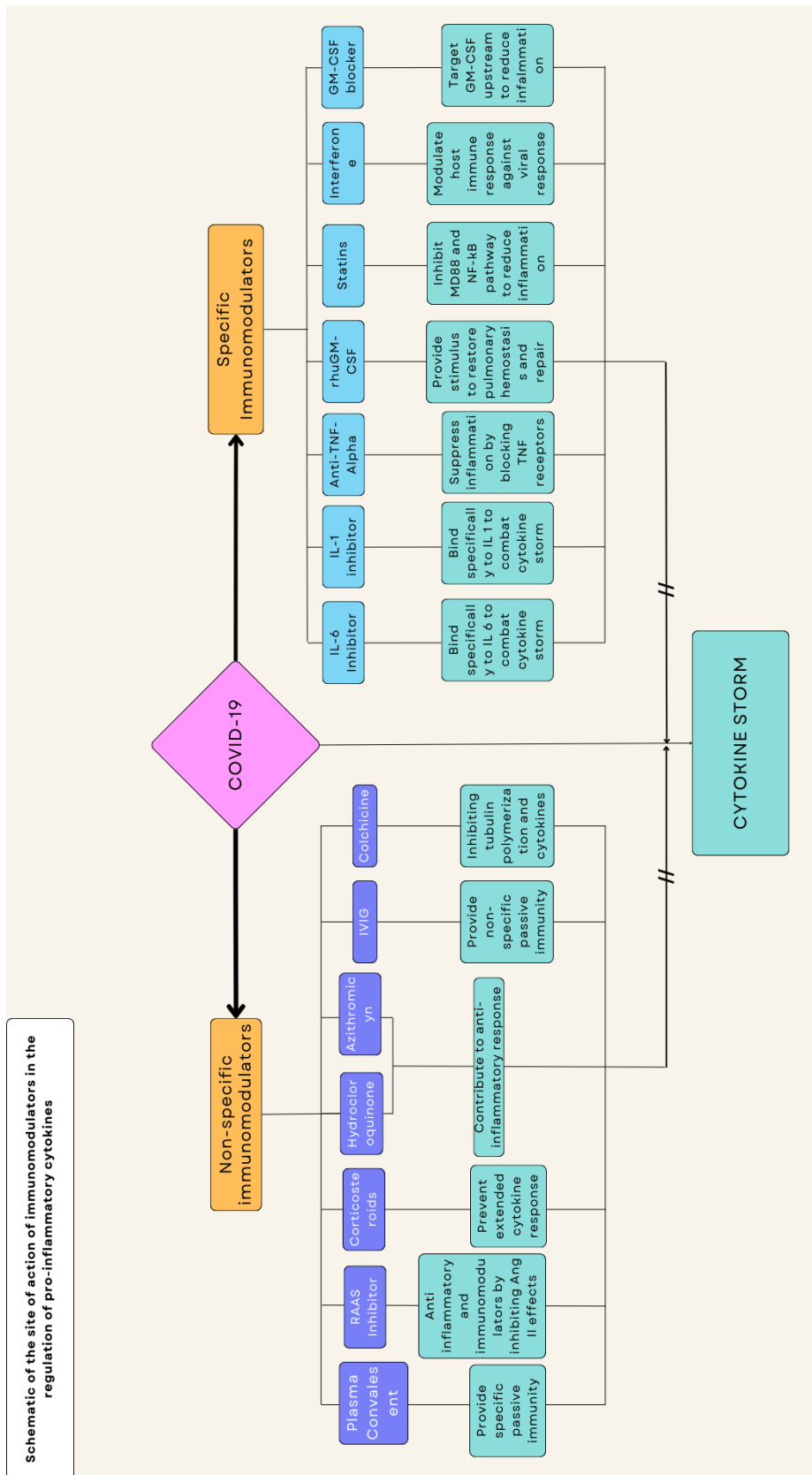


Figure. 1 Adapted version of the schematic of the site of action of immunomodulators in the regulation of proinflammatory cytokines (Rizk et al., 2020)

Due to the limited effectiveness and numerous side effects associated with conventional COVID-19 treatments, an increasing number of researchers and clinical practitioners are exploring the integration of traditional herbal medicines, which are already prevalent in communities, into the therapeutic management of COVID-19. The administration of herbal medicines is anticipated to enhance immunity and accelerate patient recovery. Compared to standard pharmaceuticals, herbal remedies are often regarded as highly efficacious, cost-effective, safer, and associated with fewer side effects. Traditional herbal medicine, particularly in Asia, has a long-standing history of therapeutic use and has gained significant traction in recent years (WHO, 2021; Liu, 2021). Furthermore, the public appears to have greater familiarity with herbal remedies than with generic medications. It is estimated that over 80,000 distinct species of herbal plants are utilized by nearly 80% of the global population, with 25,000 herbal extracts and formulations employed in daily practice throughout South Asia. The Food and Drug Administration (FDA) has patented hundreds of herbal remedies, which contain around 200,000 active metabolites (Liu et al., 2021). The utilization of natural remedies has surged during the pandemic. A cross-sectional study conducted in Peru found that among 1,747 participants, 80.2% reported using medicinal plants as a preventive measure. Of these, 71% indicated that they used herbal remedies to treat respiratory symptoms, while 24% reported using herbal medicine for two or more respiratory symptoms. Notably, the majority of individuals infected with COVID-19, particularly the elderly or those with relatives affected by the virus, have turned to herbal remedies (Liu, 2021).

Similar trends were observed in Europe, where Traditional Chinese Medicine (TCM) experienced a surge in demand during the early stages of the pandemic. A study conducted in Norway among complementary and alternative medicine (CAM) practitioners revealed that many advised their patients to use ginger and fish oil. Notably, over 40% of these practitioners reported that they would not refer COVID-19 patients to conventional medical doctors for treatment (Lin et al., 2022). In a cross-sectional study carried out in several Asian countries, including Vietnam, 249 out of 508 respondents (49%) reported using herbal remedies to alleviate the typical symptoms of COVID-19. The most commonly utilized herbs included honey, ginger (*Zingiber officinale* Rosc.),

perilla (*Perilla frutescens* (L.) Britt.), and garlic (*Allium sativum* L.), which are traditionally used to treat sore throat, cough, nasal congestion, and fever (Paudyal et al., 2020).

Mechanism of Action of Herbal Medicines

Several mechanisms of action have been identified for herbal medicines as potential therapies for COVID-19, encompassing antiviral, immunomodulatory, and anti-inflammatory properties. For example, Jinhua Qinggan Granule (JHQGG), a Traditional Chinese Medicine (TCM), acts by inhibiting the transcription and replication of the COVID-19 virus, as well as suppressing the release of interleukin-6 (IL-6), interferon-gamma (IFN- γ), immunomodulatory cytokines, and other pro-inflammatory mediators. Additionally, it inhibits the SARS-CoV 3CL protease and helicase enzymes (V'kovski et al., 2021). Other notable examples include *Lianhua Qingwen* Granule (LHQWG), *Xuanfei Baidu* Granule (XFBD), *Xuebijing* Injection (XBJ), *Qingfei Paidu* Decoction (QFPDD), and *Huashi Baidu* Granule (HSBD), all of which exhibit broad immunomodulatory and anti-inflammatory effects. These include the inhibition of Akt1 kinase, tumor necrosis factor-alpha (TNF- α), various interleukins (IL-6, IL-1 β , IL-10), IL-8 or chemokine C-X-C motif ligand (CXCL) 8, angiotensin-converting enzyme 2 (ACE2), mitogen-activated protein kinases (MAPK1, MAPK8), phosphoinositide-3-kinase-protein kinase B/Akt (PI3K-AKT), vascular endothelial growth factor A (VEGFA), caspase-3 (CASP3), and nuclear factor kappa B (NF- κ B) (Li et al., 2023; Li et al., 2021; Xu et al., 2021a). These herbal preparations also demonstrate efficacy against SARS-CoV-2 3CL protease and facilitate viral clearance, while exhibiting protective effects on various organs, including the reduction of organ damage, pulmonary fibrosis, and the risk of secondary infections (Paudyal et al., 2020; Cai et al., 2021).

The active metabolites found in Ayurveda demonstrate efficacy by inhibiting the angiotensin-converting enzyme 2 (ACE2) and the main protease (Mpro) activity, as indicated by in silico studies. Additionally, Ayurveda has the potential to inhibit RNA polymerase, although evidence regarding this mechanism of action remains limited (Gurung et al., 2020; Havranek & Islam, 2021). One of the most widely used Ayurvedic treatments for asymptomatic, mild, and moderate COVID-19 is *Kabasura Kudineer* (KSK). The components of KSK—such as chrysoeriol, 5-hydroxy-7,8-dimethoxyflavanone, magnoflorine, 6-methoxygenkwanin, vasicinone, quercetin,

scutellarein, tinosponone, cirsimaritin, chrysoeriol, and luteolin—are derived from plants including *Andrographis paniculata*, *P. adhatoda*, and *Costus speciosus*. These components exhibit strong binding affinities with the spike protein of SARS-CoV-2. Furthermore, preclinical studies in mice have demonstrated that *Justicia adhatoda* possesses anti-hypoxic properties and mitigates the severity of airway inflammation (Gheware et al., 2021).

Nilavembu Kudineer (NVK) is composed of nine herbal ingredients renowned for their anti-analgesic, anti-inflammatory, and antipyretic properties. One of its key constituents, *Andrographis paniculata*, exhibits immunomodulatory effects and alleviates symptoms associated with flu infections, attributed to its relatively high solubility and favorable pharmacodynamic characteristics (Enmozhi et al., 2020; Shirkande, 2022).

Ayurvedic Rasayana is a dietary supplement that demonstrates both immunomodulatory and antioxidant effects. Its primary constituents include *Asparagus racemosus*, *T. cordifolia*, and *Withania somnifera*. In silico studies have indicated that Rasayana inhibits the activity of protein S, Mpro, and RNA polymerase (Borse et al., 2021; Mahaboob et al., 2022).

Asgandh Safoof, an Unani herbal remedy derived from Arabic traditions, exhibits notable immunomodulatory effects. It is known to enhance CD4+ and CD8+ lymphocyte counts, as well as improve hematologic profiles, particularly platelet and white blood cell levels. In addition, *Asgandh Safoof* inhibits T cell proliferation and prevents SARS-CoV-2 entry by binding to the spike protein and ACE2 receptors (Balkrishna et al., 2020).

Efficacy and Safety

Numerous clinical studies, including case reports, case series, cohort studies, cross-sectional studies, and randomized controlled trials (RCTs), have demonstrated the efficacy and safety of traditional Asian herbal medicines in the prevention and treatment of COVID-19 (Table III).

Comparison of Conventional and Herbal Traditional Chinese Medicine (TCM)

A comprehensive analysis revealed that the *Qingfei Paidu* Decoction (QFPD) achieved a treatment response rate exceeding 90% when administered to 214 COVID-19 patients across four provinces in China (Xia et al., 2022). Numerous evidence-based investigations, both direct and

indirect, support the efficacy of QFPD in treating COVID-19 patients (Cao et al., 2020; Zhang et al., 2020). Notably, QFPD is the only traditional Chinese medicine (TCM) that has been demonstrated to be effective in managing COVID-19 across various stages, preventing the progression from mild to severe illness (Zhao et al., 2021; Zhong et al., 2020). In a retrospective multicenter trial involving 782 participants with mild to moderate COVID-19, early administration of QFPD was found to accelerate recovery, reduce the duration of hospitalization, and facilitate faster viral clearance.

Moreover, QFPD was associated with a 0.3% reduction in mortality, which is below the global average (Shi et al., 2020). A separate study by Xin et al. (2020) found that the combination of Western medicine and QFPD led to improved symptoms of COVID-19 and pneumonia. Additionally, research indicates that the concurrent use of QFPD with medications such as IFN- α , oseltamivir phosphate, chloroquine, arbidol, and ribavirin can shorten hospital stays, enhance clinical outcomes, and produce more favorable results on lung CT scans in COVID-19 patients (Hu et al., 2020; Yang et al., 2020). According to Zhang et al. (2021), QFPD administration is also associated with a reduction in mortality rates and does not increase the risk of organ damage. A study conducted in Hebei province, China, involving 76 COVID-19 patients demonstrated that QFPD could improve blood parameters and regulate clinical symptoms with minimal side effects (Rahaman et al., 2019; Li et al., 2022).

The administration of *Hua Shi Bai Du* granule (HSBD) has been shown to significantly decrease the likelihood of a patient's admission to the intensive care unit (ICU) and the need for artificial oxygen support. Combined with injections of three other Traditional Chinese Medicines (TCM) — *Xiyanping*, *Xuebijing*, and *Shenmai* — HSBD exhibits superior antiviral activity compared to standard Western medical approaches and is effective in mitigating lung inflammation (Wang et al., 2022). A separate study reported that HSBD alleviated clinical symptoms and reduced viral load in rat lung tissue by 30% (Li et al., 2020). Additionally, HSBD in conjunction with lopinavir-ritonavir therapy appears more effective than lopinavir-ritonavir monotherapy alone for COVID-19 treatment (Shi et al., 2021). Studies also indicate that HSBD enhances symptom relief, decreases disease severity, and lowers mortality rates in patients with severe COVID-19 infection (Pan et al., 2020; Liu et al., 2020).

Table III. Herbal Medicine Efficacy and Safety in COVID-19 Infection

Herbal medicine	Type of Study	Effectiveness of Efficacy	Side Effect
<i>Jinhua</i> granule (JHQGG)	Randomized controlled trial	Significantly reduces fever symptoms significantly faster, with a significant % recovery rate of 42.2%, and decreased inflammatory mediators IFN- γ and IL-6 (Kageyama et al., 2021; Liang et al., 2021b).	No noticeable side effects (An et al., 2021; Zhang et al., 2022).
<i>Lianhua</i> granule (UNWG)	Randomized controlled trial	Significantly improves symptoms of fever, muscle aches, sputum, chest tightness, breathing difficulties, nausea and vomiting, and appetite loss (Zeng et al., 2020; Li et al., 2020; Liang et al., 2021a).	Two adverse events reported (Zhang et al., 2022).
<i>Qingfei</i> decoction (QFPDD)	Randomized controlled trial	Reduces time to viral nucleic acid conversion and a reduction of the duration of hospitalization, and speeds up the recovery duration and reduces WBC, PCO ₂ , PO ₂ , AST, eGFR, CD3, CD4, and CD8 (Wang et al., 2021).	No severe side effects reported (Wang et al., 2021).
<i>Xuebijing</i> injection (XBJ)	Clinical trial	No notable difference in hospital stay duration, negative nucleic acid test time, cough, sputum, exhaustion, or diarrhea, but CT and viral conversion times were shorter in the XBJ group (Wang et al., 2021).	Incidence of adverse reactions (ADR) at 0.3%; no severe side effects (Wang et al., 2021).
<i>Kabasura Kudineer</i>	Randomized controlled trial	Accelerates recovery and viral conversion and improved CT values (Natarajan et al., 2021).	Two adverse events (nausea and diarrhea) reported (Natarajan et al., 2021).
<i>Nilavembu Kudineer</i>	Clinical trial	Promotes faster recovery and viral conversion and improved CT values value and clinical symptoms significantly compared to controls (Aarthi Velmurugan, 2021).	Two adverse events (nausea and diarrhea) reported (Aarthi Velmurugan, 2021).
<i>Rasayana</i> (<i>Guduchighana vati</i>)	Clinical trial	Faster COVID-19 RT-PCR conversion than conventional treatments; significant IL-6 reduction post-treatment in both groups.	No adverse reactions/events reported (Natarajan et al., 2021).
Herbal (ImmuActive™)	Clinical trial	Significantly decreases disease severity with a better therapeutic response than controls, although no virological activity was observed (Reddy et al., 2020).	No adverse effect reported (Reddy et al., 2020).

National treatment guidelines for severe and critical COVID-19 cases have recommended *Xuebijing* injection (XBJ), a proprietary Traditional Chinese Medicine (TCM) preparation derived from the traditional *Xuefu Zhuyu* decoction. Originally developed in 2003, XBJ was initially employed in managing diseases such as Ebola, MERS, dengue, and influenza (Tong et al., 2020). In a study monitoring 42 COVID-19 cases over a week, 60% of patients experienced improved lung function, resulting in shorter hospital stays and faster negative RT-PCR test results. Blood panel findings indicated an increase in white blood cells, neutrophils, platelets, and fibrinogen. In addition, levels of inflammatory markers, including IL-6, IL-10, CRP, and D-dimer, decreased post-treatment. In a comparative study, patients treated with XBJ alongside standard medication had a lower incidence of acute respiratory distress syndrome (ARDS) than those in the control group who received 0.9% NaCl with routine drug regimens (Tong et al., 2020).

Furthermore, *Xuebijing* injection (XBJ) has been shown to reduce the risk of septic shock and prevent progression to critical stages of illness. Clinical symptoms, including cough, fever, fatigue, and shortness of breath, resolved more swiftly in the XBJ-treated group compared to the control group, with the XBJ group also requiring less time in the ICU. Importantly, no cases of anaphylactic shock were reported, and significant reductions in inflammatory markers—IL-6, IL-8, and TNF—were observed. XBJ has also been noted to enhance pulmonary absorption in patients with pneumonia. In vitro studies demonstrated XBJ's protective effects on cells against viral-induced death, revealing a dose-dependent reduction in viral plaques and preservation of cellular morphology in treated cells compared to controls. A large-scale study involving 31,913 patients treated with XBJ reported a minimal incidence of side effects, with a probability of 0.3% (Xia et al., 2022).

Lianhua Qingwen (LHQW), a traditional Chinese medicine (TCM) available in both granule and capsule forms, has gained recognition for its antiviral and immunomodulatory effects. Originally utilized in China for managing SARS in 2002-2003, as well as influenza and other respiratory infections, LHQW was incorporated into China's COVID-19 treatment guidelines as an alternative therapy during the pandemic (Zhong et al., 2017). In a clinical study involving 245 COVID-19 patients, LHQW was shown to effectively relieve symptoms such as fever, cough, and fatigue, while also

reducing disease severity (Zhuang et al., 2020; Shen et al., 2021). Studies further indicate that substituting arbidol with LHQW can successfully treat pneumonia without significant adverse effects, with LHQW showing superior efficacy in fever reduction (Yu et al., 2020; Zeng et al., 2020). In a clinical retrospective study of 154 COVID-19 patients, those treated with LHQW exhibited higher symptom remission rates than the control group (Zeng et al., 2020). Another trial with 142 COVID-19 patients demonstrated significant improvements in lung CT scans and an increased recovery rate following a 14-day course of LHQW. Additionally, a combined treatment regimen of LHQW, *Huoxiang Zengqi*, and Western medicine has been reported to enhance the clinical outcomes of COVID-19 patients by improving both drug efficacy and prognosis (Xiao et al., 2020).

Jinhua Qinggan (JHQG), a Traditional Chinese Medicine (TCM), is widely employed in treating COVID-19 patients (Huang et al., 2021). In a clinical study involving 80 COVID-19 patients treated with JHQG, findings indicated a faster conversion to negative nucleic acid test results and reduced lung inflammation. Additionally, patients in the JHQG group showed significantly higher levels of leukocytes and granulocytes compared to the control group (Liu et al., 2020). Another study on the combined use of JHQG and Western medicine in treating 129 patients with mild COVID-19 reported notable improvements in symptoms such as fever, fatigue, and cough. However, gastrointestinal side effects, including diarrhea, were observed (Duan et al., 2011; Shah et al., 2022).

The *Shufeng Jiedu* capsule (SFJDC) demonstrates notable antiviral properties. In studies, SFJDC significantly decreased the nucleic acid expression of HCoV-229E and lowered the pulmonary index in mice lungs compared to the control group. It also reduced levels of inflammatory mediators such as IL-6, IL-10, TNF, and IFN in lung tissue, further supporting its established anti-inflammatory effects previously noted in cases of upper respiratory tract infections and influenza. Xu et al. (2021b) found that SFJDC effectively prevents or mitigates lymphopenia associated with COVID-19 by increasing the percentages of CD4+ and CD8+ T cells in peripheral blood relative to the model group. Additionally, SFJDC's bioactive components modulate 11 immune and inflammatory pathways, including PI3K-Akt, toll-like receptor, MAPK, ErbB, and NF- κ B signaling pathways (Tao et al., 2014). The antiviral efficacy of SFJDC is attributed to three key

bioactive compounds—polydatin, quercetin, and wogonin—which directly inhibit the Mpro enzyme (Xia et al., 2020; Li et al., 2017).

Bufei Huoxue (BFHX) has shown promising effects in patients recovering from COVID-19, supporting functional recovery, improving tolerance and endurance in physical activities, and enhancing rehabilitation outcomes. BFHX effectively alleviates cough and symptoms related to chronic obstructive pulmonary disease (COPD) while significantly improving lung function and pulmonary vascular hemodynamics. The treatment exerts therapeutic benefits by modulating several cytokines and signaling pathways, notably IL-6, MAPK8, and specific post-transcriptional genes. In addition, BFHX targets nuclear receptor coactivator 2 (NCOA2) and prostaglandin-endoperoxide synthases PTGS1 and PTGS2, which play key roles in its therapeutic mechanism (Chen et al., 2020).

Xiyanping (XYP), a Chinese herbal medicine, is widely used for treating pneumonia and respiratory infections, demonstrating notable efficacy in community-acquired pneumonia. Compared to traditional antibiotics and antiviral medications, XYP offers superior therapeutic outcomes, particularly through injection, which is both effective and safe. XYP treatment provides rapid symptom relief (such as fever and cough) and accelerates SARS-CoV-2 clearance when compared to standard supportive care. Additionally, XYP has been shown to reduce or prevent further disease progression relative to a placebo. Its excellent safety profile in COVID-19 patients is evident, as no significant side effects or complications have been reported (Chen et al., 2020).

For over 40 years, *Jiangyin* granules (JY) have been widely used to manage infectious diseases. Clinical applications have demonstrated JY's effectiveness in antiviral and anti-inflammatory therapies, solidifying its role as a valuable treatment option (Yong-Li et al., 2020).

Wang et al. (2021) suggest that *Jiangyin* granules (JY) may target the ACE gene, which SARS-CoV-2 utilizes to enter host cells. JY herbal extracts that inhibit CYP3A may alter the pharmacokinetics of drugs, such as licochalcone B and glycyrrhizin. The component *Radix Glycyrrhizae* inhibits SARS-CoV-2 by blocking IL-6 activation and can directly influence the IL-6/STAT3 pathway (Luo et al., 2020). Although JY may alleviate various symptoms—including fever, cough, fatigue, headache, sneezing, nasal discharge, throat irritation, muscle aches, chest discomfort, vomiting, bloating, and abdominal pain—its effects

do not appear significantly faster than those of a placebo. Minor side effects, such as diarrhea, are reported but not directly attributed to the treatment itself. As a result, JY is recommended primarily for mild COVID-19 cases (Zhang et al., 2022).

A randomized controlled trial (RCT) examined the effects of a mixture of traditional Chinese medicine (TCM) on chronic symptoms associated with SARS-CoV-2, including recurrent fever, chills, alternating fever, cough (with minimal or yellow phlegm), flatulence or constipation, shortness of breath, a red tongue, a greasy or burning yellow hairy tongue, and a rolling, rapid pulse. The proposed TCM combinations included *Kuxingren*, *Shengshigao*, *Gualou*, *Shengdahuang*, *Shengmahuang*, *Zhimahuang*, *Tinglizi*, *Taoren*, *Caoguo*, *Binglang*, and *Cangzhu*. Compared to conventional treatments, this combination was effective in reducing levels of IL-16 and TNF. Beyond addressing coughs, the herbal mixture demonstrated clinical efficacy in reducing lung heat, eliminating phlegm, alleviating chest pressure, lubricating the intestines, and promoting relaxation of the large intestine. Furthermore, it exhibited anti-inflammatory, antioxidant, and anticoagulant properties (Zhao et al., 2020).

Ayurveda Medicine

The Indian Ministry of Ayush has recommended homeopathic medications for the prophylaxis and treatment of COVID-19. Alongside conventional treatments, homeopathy is utilized as an adjunctive therapy (Rastogi et al., 2022). A randomized controlled trial (RCT) involving 320 patients with confirmed COVID-19 compared the efficacy of standard therapy—which included azithromycin, pantoprazole, calcium, montelukast/levocetirizine, zinc, and vitamins—against standard therapy combined with homeopathy. The most commonly prescribed homeopathic remedies included herbal mixtures such as *Arsenicum album*, *phosphorus*, and *Bryonia*. The results indicated that homeopathy significantly shortened the time to fever relief, thereby reducing the need for antipyretics. In addition, symptoms such as dyspnea, sputum production, fatigue, and headache resolved more rapidly in patients receiving supplemental homeopathy compared to those receiving standard care alone. This evidence suggests that the addition of homeopathy has led to a decreased dosage and duration of standard medication administration, as well as a reduction in the incidence of complications. No severe side effects were reported during the treatment (Panda

et al., 2022). Other RCTs demonstrated that Ayurvedic interventions, including *Giloy Ghanvati*, *Tinospora cordifolia*, *Swasari Ras*, *Ashwagandha*, *Withania somnifera*, *Tulsi Ghanvati*, and *Ocimum sanctum*, effectively decreased cytokine and inflammatory parameters such as serum hs-CRP, IL-6, and TNF compared to a placebo. Moreover, Ashwagandha was found to be as effective as hydroxychloroquine for COVID-19 chemoprophylaxis, with the added benefit of reducing mental stress in patients (Chopra et al., 2020; Thakar et al., 2022).

Polyherbal remedies from the Siddha medical system, such as NVK and KSK, have been employed as public health interventions for dengue and chikungunya, and more recently, for mild to moderate COVID-19. The NVK regimen, known for its antiviral activity and minimal toxicity, has effectively treated dengue fever and chikungunya (Jain et al., 2020). Research conducted by Natarajan et al. (2002) has demonstrated that NVK possesses antimicrobial, antipyretic, anti-inflammatory, and immunostimulant properties. KSK, which consists of 15 plants, is recognized for its antiviral effects and has shown safety in toxicity studies, as well as exhibiting antipyretic, anti-inflammatory, immunomodulatory, thrombolytic, and antibacterial properties (Parameswaran et al., 2021; Maurya et al., 2022b). In a randomized controlled trial (RCT), the combination treatment of NVK and CIC was found to accelerate recovery in patients. Notably, the results of the RT-PCR test for the NVK and KSK group on day 6 were negative, contrasting with the positive results observed in the control group.

KSK has demonstrated superior outcomes compared to NVK in terms of the time required for RT-PCR conversion to negative results. One study reported that 50% of patients receiving KSK along with standard therapy achieved negative RT-PCR values by the third day. Additionally, patients in the KSK group had the shortest hospital stays among the three treatment arms. Statistically significant differences in IL-6 indicators were observed between the Siddha therapy group and the placebo group throughout the trial, and no adverse effects were reported. When used in conjunction with allopathic treatment, both NVK and KSK exhibited good safety and efficacy in managing mild to moderate COVID-19 infections (Srivastava et al., 2021). Similar results were observed in a randomized controlled trial (RCT) involving the novel Ayurvedic formulations ZngiVir-H and Ayurcov, which were administered as adjuncts to

conventional therapy. In cases of mild to moderate COVID-19, these Ayurvedic remedies accelerated recovery by reducing the duration to negative RT-PCR results and swiftly alleviating symptoms such as cough, dyspnea, and fever in the intervention group compared to the control group. Importantly, no significant adverse effects were noted during the study (Sasidharan et al., 2022).

The Ayurvedic regimens *Sanshamani Vati*, *AYUSH Kadha*, and *Anu Taila* have been shown to enhance immunity while simultaneously reducing levels of pro-inflammatory cytokines such as IL-2, IL-4, IL-6, IL-10, IL-12, and GI markers. This was demonstrated in a non-randomized controlled study. Furthermore, the decline in COVID-19-related indicators, including CD3+, CD4+, and CD8+ cells, was less pronounced in patients receiving these Ayurvedic treatments compared to the control group. Collectively, these findings suggest an overall improvement in quality of life (QoL) for patients (Maurya et al., 2022a; Nesari et al., 2022).

A case study illustrates how the use of Ayurveda prior to COVID-19 infection accelerated the healing process in a patient. The individual had been utilizing Ayurvedic treatments for seven years to manage hypothyroidism, skin disorders, and sleep disturbances. His regimen included *Guggulutikta Ghrita*, *Kaishora Guggulu*, *Ekavimshatika Guggulu*, *Khadirarishta*, *Durvadi Taila/Nalpamaradi Taila*, and *Anu Taila*. Upon developing symptoms such as stomach pain, cough, fever, body aches, and loss of taste and smell, the patient found that Ayurveda facilitated a more rapid and safe recovery from COVID-19 compared to conventional pharmacological treatments, effectively preventing the condition from worsening even after experiencing a seven-day fever (Girija & Sivan, 2022; Reddy et al., 2020).

A clinical study involving 855 COVID-19-positive patients demonstrated that a combination of Ayurvedic treatments, specifically *Samshamni Vati* and *Kalmegh Vati* at a dosage of two 250 mg tablets each, coupled with 30 minutes of structured yoga, effectively reduced COVID-19 symptoms (Sharma et al., 2020).

Other Herbal Medicines

Persian medicine utilizes clinical experience and appropriate herbal treatments to prevent and treat microbiological infections and respiratory disorders. Some notable herbs include *Punica granatum* L., *Rheum palmatum* L., *Glycyrrhiza glabra* L., *N. sativa* L., *Althaea officinalis* L., *Zataria multiflora* Boiss., *Matricaria chamomilla* L., *Ziziphus racte* Mill., *Ficus carica* L., *Urtica dioica* L., and

Nepeta racteate Benth. These substances exhibit impressive profiles, demonstrating antioxidant, anti-inflammatory, antitussive, immunomodulatory, bronchodilator, antiviral, mucolytic, and anti-SARS-CoV activities. Compared to standard therapies, these herbs significantly shorten hospital stays, accelerate clinical improvement, and alleviate symptoms such as dry cough, fever, muscle pain, anorexia, and runny nose (Karimi et al., 2021).

Nigella sativa oil (NSO) is recognized for its immunomodulatory and antiviral properties, making it a potential treatment for COVID-19. A randomized controlled trial (RCT) demonstrated that NSO significantly improved recovery rates among mild COVID-19 patients by day 14, with nearly 62% of those treated with NSO showing recovery. The NSO-treated group also experienced an average recovery time that was about two days shorter than the control group. In addition, significant reductions in COVID-19 symptoms, including anosmia, runny nose, chills, and loss of appetite, were observed post-treatment, suggesting that *N. sativa* L. may help reduce inflammation (Koshak et al., 2020). Furthermore, NSO has demonstrated efficacy as a mucolytic agent, outperforming bromhexine, which is commonly used in bronchopulmonary infections (Mitjà et al., 2020; Skipper et al., 2020). Given these benefits, *N. sativa* L. may also offer therapeutic effects on autophagy dysfunction, oxidative stress, ischemia, and inflammation in various conditions, including diabetes, cardiovascular disease, and co-infections with bacterial and viral pathogens associated with COVID-19 (Koshak et al., 2020; Islam et al., 2021).

Nano-curcumin is recognized for its anti-inflammatory properties, particularly in modulating and decreasing the production of inflammatory cytokines such as IL-1 and IL-6. A study comparing the effects of curcumin to a placebo demonstrated that curcumin effectively inhibited the expression of several pro-inflammatory cytokines and chemokines, including IL-6, IL-10, TNF- α , and IL-12. By limiting cytokine storms, nano-curcumin has the potential to reduce mortality associated with severe inflammatory responses (Hamed et al., 2020).

Saliravira® is a herbal medicine formulated from a blend of ingredients, including *Glycyrrhiza glabra*, *Rheum palmatum*, *Echinacea purpurea*, *Hyssopus officinalis*, *Rosmarinus officinalis*, and *Panax ginseng*. It has emerged as a candidate for a new drug to combat COVID-19 due to its anti-

inflammatory, antiviral, and immune-boosting properties. This herbal combination is believed to enhance several biological pathways, notably improving the NF- κ B signaling pathway and the type 1 interferon pathway, while also suppressing the viral replication and infection processes in COVID-19 patients. Saliravira® has been shown to accelerate the relief of symptoms such as pain, sore throat, and muscle and joint pain. Clinically, it contributes to shortening treatment duration, preventing chronic complications, and reducing mortality rates among COVID-19 patients. Consequently, Saliravira® is recommended for both treatment and prophylaxis of COVID-19 (Ramazani et al., 2020).

Hyoscyamus niger is commonly utilized as a sedative and analgesic. Beyond this, it is traditionally used to address respiratory conditions like asthma and lung infections, as well as spasmodic coughs, stomach colic, and pain associated with intestinal worms (Alamgeer et al., 2018). Propolis, also known as bee glue, is a complex resinous substance produced by honey bees (*Apis mellifera*). One of its components, quercetin, has demonstrated the ability in vitro to inhibit protease enzymes of SARS-CoV-1 and MERS-CoV viruses and modulate the cellular unfolded protein response (UPR) (Polansky, 2020).

A randomized controlled trial (RCT) conducted in China combining *Hyoscyamus niger* and propolis demonstrated that these agents can alleviate symptoms such as runny nose, laryngeal irritation, fever, muscle aches, dry cough, sore throat, and fatigue. Additionally, propolis has shown potential to enhance lung vital capacity, significantly increase forced expiratory volume in one second (FEV1), elevate blood oxygen levels, and reduce proinflammatory cytokines (Forte et al., 2018). An in vitro antimicrobial study further indicated that propolis inhibits the growth of several bacterial pathogens, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, and *Moraxella catarrhalis* (Kosari et al., 2021).

Persian barley water (PBW), derived from *Hordeum vulgare*, has been recommended as a home remedy for systemic inflammatory disorders, particularly respiratory inflammation and related fevers. Barley is rich in nutrients such as selenium, tocotrienols, phytic acid, lutein, vitamin E, catechins, and vitamin C, which contribute to its anti-inflammatory, antioxidant, and immune-boosting properties. These compounds also support gastrointestinal and liver health, exhibit

anti-cancer effects, and reduce uric acid levels (Robles-Escajeda et al., 2013). In a randomized controlled trial by Tavakoli et al. (2022), PBW was shown to expedite hospital recovery, reduce fever, and rapidly balance inflammatory markers, including ESR, CRP, serum creatinine, and albumin. However, it had no significant effect on respiration rate, blood neutrophil count, cough, body pain, or oxygen saturation (Tavakoli et al., 2022).

Zufa syrup, a traditional Persian herbal remedy composed of various plant extracts—including *Nepeta bracteata*, *Ziziphus jujube*, *Adas*, *Cordia myxa*, *Papaver somniferum*, *Glycyrrhiza glabra*, *Lavender*, *Ficus carica*, *Adiantum capillus veneris*, *Viola*, *Viper's buglosses*, *Iris*, and sugar—is used to treat respiratory ailments. For patients exhibiting mild-to-moderate COVID-19 symptoms, Zufa syrup has shown promising effects. In a 10-day follow-up trial, all symptoms gradually resolved, with no patients requiring hospitalization or supplemental oxygen. Reported symptoms—such as myalgia, cough, headache, anorexia, anxiety, and insomnia—remained stable throughout the trial. Dyspnea intensity remained consistent until day 8 but was observed to be less severe in the placebo group by day 10. Oxygen saturation and heart rate maintained stable trends, and were similar across both intervention and control groups, with no adverse effects reported (Borujerdi et al., 2022).

Bio-shield Superfood (NBS), a natural and health-promoting herbal supplement, has shown promising effects in enhancing immune system functionality. It is enriched with essential vitamins—A, B1, B2, B3, B5, B6, B9, C, D, and K—and minerals, including calcium, iron, boron, copper, manganese, zinc, magnesium, potassium, phosphorus, and sulfur, as well as omega-3, -6, and -9 fatty acids. Research indicates that NBS significantly reduces levels of LDH, serum CRP, and ESR, underscoring its organ-protective benefits. Administered over a 14-hour period, NBS has been shown to lower CPK, a marker of cardiac muscle stress, and decrease SGOT and SGPT enzyme levels, which are indicators of liver health. Moreover, NBS demonstrates substantial anti-inflammatory effects, particularly in reducing inflammatory cytokines like IL-6 in COVID-19 infection, increasing blood oxygen levels, and mitigating lymphopenia post-infection (Mosadegh et al., 2020).

To support the treatment of COVID-19 patients in Vietnam, the herbal capsule medication Kovir was recently developed, drawing upon the

traditional Ren Shen Bai Du San formula. Kovir contains a blend of 12 herbal ingredients, including *Radix Bupleuri chinensis*, *Poria cocos*, *Radix et Rhizoma Glycyrrhizae*, *Radix Platycodi urantiara*, *Radix Codonopsis pilosulae*, *Radix Peucedani*, *Fructus urantia*, *Rhizoma Ligustici wallichii*, *Radix Angelicae pubescentis*, *Rhizoma et Radix Notopterygii*, *Rhizoma Zingiberis*, and *menthae herb*. Results from a randomized controlled trial (RCT) indicate that Kovir significantly reduced the duration of symptoms for patients with mild COVID-19, in comparison to a placebo. However, it did not yield significant differences in the neutrophil-to-lymphocyte ratio, total leukocyte count, or viral clearance (Mosadegh et al., 2020).

Recent Non-Pharmacological therapy Stem Cell-Based Therapy

The development of COVID-19 therapies has also expanded to include non-pharmacological approaches, such as stem cell therapy, which has garnered significant interest from clinicians. Stem cells are primarily utilized as immunomodulatory agents to mitigate inflammatory responses and help prevent cytokine storms. Historically, stem cells have been employed in the treatment of various conditions, including autoimmune diseases (Munir & McGettrick, 2016) and infectious diseases (Mezey & Nemeth, 2015).

Researchers are utilizing stem cells in COVID-19 treatment due to their regenerative capabilities, their ability to clear alveolar fluid, and their potential to reduce thrombotic events, among other therapeutic mechanisms (Jamshidi et al., 2021). Inflammatory modulation through stem cells involves the secretion of chemokines (such as CCL5, CXCL9, CXCL10, and CXCL11), as well as indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), transforming growth factor-beta (TGF- β), and prostaglandin E2 (PGE2). Mesenchymal stem cells (MSCs) play a key role in these processes. Additional mechanisms include inhibiting dendritic cell antigen maturation and presentation, promoting M2 macrophage activation, and suppressing cytokine storms (Wang et al., 2018; Arabpour et al., 2021).

Numerous studies have highlighted the potential of stem cells to enhance life expectancy, improve pulmonary health, and expedite recovery in COVID-19 patients. However, further research is still needed to fully understand these effects. Prior investigations have demonstrated that mesenchymal stem cells (MSCs) can convert mature dendritic cells (DCs) into a novel type of

Jagged-2-dependent DC regulator. The regulation of these DCs is immunosuppressive and plays a crucial role in maintaining immunological homeostasis (Liu et al., 2012). Notably, the extent of DC upregulation increased significantly following MSC treatment. In addition, MSC therapy was associated with reduced levels of tumor necrosis factor (TNF) and interleukin-10 (IL-10) in critically ill COVID-19 patients (Chen et al., 2022).

A study conducted in Beijing, China, divided participants into two groups: a control group and a stem cell therapy group. The results indicated that, within the stem cell therapy group, peripheral lymphocyte counts increased after 14 days. Furthermore, there was a notable reduction in hyperactive cytokine lymphocytes three days post-injection, followed by improvements in pulmonary function and overall health after the 14-day period (Xiong et al., 2021). Similar findings were reported in additional studies and systematic reviews conducted in China, which demonstrated a significant reduction in patient mortality. Importantly, no substantial differences in the incidence of side effects or severe adverse reactions were observed. However, it was noted that this therapy did not shorten the length of hospitalization for patients (Zhang et al., 2022).

Qu et al. (2020) reported findings consistent with these observations. Their study, which analyzed data from nine studies encompassing 200 patients, found no serious adverse events (SAEs) associated with mesenchymal stem cell (MSC) administration. Although some adverse events (AEs) were noted across several studies, all side effects resolved without complications. Additionally, the stem cell therapy group demonstrated a reduction in mortality rates, with 25% of patients experiencing fatal outcomes compared to 43% in the control group. However, despite these promising trends, the differences in mortality rates did not reach statistical significance, primarily due to methodological limitations that hindered the robustness of the evidence (Qu et al., 2020). These findings suggest that stem cell therapy could serve as a potential alternative treatment to enhance the clinical outcomes of COVID-19 patients.

However, it appears that current research on this topic is limited to a small sample size and lacks adequate control groups, making it difficult to draw definitive conclusions. Furthermore, it remains uncertain whether the observed effects in patients

were directly attributable to the administered stem cells, as these were provided to the treatment group concurrently with conventional therapy.

To thoroughly assess the efficacy and safety of stem cell therapies for COVID-19, it is essential to conduct multicenter studies that incorporate appropriate randomization, larger sample sizes, and suitable control groups, along with extended follow-up periods (Choudhery & Harris, 2020).

Suggestions and Recommendations for Using Recent COVID-19 Therapy

Based on the clinical studies conducted, the incorporation of herbal ingredients in the treatment and prevention of severe COVID-19 infections has shown satisfactory outcomes and appears promising as a complementary or adjuvant therapy to conventional treatments. Furthermore, the side effects reported in these studies were generally mild and, in some cases, not directly attributable to the administration of herbal remedies. Overall, the use of herbal medicines holds potential to enhance treatment efficacy compared to standard therapies alone.

Nonetheless, the use of herbal medicines necessitates careful consideration of potential side effects and interactions when used in conjunction with conventional therapies. Identifying the source of any adverse effects—whether they stem from herbal remedies, standard treatments, or their combination—remains challenging due to the limitations of current research findings. Additionally, long-term effects associated with these therapies have not been adequately studied. The definition of herbal medicines is broad and varies across regions and countries, which can lead to the distribution of herbal products lacking rigorous certification. Some of these products may not have undergone patenting, research, or oversight by local drug regulatory agencies, raising concerns about their safety and efficacy.

The same considerations apply to standard pharmacological therapies for COVID-19 patients. Even in clinical studies demonstrating the efficacy and safety of these conventional treatments, the administration of standard medications must adhere to established guidelines and be tailored to the individual patient's condition. This careful approach is crucial to prevent side effects that may worsen the current conditions experienced by patients with COVID-19 infection.

Clinical studies on mesenchymal stem cell (MSC) treatment for COVID-19 patients have indicated promising results, with minimal side effects. These findings position MSC therapy as a potential alternative for treating individuals with COVID-19. However, there are drawbacks associated with stem cell therapy, including the high costs associated with comprehensive and prolonged hospitalization, which can exceed those of conventional treatments. Consequently, careful consideration is necessary when selecting stem cell therapy as an option for COVID-19 treatment.

Suggestion

The combination of herbal medicines with standard pharmacological treatments necessitates careful monitoring of both clinical and side effects in patients. It is advisable to select herbal remedies supported by existing clinical studies and, whenever possible, to opt for those that are patented or recommended by local authorities. Regarding alternative stem cell therapy, meticulous consideration is essential due to the elevated costs associated with the treatment, which may be comparable to or even exceed those of conventional therapies, as well as the extended duration of hospitalization required.

CONCLUSION

Several of the latest treatment options for COVID-19, including pharmacological therapies, herbal medicines, and stem cell therapies, demonstrate significant efficacy and safety in addressing the active phase of the disease and preventing post-infection multi-organ damage. The mechanisms of action of these therapies primarily encompass antiviral effects, immunomodulation, organ protection, and anti-inflammatory properties. Notably, stem cell therapy appears particularly promising as a regenerative treatment for COVID-19, owing to its capacity to repair damaged lung tissue following the acute cytokine storm associated with the disease and its inherent antiviral properties. Consequently, these therapies hold substantial potential for effectively combating COVID-19 infection.

ACKNOWLEDGMENTS

The author wishes to express gratitude to our supervisor and mentor for their inspiration and guidance throughout the completion of this literature review.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this review.

REFERENCES

- Alamgeer, W., Asif, H., Sharif, A., Riaz, H., Bukhari, I. A., & Assiri, A. M. (2018). Traditional medicinal plants used for respiratory disorders in Pakistan: a review of the ethno-medicinal and pharmacological evidence. *Chinese Medicine*, *13*(1). <https://doi.org/10.1186/s13020-018-0204-y>
- Ali, M. J., Hanif, M., Haider, M. A., Ahmed, M. U., Sundas, F., Hirani, A., Khan, I. A., Anis, K., & Karim, A. H. (2020). Treatment Options for COVID-19: A Review. *Frontiers in Medicine*, *7*(480). <https://doi.org/10.3389/fmed.2020.00480>
- Alon, R., Sportiello, M., Kozlovski, S., Kumar, A., Reilly, E. C., Zarbock, A., Garbi, N., & Topham, D. J. (2020). Leukocyte trafficking to the lungs and beyond: lessons from influenza for COVID-19. *Nature Reviews. Immunology*, *21*, 49–64. <https://doi.org/10.1038/s41577-020-00470-2>
- An, X., Xu, X., Xiao, M., Min, X., Lyu, Y., Tian, J., Ke, J., Lang, S., Zhang, Q., Fan, A., Liu, B., Zhang, Y., Hu, Y., Zhou, Y., Shao, J., Li, X., Lian, F., & Tong, X. (2021). Efficacy of Jinhua Qinggan Granules Combined With Western Medicine in the Treatment of Confirmed and Suspected COVID-19: A Randomized Controlled Trial. *Frontiers in Medicine*, *8*. <https://doi.org/10.3389/fmed.2021.728055>
- Arabpour, E., Khoshdel, S., Tabatabaie, N., Akhgarzad, A., Zangiabadian, M., & Nasiri, M.J. (2021). Stem Cells Therapy for COVID-19: A Systematic Review and Meta-Analysis. *Frontiers in Medicine*, *8*. <https://doi.org/10.3389/fmed.2021.737590>
- Baig, A. M., Khaleeq, A., Ali, U., & Syeda, H. (2020). Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chemical Neuroscience*, *11*(7), 995–998. <https://doi.org/10.1021/acscchemneuro.0c00122>

- Balkrishna, A., Pokhrel, S., Singh, J., & Varshney, A. (2020). Withanone from *Withania somnifera* May Inhibit Novel Coronavirus (COVID-19) Entry by Disrupting Interactions between Viral S-Protein Receptor Binding Domain and Host ACE2 Receptor. *Research Square*. <https://doi.org/10.21203/rs.3.rs-17806/v1>
- Borse, S., Joshi, M., Saggam, A., Bhat, V., Walia, S., Marathe, A., Sagar, S., Chavan-Gautam, P., Girme, A., Hingorani, L., & Tillu, G. (2021). Ayurveda botanicals in COVID-19 management: An in silico multi-target approach. *PLoS ONE*, *16*(6), e0248479. <https://doi.org/10.1371/journal.pone.0248479>
- Borujerdi, R., Adeli, S., Mohammadbeigi, A., Aliasl, F., Asghari, A., Hormati, A., Dehnavi, H., Hoseini, F., & Asghari, M. (2022). Effects of Iranian Polyherbal Syrup (Zufa syrup) on oxygen saturation and clinical symptoms in suspected patients with COVID-19: a triple-blinded, randomized, placebo-controlled trial. *Medical Gas Research*, *12*(2), 44–50. <https://doi.org/10.4103/2045-9912.325991>
- Cai, Y., Zeng, M., & Chen, Y.Z. (2021). The pharmacological mechanism of Huashi Baidu Formula for the treatment of COVID-19 by combined network pharmacology and molecular docking. *Annals of Palliative Medicine*. *10*(4), 3864–95.
- Cao, P., Wu, S., Wu, T., Deng, Y., Zhang, Q., Wang, K., & Zhang, Y. (2020). The important role of polysaccharides from a traditional Chinese medicine-Lung Cleansing and Detoxifying Decoction against the COVID-19 pandemic. *Carbohydrate Polymers*, *240*, 116346. <https://doi.org/10.1016/j.carbpol.2020.116346>
- Cha, M. H., Regueiro, M., & Sandhu, D. S. (2020). Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. *World Journal of Gastroenterology*, *26*(19), 2323–2331. <https://doi.org/10.3748/wjg.v26.i19.2323>
- Chan, J. F.-W., Kok, K.-H., Zhu, Z., Chu, H., To, K. K.-W., Yuan, S., & Yuen, K.-Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*, *9*(1), 221–236. <https://doi.org/10.1080/22221751.2020.1719902>
- Chakraborty, R., & Parvez, S. (2020). COVID-19: An overview of the current pharmacological interventions, vaccines, and clinical trials. *Biochemical pharmacology*, *180*, 114184. <https://doi.org/10.1016/j.bcp.2020.114184>
- Chen, I.-Yin., Moriyama, M., Chang, M.-F., & Ichinohe, T. (2019). Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome. *Frontiers in Microbiology*, *10*. <https://doi.org/10.3389/fmicb.2019.00050>
- Chen, L., Qu, J., Kalyani, F. S., Zhang, Q., Fan, L., Fang, Y., Li, Y., & Xiang, C. (2022). Mesenchymal stem cell-based treatments for COVID-19: status and future perspectives for clinical applications. *Cellular and molecular life sciences: CMLS*, *79*(3), 142. <https://doi.org/10.1007/s00018-021-04096-y>
- Chen, Y., Guo, Y., Pan, Y., & Zhao, Z. J. (2020). Structure analysis of the receptor binding of 2019-nCoV. *Biochemical and Biophysical Research Communications*, *525*(1). <https://doi.org/10.1016/j.bbrc.2020.02.071>
- Chen, Y., Liu, C., Wang, T., Qi, J., Jia, X., Zeng, X., Bai, J., Lu, W., Deng, Y., Zhong, B., He, W., Xing, Y., Lian, Z., Zhou, H., Yan, J., Yang, X., Yu, H., Zhou, J., Zhou, D., & Qiu, L. (2022). Efficacy and safety of Bufeì Huoxue capsules in the management of convalescent patients with COVID-19 infection: A multicentre, double-blind, and randomised controlled trial. *Journal of Ethnopharmacology*, *284*, 114830–114830. <https://doi.org/10.1016/j.jep.2021.114830>
- Cheng, Y., Luo, R., Wang, K., Zhang, M., Wang, Z., Dong, L., Li, J., Yao, Y., Ge, S., & Xu, G. (2020). Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney International*, *97*(5). <https://doi.org/10.1016/j.kint.2020.03.005>
- Chien, T.-J., Liu, C.-Y., Chang, Yuan-I., Fang, C.-J., Pai, J.-H., Wu, Y.-X., & Chen, S.-W. (2022). Therapeutic effects of herbal-medicine combined therapy for COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Frontiers in Pharmacology*, *13*, 950012. <https://doi.org/10.3389/fphar.2022.950012>

- Chopra, A., Srikanth, N., & Patwardhan, B. (2020). Withania somnifera as a safer option to hydroxychloroquine in the chemoprophylaxis of COVID-19: Results of interim analysis. *Complementary Therapies in Medicine*, 62, 102768.
- Choudhery, M. S., & Harris, D. T. (2020). Stem cell therapy for COVID-19: Possibilities and challenges. *Cell Biologi International*, 44(11), 2182–2191. <https://doi.org/10.1002/cbin.11440>
- Coutard, B., Valle, C., de Lamballerie, X., Canard, B., Seidah, N. G., & Decroly, E. (2020). The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Research*, 176(176), 104742. <https://doi.org/10.1016/j.antiviral.2020.104742>
- Duan, Z. P., Jia, Z. H., Zhang, J., Liu, S., Chen, Y., Liang, L. C., Zhang, C. Q., Zhang, Z., Sun, Y., Zhang, S. Q., Wang, Y. Y., & Wu, Y. L. (2011). Natural herbal medicine Lianhuaqingwen capsule anti-influenza A (H1N1) trial: a randomized, double blind, positive controlled clinical trial. *Chinese medical journal*, 124(18), 2925–2933.
- Enmozhi, S. K., Raja, K., Sebastine, I., & Joseph, J. (2021). Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. *Journal of biomolecular structure & dynamics*, 39(9), 3092–3098. <https://doi.org/10.1080/07391102.2020.1760136>
- Forte, G. C., da Silva, D. T. R., Hennemann, M. L., Sarmiento, R. A., Almeida, J. C., & de Tarso Roth Dalcin, P. (2018). Diet effects in the asthma treatment: A systematic review. *Critical Reviews in Food Science and Nutrition*, 58(11), 1878–1887. <https://doi.org/10.1080/10408398.2017.1289893>
- Gennaro, F. Di, Pizzol, D., Marotta, C., Antunes, M., Racialbuto, V., Veronese, N., & Smith, L. (2020). Coronavirus Diseases (COVID-19) Current Status and Future Perspectives : A Narrative Review. *International Journal of Environmental Research and Public Health*, 17(2690), 1–11.
- Gheware, A., Dholakia, D., Kannan, S., Panda, L., Rani, R., Pattnaik, B. R., Jain, V., Parekh, Y., Enayathullah, M. G., Bokara, K. K., Subramanian, V., Mukerji, M., Agrawal, A., & Prasher, B. (2021). Adhatoda Vasica attenuates inflammatory and hypoxic responses in preclinical mouse models: potential for repurposing in COVID-19-like conditions. *Respiratory research*, 22(1), 99. <https://doi.org/10.1186/s12931-021-01698-9>
- Girija, P. L. T., & Sivan, N. (2022). Ayurvedic treatment of COVID-19/SARS-CoV-2: A case report. *Journal of Ayurveda and Integrative Medicine*, 13(1), 100329. <https://doi.org/10.1016/j.jaim.2020.06.001>
- Guo, H., Zheng, J., Huang, G., Xiang, Y., Lang, C., Li, B., Huang, D., Sun, Q., Luo, Y., Zhang, Y., Huang, L., Fang, W., Zheng, Y., & Wan, S. (2020). Xuebijing injection in the treatment of COVID-19: A retrospective case-control study. *Annals of Palliative Medicine*, 9(5), 3235–3248. <https://doi.org/10.21037/apm-20-1478>
- Gurung, A. B., Ali, M. A., Lee, J., Abul Farah, M., & Al-Anazi, K. M. (2020). In silico screening of FDA approved drugs reveals ergotamine and dihydroergotamine as potential coronavirus main protease enzyme inhibitors, *Saudi Journal of Biological Sciences*, vol 27(10), pp2674-2682. <https://doi.org/10.1016/j.sjbs.2020.06.005>
- Havranek, B., & Islam, S. M. (2021). An in silico approach for identification of novel inhibitors as potential therapeutics targeting COVID-19 main protease, *Journal of Biomolecular Structure and Dynamics*, 39(12), pp4304-4315. <https://doi.org/10.1080/07391102.2020.1776158>
- Hertanto, D. M., Wiratama, B. S., Sutanto, H., & Wungu, C. D. K. (2021). Immunomodulation as a Potent COVID-19 Pharmacotherapy: Past, Present and Future. *Journal of inflammation research*, 14, 3419–3428. <https://doi.org/10.2147/JIR.S322831>
- Hu, G. M., He, C. X., Sun, Q. L., Wan, B. B., Li, Y. B., and Gao, J. Y. (2020). Preliminary Study on Clinical Efficacy of “Qingfei Paidu Granule” in Treating Coronavirus Disease 2019. *Tianjin J. Tradit. Chin. Med.*, 37 (9), 999–1004.
- Hu, B., Huang, S., & Yin, L. (2021). The cytokine storm and COVID-19. In *Journal of Medical Virology*, 93(1), 250–256. <https://doi.org/10.1002/jmv.26232>

- Huang, K., Zhang, P., Zhang, Z., Youn, J. Y., Wang, C., Zhang, H., & Cai, H. (2021). Traditional Chinese Medicine (TCM) in the treatment of COVID-19 and other viral infections: Efficacies and mechanisms. *Pharmacology & therapeutics*, 225, 107843. <https://doi.org/10.1016/j.pharmthera.2021.107843>
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*, 395(10223), 497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2), 271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>
- Islam, M. N., Hossain, K. S., Sarker, P. P., Ferdous, J., Hannan, M. A., Rahman, M. M., Chu, D. T., & Uddin, M. J. (2021). Revisiting pharmacological potentials of *Nigella sativa* seed: A promising option for COVID-19 prevention and cure. *Phytotherapy Research*, 35(3), 1329–1344. <https://doi.org/10.1002/ptr.6895>
- Izcovich, A., Siemieniuk, R. A., Bartoszko, J. J., Ge, L., Zeraatkar, D., Kum, E., Qasim, A., Khamis, A. M., Rochwerg, B., Agoritsas, T., Chu, D. K., McLeod, S. L., Mustafa, R. A., Vandvik, P., dan Brignardello-Petersen, R. (2022). Adverse effects of remdesivir, hydroxychloroquine and lopinavir/ritonavir when used for COVID-19: systematic review and meta-analysis of randomised trials. *BMJ open*, 12(3). <https://doi.org/10.1136/bmjopen-2020-048502>
- Jain, J., Kumar, A., Narayanan, V., Ramaswamy, R. S., Sathiyarajewaran, P., Shree Devi, M. S., Kannan, M., & Sunil, S. (2020). Antiviral activity of ethanolic extract of *Nilavembu Kudineer* against dengue and chikungunya virus through in vitro evaluation. *Journal of Ayurveda and integrative medicine*, 11(3), 329–335. <https://doi.org/10.1016/j.jaim.2018.05.006>
- Jamshidi, E., Babajani, A., Soltani, P., & Niknejad, H. (2021). Proposed Mechanisms of Targeting COVID-19 by Delivering Mesenchymal Stem Cells and Their Exosomes to Damaged Organs. *Stem cell reviews and reports*, 17(1), 176–192. <https://doi.org/10.1007/s12015-020-10109-3>
- Jean, S. S., Lee, P. I., & Hsueh, P. R. (2020). Treatment options for COVID-19: The reality and challenges. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi*, 53(3), 436–443. <https://doi.org/10.1016/j.jmii.2020.03.034>
- Kageyama, Y., Aida, K., Kawauchi, K., Morimoto, M., Ebisui, T., Akiyama, T., dan Nakamura, T. (2021). Jinhua Qinggan granule, a Chinese herbal medicine against COVID-19, induces rapid changes in the neutrophil/lymphocyte ratio and plasma levels of IL-6 and IFN- γ : An open-label, single-arm pilot study. *World Academy of Sciences Journal*, 4(1), 1-8. <https://doi.org/10.3892/wasj.2021.137>
- Karimi, M., Zarei, A., Soleymani, S., Jamalimoghadamsiahkali, S., Asadi, A., Shati, M., Jafari, M., Rezadoost, H., Kordafshar, G., Naghizadeh, A., Mardi, R., Namiranian, P., Khamechi, S. P., Ansari, N., Adel Mehraban, M. S., Aliakbarzadeh, H., Khanavi, M., Esmaealzadeh, N., Moravveji, A., ... Zargarani, A. (2021). Efficacy of Persian medicine herbal formulations (capsules and decoction) compared to standard care in patients with COVID-19, a multicenter open-labeled, randomized, controlled clinical trial. *Phytotherapy Research*, 35(11), 6295–6309. <https://doi.org/10.1002/ptr.7277>
- Kosari, M., Nouredini, M., Khamechi, S. P., Najafi, A., Ghaderi, A., Sehat, M., & Banafshe, H. R. (2021). The effect of propolis plus *Hyoscyamus niger* L. methanolic extract on clinical symptoms in patients with acute respiratory syndrome suspected to COVID-19: A clinical trial. *Phytotherapy Research*, 35(7), 4000–4006. <https://doi.org/10.1002/ptr.7116>
- Koshak, A. E., Koshak, E. A., Mobeireek, A. F., & Badawi, M. A. (2020). *Nigella sativa* for the treatment of COVID-19: An open-label randomized controlled clinical trial. *Complementary Therapies in Medicine*, 61, 102769. <https://doi.org/10.1016/j.jmii.2020.03.034>

- Kumar, D., Kumar, A., Kumar, V., Poyoja, R., dan Ghosh, A. (2021). Agra: An Old Cluster Facing the New Competition, *Environmental Pollution Journal*, 274, 1-10. <https://www.sciencedirect.com/science/article/abs/pii/S0305750X99000704>
- Lauring, A. S., & Malani, P. N. (2021). Variants of SARS-CoV-2. *AMA - Journal of the American Medical Association*, 326(9), 880. <https://doi.org/10.1001/jama.2021.14181>
- Lazzaroni, M. G., Piantoni, S., Masneri, S., Garrafa, E., Martini, G., Tincani, A., Andreoli, L., & Franceschini, F. (2021). Coagulation dysfunction in COVID-19: The interplay between inflammation, viral infection and the coagulation system. *Blood reviews*, 46, 100745. <https://doi.org/10.1016/j.blre.2020.100745>
- Lechien, J. R., Chiesa-Estomba, C. M., De Siati, D. R., Horoi, M., Le Bon, S. D., Rodriguez, A., Dequanter, D., Blecic, S., El Afia, F., Distinguin, L., Chekkoury-Idrissi, Y., Hans, S., Delgado, I. L., Calvo-Henriquez, C., Lavigne, P., Falanga, C., Barillari, M. R., Cammaroto, G., Khalife, M., Leich, P., ... Saussez, S. (2020). Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, 277(8), 2251-2261. <https://doi.org/10.1007/s00405-020-05965-1>
- Letko, M., Marzi, A., & Munster, V. (2020). Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature microbiology*, 5(4), 562-569. <https://doi.org/10.1038/s41564-020-0688-y>
- Li, C., Li, Y., Zhang, H., Zhuo, Y., Zhang, L., Yang, L., Gao, Q., Tu, Z., Shao, R., Wang, Y., Zhang, J., Cui, L., & Zhang, S. (2023). Xuanfei Baidu Decoction suppresses complement overactivation and ameliorates IgG immune complex-induced acute lung injury by inhibiting JAK2/STAT3/SOCS3 and NF- κ B signaling pathway. *Phytomedicine*, 109, 154551. <https://doi.org/10.1016/j.phymed.2022.154551>
- Li, L. C., Zhang, Z. H., Zhou, W. C., Chen, J., Jin, H. Q., Fang, H. M., Chen, Q., Jin, Y. C., Qu, J., & Kan, L. D. (2020). Lianhua Qingwen prescription for Coronavirus disease 2019 (COVID-19) treatment: Advances and prospects. *Biomedicine & pharmacotherapy*, 130, 110641. <https://doi.org/10.1016/j.biopha.2020.110641>
- Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K. S. M., Lau, E. H. Y., Wong, J. Y., Xing, X., Xiang, N., Wu, Y., Li, C., Chen, Q., Li, D., Liu, T., Zhao, J., Li, M., Tu, W., ... Feng, Z. (2020). Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *The New England Journal of Medicine*, 382(13), 1199-1207. <https://doi.org/10.1056/NEJMoa2001316>
- Li, Q., Wang, H., Li, X., Zheng, Y., Wei, Y., Zhang, P., Ding, Q., Lin, J., Tang, S., Zhao, Y., Zhao, L., & Tong, X. (2020). The role played by traditional Chinese medicine in preventing and treating COVID-19 in China. *Frontiers of Medicine*, 14(5). <https://doi.org/10.1007/s11684-020-0801-x>
- Li, Y., Chang, N., Han, Y., Zhou, M., Gao, J., Hou, Y., Jiang, M., Zhang, T., & Bai, G. (2017). Anti-inflammatory effects of Shufengjiedu capsule for upper respiratory infection via the ERK pathway. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, 94, 758-766. <https://doi.org/10.1016/j.biopha.2017.07.118>
- Li, Y., Li, B., Wang, P., & Wang, Q. (2021). Traditional Chinese Medicine, Qingfei Paidu Decoction and Xuanfei Baidu Decoction, Inhibited Cytokine Production via NF- κ B Signaling Pathway in Macrophages: Implications for Coronavirus Disease 2019 (COVID-19) Therapy. *Frontiers in pharmacology*, 12, 722126. <https://doi.org/10.3389/fphar.2021.722126>
- Li, Y., Yu, W., Zhai, J., Wang, K., Huo, H., & Du, Z. (2022). The efficacy of combined therapy of qingfeiPaidu capsule and lianhuaqingwen capsule nursing interventions for hospitalized patients with COVID-19: A retrospective study of medical records. *Medicine (United States)*, 101(32), E29964. <https://doi.org/10.1093/med/kaab322>

- <https://doi.org/10.1097/MD.00000000000029964>
- Li, G. Q., Zhao, J., Tu, Z. T., Li, J. B., Liu, Q. Q., Shi, L. Q., Miao, Q., Yuan, H. Q., Liu, X. Q., Long, Y. Y., Liu, Z. G., Zhao, T., Li, L., Tant, Q. H., He, Y. C., Bian, Y. J., & Hu, J. Q. (2013). Treating influenza patients of wind-heat affecting Fei syndrome by jinhua qinggan granule: a doubleblinded randomized control trial. *Chinese journal of integrated traditional and Western medicine*, 33(12), 1631–1635.
- Liang, C., Hui, N., Liu, Y., Qiao, G., Li, J., Tian, L., Ju, X., Jia, M., Liu, H., Cao, W., Yu, P., Li, H., & Ren, X. (2021). Insights into forsythia honeysuckle (Lianhuaqingwen) capsules: A Chinese herbal medicine repurposed for COVID-19 pandemic. *Phytomedicine plus: international journal of phytotherapy and phytopharmacology*, 1(2), 100027. <https://doi.org/10.1016/j.phyplu.2021.100027>
- Liang, S.-B., Zhang, Y.-Y., Fang, M., Liang, C.-H., Lan, H.-D., Shen, C., Yan, L.-J., Hu, X.-Y., Han, M., Robinson, N., & Liu, J.-P. (2021). Therapeutic effects and safety of oral Chinese patent medicine for COVID-19: A rapid systematic review and meta-analysis of randomized controlled trials. *European Journal of Integrative Medicine*, 60, 101979–101979. <https://doi.org/10.1016/j.eujim.2021.101979>
- Lin, Y., Cai, C. Z., Alias, H., Wong, L. P., & Hu, Z. (2022). A cross-sectional survey of self-medication with Traditional Chinese Medicine for treatment and prevention of COVID-19. *Complementary therapies in medicine*, 71, 102898. <https://doi.org/10.1016/j.ctim.2022.102898>
- Liu C. X. (2021). Overview on development of ASEAN traditional and herbal medicines. *Chinese herbal medicines*, 13(4), 441–450. <https://doi.org/10.1016/j.chmed.2021.09.02>
- Liu, X., Qu, X., Chen, Y., Liao, L., Cheng, K., Shao, C., Zenke, M., Keating, A., & Zhao, R. C. H. (2012). Mesenchymal Stem/Stromal Cells Induce the Generation of Novel IL-10–Dependent Regulatory Dendritic Cells by SOCS3 Activation. *The Journal of Immunology*, 189(3), 1182–1192. <https://doi.org/10.4049/jimmunol.1102996>
- Liu, Z., Li, X., Gou, C., Li, L., Luo, X., Zhang, C., Zhang, Y., Zhang, J., Jin, A., Li, H., Zeng, Y., Li, T., & Wang, X. (2020). Effect of Jinhua Qinggan granules on novel coronavirus pneumonia in patients. *Journal of Traditional Chinese Medicine = Chung I Tsa Chih Ying Wen Pan*, 40(3), 467–472. <https://doi.org/10.19852/j.cnki.jtcm.2020.03.016>
- Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Chen, J., ... Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, 395(10224), 565–574. [https://doi.org/10.1016/s0140-6736\(20\)30251-8](https://doi.org/10.1016/s0140-6736(20)30251-8)
- Luo, W., Ding, R., Guo, X., Zhan, T., Tang, T., & Fan, R. (2020). Clinical data mining reveals Gancao-Banxia as a potential herbal pair against moderate COVID-19 by dual binding to IL-6/STAT3. *Computers in Biology and Medicine*, 145, 105457. <https://doi.org/10.1016/j.cbm.2020.105457>
- Mahaboob Ali, A. A., Bugarcic, A., Naumovski, N., & Ghildyal, R. (2022). Ayurvedic formulations: Potential COVID-19 therapeutics? *Phytomedicine Plus*, 2(3), 100286. <https://doi.org/10.1016/j.phyplu.2022.100286>
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA neurology*, 77(6), 683–690. <https://doi.org/10.1001/jamaneurol.2020.1127>
- Marinosci, A., Landis, B. N., & Calmy, A. (2020). Possible link between anosmia and COVID-19: sniffing out the truth. *European Archives of Oto-Rhino-Laryngology*. <https://doi.org/10.1007/s00405-020-05966-0>
- Maurya, D. K., & Sharma, D. (2022). Evaluation of traditional ayurvedic Kadha for prevention and management of the novel Coronavirus (SARS-CoV-2) using in silico approach. *Journal of biomolecular structure & dynamics*, 40(9), 3949–3964. <https://doi.org/10.1080/07391102.2020.1852119>

- Maurya, V. K., Kumar, S., Bhatt, M. L. B., & Saxena, S. K. (2022). Antiviral activity of traditional medicinal plants from Ayurveda against SARS-CoV-2 infection. *Journal of biomolecular structure & dynamics*, 40(4), 1719–1735. <https://doi.org/10.1080/07391102.2020.1832577>
- Mezey, É., & Nemeth, K. (2015). Mesenchymal stem cells and infectious diseases: Smarter than drugs. *Immunology Letters*, 168(2), 208–214. <https://doi.org/10.1016/j.imlet.2015.05.020>
- Munir, H., & McGettrick, H. M. (2016). Mesenchymal stem cells therapy for autoimmune disease: risks and rewards. *Stem Cells and Development*, 44(0), 1–25.
- Mosadegh, M., Khalkhali, A., Erfani, Y., & Nezamdoost, M. (2020). The effect of Nutrition Bio-shield superfood (NBS) on disease severity and laboratory biomarkers in patients with COVID-19: A randomized clinical trial. *Microbial Pathogenesis*, 172, 105792.
- Natarajan, S., Anbarasi, C., Sathiyarajeswaran, P., Manickam, P., Geetha, S., Kathiravan, R., Prathiba, P., Pitchiahkumar, M., Parthiban, P., Kanakavalli, K., & Balaji, P. (2021). Kabasura Kudineer (KSK), a poly-herbal Siddha medicine, reduced SARS-CoV-2 viral load in asymptomatic COVID-19 individuals as compared to vitamin C and zinc supplementation: findings from a prospective, exploratory, open-labeled, comparative, randomized controlled trial, Tamil Nadu, India. *Trials*, 22(1), 623. <https://doi.org/10.1186/s13063-021-05583-0>
- Nesari, T., Kadam, S., Vyas, M., Huddar, V. G., Prajapati, P. K., Rajagopala, M., More, A., Rajagopala, S. K., Bhatted, S. K., Yadav, R. K., Mahanta, V., Mandal, S. K., Mahto, R. R., Kajaria, D., Sherkhane, R., Bavalatti, N., Kundal, P., Dharmarajan, P., Bhojani, M., Bhide, B., ... Tripathi, R. (2022). AYURAKSHA, a prophylactic Ayurvedic immunity boosting kit reducing positivity percentage of IgG COVID-19 among frontline Indian Delhi police personnel: A non-randomized controlled intervention trial. *Frontiers in public health*, 10, 920126. <https://doi.org/10.3389/fpubh.2022.920126>
- Niazkar, H. R., Zibaee, B., Nasimi, A., & Bahri, N. (2020). The neurological manifestations of COVID-19: a review article. *Neurological Sciences*. <https://doi.org/10.1007/s10072-020-04486-3>
- Mitjà, O., Corbacho-Monné, M., Ubals, M., Tebe, C., Peñafiel, J., Tobias, A., Ballana, E., Alemany, A., Riera-Martí, N., Pérez, C. A., Suñer, C., Laporte, P., Admella, P., Mitjà, J., Clua, M., Bertran, L., Sarquella, M., Gavilán, S., Ara, J., & Argimon, J. M. (2020). Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. *Clinical Infectious Diseases*, 73(11). <https://doi.org/10.1093/cid/ciaa1009>
- Pan, X., Dong, L., Yang, L., Chen, D., & Peng, C. (2020). Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China. *Virus Research*, 286, 198057. <https://doi.org/10.1016/j.virusres.2020.198057>
- Panda, A. K., Kar, S., Rai, A. K., Rao, B. C. S., & Srikanth, N. (2022). AYUSH- 64: A potential therapeutic agent in COVID-19. *Journal of Ayurveda and integrative medicine*, 13(2), 100538. <https://doi.org/10.1016/j.jaim.2021.100538>
- Parameswaran, S., Ramulu, S. D. M. S., Arivarasan, V. K., Kadarkarai, K., Dhanakoti, R. K., & Loganathan, K. (2021). Evaluation of in-vitro immunomodulatory activity and thrombolytic potential of kabasura kudineer (Ksk): An official siddha polyherbal formulation. *Indian Journal of Pharmaceutical Education and Research*, 55(3), 774–781. <https://doi.org/10.5530/ijper.55.3.150>
- Paudyal, V., Sun, S., Hussain, R., Abutaleb, M. H., & Hedima, E. W. (2022). Complementary and alternative medicines use in COVID-19: A global perspective on practice, policy and research. *Research in social & administrative pharmacy: RSAP*, 18(3), 2524–2528. <https://doi.org/10.1016/j.sapharm.2021.05.004>
- Perazzolo, S., Zhu, L., Lin, W., Nguyen, A., & Ho, R. J. Y. (2021). Systems and Clinical Pharmacology of COVID-19 Therapeutic Candidates: A Clinical and Translational Medicine Perspective. *Journal of Pharmaceutical Sciences*, 110(3), 1002–1017.

- <https://doi.org/10.1016/j.xphs.2020.11.019>
- Polansky, H. (2020). Coronavirus disease 2019 (COVID-19): first indication of efficacy of Gene-Eden-VIR/Novirin in SARS-CoV-2 infection. *International Journal of Antimicrobial Agents*, 55, 1–2.
- Qu, W., Wang, Z., Hare, J. M., Bu, G., Mallea, J. M., Pascual, J. M., Caplan, A. I., Kurtzberg, J., Zubair, A. C., Kubrova, E., Engelberg-Cook, E., Nayfeh, T., Shah, V. P., Hill, J. C., Wolf, M. E., Prokop, L. J., Murad, M. H., & Sanfilippo, F. P. (2020). Cell-based therapy to reduce mortality from COVID-19: Systematic review and meta-analysis of human studies on acute respiratory distress syndrome. *Stem cells translational medicine*, 9(9), 1007–1022. <https://doi.org/10.1002/sctm.20-0146>
- Rahaman, A., Zeng, X.-A., Kumari, A., Rafiq, M., Siddeeg, A., Manzoor, M. F., Baloch, Z., & Ahmed, Z. (2019). Influence of ultrasound-assisted osmotic dehydration on texture, bioactive compounds and metabolites analysis of plum. *Ultrasonics Sonochemistry*, 58, 104643. <https://doi.org/10.1016/j.ultsonch.2019.104643>
- Ramazani, R., Ramazani, S., & Hosseinabadi, T. (2020). Efficacy of a multiple-indication antiviral herbal drug (Saliravira®) for COVID-19 outpatients: A pre-clinical and randomized clinical trial study. *Biomedicine & Pharmacotherapy*, 149, 112729.
- Rastogi, S., Pandey, D. N., & Singh, R. H. (2022). COVID-19 pandemic: A pragmatic plan for ayurveda intervention. *Journal of Ayurveda and integrative medicine*, 13(1), 100312. <https://doi.org/10.1016/j.jaim.2020.04.002>
- Reddy, R. G., Gosavi, R. V., Yadav, B., Rai, A. K., Holay, M. P., Talekar, M., Jameela, S., Sharma, B. S., Khanduri, S., Rana, R., Tripathi, A., Chandrasekhararao, B., Srikanth, N., & Dhiman, K. S. (2020). AYUSH-64 as an add-on to standard care in asymptomatic and mild cases of COVID-19: A randomized controlled trial. *AYU (An international quarterly journal of research in Ayurveda)*, 41(2), 107–116. <https://doi.org/10.4103/ayu.ayu.14.21>
- Rizk, J. G., Kalantar-Zadeh, K., Mehra, M. R., Lavie, C. J., Rizk, Y., & Forthal, D. N. (2020). Pharmacological Immunomodulatory Therapy in COVID-19. *Drugs*, 80(13), 1267–1292. <https://doi.org/10.1007/s40265-020-01367-z>
- Robles-Escajeda, E., Lerma, D., Nyakeriga, A. M., Ross, J. A., Kirken, R. A., Aguilera, R. J., & Varela-Ramirez, A. (2013). Searching in Mother Nature for Anti-Cancer Activity: Anti-Proliferative and Pro-Apoptotic Effect Elicited by Green Barley on Leukemia/Lymphoma Cells. *PLoS ONE*, 8(9), 118. <https://doi.org/10.1371/journal.pone.0073508>
- Rommasi, F., Nasiri, M. J., & Mirsaiedi, M. (2022). Immunomodulatory agents for COVID-19 treatment: possible mechanism of action and immunopathology features. *Molecular and cellular biochemistry*, 477(3), 711–726. <https://doi.org/10.1007/s11010-021-04325-9>
- Rostami, M., & Mansouritorghabeh, H. (2020). D-dimer level in COVID-19 infection: a systematic review. *Expert review of hematology*, 13(11), 1265–1275. <https://doi.org/10.1080/17474086.2020.1831383>
- Sasidharan, S., Nair, J. H., K P, S., Paul, J., R, M. K., Rajendran, K., Saibannavar, A. A., & Nirali, S. (2022). An efficacy and safety report based on randomized controlled single-blinded multi-centre clinical trial of ZingiVir-H, a novel herbo-mineral formulation designed as an add-on therapy in adult patients with mild to moderate COVID-19. *PloS one*, 17(12), e0276773. <https://doi.org/10.1371/journal.pone.0276773>
- Sharma, V., Krushna, B., Soneja, M., & Huddar, V. G. (2020). Efficacy of add-on Ayurveda and Yoga intervention in health care workers of tertiary care hospital during COVID-19: Randomized controlled trial. *Complementary Therapies in Clinical Practice*, 48, 101601.
- Schnappauf, O., Chae, J. J., Kastner, D. L., & Aksentjevich, I. (2019). The Pyrin Inflammasome in Health and Disease. *Frontiers in immunology*, 10, 1745. <https://doi.org/10.3389/fimmu.2019.01745>
- Shah, M. R., Fatima, S., Khan, S. N., Ullah, S., Himani, G., Wan, K., Lin, T., Lau, J. Y. N., Liu, Q., & Lam, D. S. C. (2022). Jinhua Qinggan granules for non-hospitalized COVID-19 patients: A double-blind, placebo-controlled, and

- randomized controlled trial. *Frontiers in medicine*, 9, 928468. <https://doi.org/10.3389/fmed.2022.928468>
- Shen, X., & Yin, F. (2021). The mechanisms and clinical application of Traditional Chinese Medicine Lianhua-Qingwen capsule. *Biomedicine & Pharmacotherapy*, 142, 111998. <https://doi.org/10.1016/j.biopha.2021.111998>
- Shi, N., Guo, L., Liu, B., Bian, Y., Chen, R., Chen, S., Chen, Y., Chen, Y., Cong, X., Dong, G., Guo, J., Hu, L., Jiang, J., Leng, L., Li, B., Li, D., Li, H., Li, J., Li, L., & Liu, J. (2021). Efficacy and safety of Chinese herbal medicine versus Lopinavir-Ritonavir in adult patients with coronavirus disease 2019: A non-randomized controlled trial. *Phytomedicine*, 81, 153367. <https://doi.org/10.1016/j.phymed.2020.153367>
- Shi, N., Liu, B., Liang, N., Ma, Y., Ge, Y., Yi, H., Wo, H., Gu, H., Kuang, Y., Tang, S., Zhao, Y., Tong, L., Liu, S., Zhao, C., Chen, R., Bai, W., Fan, Y., Shi, Z., Li, L., Liu, J., ... Wang, Y. (2020). Association between early treatment with Qingfei Paidu decoction and favorable clinical outcomes in patients with COVID-19: A retrospective multicenter cohort study. *Pharmacological research*, 161, 105290. <https://doi.org/10.1016/j.phrs.2020.105290>
- Shirkande, A. (2022). Ayurvedic evaluation and treatment of Covid 19: A case report. *Journal of Ayurveda and integrative medicine*, 13(1), 100489. <https://doi.org/10.1016/j.jaim.2021.07.005>
- Şimşek-Yavuz, S., & Komsuoğlu Çelikyurt, F. I. (2021). An update of anti-viral treatment of COVID-19. *Turkish journal of medical sciences*, 51(SI-1), 3372-3390. <https://doi.org/10.3906/sag-2106-250>
- Skipper, C. P., Pastick, K. A., Engen, N. W., Bangdiwala, A. S., Abassi, M., Lofgren, S. M., Williams, D. A., Okafor, E. C., Pullen, M. F., Nicol, M. R., Nascene, A. A., Hullsiek, K. H., Cheng, M. P., Luke, D., Lother, S. A., MacKenzie, L. J., Drobot, G., Kelly, L. E., Schwartz, I. S., ... Boulware, D. R. (2020). Hydroxychloroquine in nonhospitalized adults with early covid-19: A randomized trial. *Annals of Internal Medicine*, 173(8), 623-631. <https://doi.org/10.7326/M20-4207>
- Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., & Kayhan, S. (2020). Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical Rheumatology*, 39(7), 2085-2094. <https://doi.org/10.1007/s10067-020-05190-5>
- Srivastava, A., Rengaraju, M., Srivastava, S., Narayanan, V., Gupta, V., Upadhayay, R., Kumar, J., Parameswaran, S., KanakavalliKadarkarai, & AarthiVelmurugan (2021). Efficacy of two siddha polyherbal decoctions, Nilavembu Kudineer and Kaba Sura Kudineer, along with standard allopathy treatment in the management of mild to moderate symptomatic COVID-19 patients-a double-blind, placebo-controlled, clinical trial. *Trials*, 22(1), 570. <https://doi.org/10.1186/s13063-021-05478-0>
- Tao, Z., Gao, J., Zhang, G., Xue, M., Yang, W., Tong, C., & Yuan, Y. (2014). Shufeng Jiedu Capsule protect against acute lung injury by suppressing the MAPK/NF-κB pathway. *Bioscience trends*, 8(1), 45-51. <https://doi.org/10.5582/bst.8.45>
- Tavakoli, A., Molavi Vardanjani, H., Namjouyan, F., Cramer, H., & Pasalar, M. (2022). Efficacy of Persian barley water on clinical outcomes of hospitalized moderate-severity COVID-19 patients: A single-blind, add-on therapy, randomized controlled clinical trial. *European Review for Medical and Pharmacological Sciences*, 26(3), 1033-1041. https://doi.org/10.26355/eurev_202202_28013
- Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. F. P. (2020). The trinity of COVID-19: immunity, inflammation and intervention. *Nature reviews. Immunology*, 20(6), 363-374. <https://doi.org/10.1038/s41577-020-0311-8>
- Thakar, A., Goyal, M., Bhide, S., Chhotala, Y., Panara, K., & Chaudhari, S. (2022). Impact of AYUSH 64 as an adjunctive to standard of care in mild COVID 19 - An open-label randomized controlled pilot study. *Journal of Ayurveda and integrative medicine*, 13(3), 100587. <https://doi.org/10.1016/j.jaim.2022.100587>

- Tian, H., Liu, Z., Pu, Y., & Bao, Y. (2019). Immunomodulatory effects exerted by Poria Cocos polysaccharides via TLR4/TRAF6/NF-κB signaling in vitro and in vivo. *Biomedicine & Pharmacotherapy*, 112, 108709–108709. <https://doi.org/10.1016/j.biopha.2019.108709>
- Tong, T., Wu, Y. Q., Ni, W. J., Shen, A. Z., & Liu, S. (2020). The potential insights of Traditional Chinese Medicine on treatment of COVID-19. *Chinese Medicine (United Kingdom)*, 15(1), 1–6. <https://doi.org/10.1186/s13020-020-00326-w>
- Toscano, G., Palmerini, F., Ravaglia, S., Ruiz, L., Invernizzi, P., Cuzzoni, M. G., Franciotta, D., Baldanti, F., Daturi, R., Postorino, P., Cavallini, A., & Micieli, G. (2020). Guillain-Barré Syndrome Associated with SARS-CoV-2. *New England Journal of Medicine*. <https://doi.org/10.1056/nejmc2009191>
- Vaira, L. A., Salzano, G., Fois, A. G., Piombino, P., & De Riu, G. (2020). Potential pathogenesis of ageusia and anosmia in COVID-19 patients. *International forum of allergy & rhinology*, 10(9), 1103–1104. <https://doi.org/10.1002/alr.22593>
- Valizadeh, H., Abdolmohammadi-Vahid, S., Danshina, S., Ziya Gencer, M., Ammari, A., Sadeghi, A., Roshangar, L., Aslani, S., Esmailzadeh, A., Ghaebi, M., Valizadeh, S., & Ahmadi, M. (2020). Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *International immunopharmacology*, 89(Pt B), 107088. <https://doi.org/10.1016/j.intimp.2020.107088>
- Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *Journal of virology*, 94(7), e00127-20. <https://doi.org/10.1128/JVI.00127-20>
- Wang, M., Yuan, Q., & Xie, L. (2018). Mesenchymal Stem Cell-Based Immunomodulation: Properties and Clinical Application. *Stem cells international*, 2018, 3057624. <https://doi.org/10.1155/2018/3057624>
- Wang, Q., Zhu, H., Li, M., Liu, Y., Lai, H., Yang, Q., Cao, X., dan Ge, L. (2021). Efficacy and Safety of Qingfe Paidu Decoction for COVID-19: A Systematic Review and Meta-Analysis. *Frontiers in Pharmacology*, 12, 1–11. <https://doi.org/10.3389/fphar.2021.688857>
- Wang, Y., Jin, X., Fan, Q., Li, C., Zhang, M., Wang, Y., Wu, Q., Li, J., Liu, X., Wang, S., Wang, Y., Li, L., Ling, J., Li, C., Wang, Q., & Liu, Y. (2022). Deciphering the Active Compounds and Mechanisms of HSBDF for Treating ALI via Integrating Chemical Bioinformatics Analysis. *Frontiers in pharmacology*, 13, 879268. <https://doi.org/10.3389/fphar.2022.879268>
- WHO Solidarity Trial Consortium, Pan, H., Peto, R., Henao-Restrepo, A. M., Preziosi, M. P., Sathiyamoorthy, V., Abdool Karim, Q., Alejandria, M. M., Hernández García, C., Kieny, M. P., Malekzadeh, R., Murthy, S., Reddy, K. S., Roses Periago, M., Abi Hanna, P., Ader, F., Al-Bader, A. M., Alhasawi, A., Allum, E., Alotaibi, A., ... Swaminathan, S. (2021). Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *The New England journal of medicine*, 384(6), 497–511. <https://doi.org/10.1056/NEJMoa2023184>
- Xia, K. Y., Zhao, Z., Shah, T., Wang, J. Y., & Baloch, Z. (2022). Composition, Clinical Efficiency, and Mechanism of NHC-Approved "Three Chinese Medicines and Three Chinese Recipes" for COVID-19 Treatment. *Frontiers in pharmacology*, 12, 781090. <https://doi.org/10.3389/fphar.2021.781090>
- Xia, Q. D., Xun, Y., Lu, J. L., Lu, Y. C., Yang, Y. Y., Zhou, P., Hu, J., Li, C., & Wang, S. G. (2020). Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. *Cell proliferation*, 53(12), e12949. <https://doi.org/10.1111/cpr.12949>
- Xiao, F., Tang, M., Zheng, X., Liu, Y., Li, X., & Shan, H. (2020). Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology*. <https://doi.org/10.1053/j.gastro.2020.02.055>
- Xiao, M., Tian, J., Zhou, Y., Xu, X., Min, X., Lv, Y., Peng, M., Zhang, Y., Yan, D., Lang, S., Zhang, Q., Fan, A., Ke, J., Li, X., Liu, B., Jiang, M., Liu, Q., Zhu, J., Yang, L., & Zhu, Z. (2020). Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of

- COVID-19: A randomized controlled trial. *Pharmacological Research*, 161, 105126. <https://doi.org/10.1016/j.phrs.2020.105126>
- Xiong, J., Bao, L., Qi, H., Feng, Z., & Shi, Y. (2020). Mesenchymal Stem Cell-Based Therapy for COVID-19: Possibility and Potential. *Current Stem Cell Research & Therapy*, 16(2), 105–108. [do10.2174/1574888x15666200601152832](https://doi.org/10.1016/j.phrs.2020.104820)
- Xin, S., Cheng, X., Zhu, B., Liao, X., Yang, F., Song, L., Shi, Y., Guan, X., Su, R., Wang, J., Xing, L., Xu, X., Jin, L., Liu, Y., Zhou, W., Zhang, D., Liang, L., Yu, Y., & Yu, R. (2020). Clinical retrospective study on the efficacy of Qingfei Paidu decoction combined with Western medicine for COVID-19 treatment. *Biomedicine & pharmacotherapy*, 129, 110500. <https://doi.org/10.1016/j.biopha.2020.110500>
- Xu, F., Hou, T., Shen, A., Jin, H., Xiao, Y., Yu, W., Li, X., Wang, J., Liu, Y., & Liang, X. (2021). Mechanism deconvolution of Qing Fei Pai Du decoction for treatment of Coronavirus Disease 2019 (COVID-19) by label-free integrative pharmacology assays. *Journal of ethnopharmacology*, 280, 114488. <https://doi.org/10.1016/j.jep.2021.114488>
- Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., & Hao, P. (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences*, 63(3). <https://doi.org/10.1007/s11427-020-1637-5>
- Xu, Y., Yang, L., Wang, L., & Chen, F. (2022). Potential therapeutic effect of Shufeng Jiedu capsule and its major herbs on coronavirus disease 2019 (COVID-19): A review. *Drug discoveries & therapeutics*, 15(6), 289–299. <https://doi.org/10.5582/ddt.2021.01099>
- Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F. S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet. Respiratory medicine*, 8(4), 420–422. [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)
- Yang, R., Liu, H., Bai, C., Wang, Y., Zhang, X., Guo, R., Wu, S., Wang, J., Leung, E., Chang, H., Li, P., Liu, T., & Wang, Y. (2020). Chemical composition and pharmacological mechanism of Qingfei Paidu Decoction and Ma Xing Shi Gan Decoction against Coronavirus Disease 2019 (COVID-19): In silico and experimental study. *Pharmacological research*, 157, 104820. <https://doi.org/10.1016/j.phrs.2020.104820>
- Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *Journal of Infection*, 80(6). <https://doi.org/10.1016/j.jinf.2020.03.037>
- Yu, P., Li, Y.-Z., Wan, S.-B., & Wang, Y. (2020). Effects of Lianhua Qingwen Granules Plus Arbidol on Treatment of Mild Corona Virus Disease-19. *Chinese Pharmaceutical Journal*. 12(55), 1042-1045. doi: [10.11669/cpj.2020.12.014](https://doi.org/10.11669/cpj.2020.12.014)
- Yong-Li, W., Cong-Cong, Z., Feng, Z., Jian, H., Dan-Dan, W., Yong-Fang, Z., Wei, L., Guang-Bo, G. E., & Jian-Guang, X. U. (2020). Chemical profiling and tissue distribution study of Jingyin Granules in rats using UHPLC-Q-Exactive Orbitrap HR-MS. *Journal of Chinese materia medica*, 45(22), 5537–5554. <https://doi.org/10.19540/j.cnki.cjcmm.20200903.201>
- Zeng, J. H., Liu, Y. X., Yuan, J., Wang, F. X., Wu, W. B., Li, J. X., Wang, L. F., Gao, H., Wang, Y., Dong, C. F., Li, Y. J., Xie, X. J., Feng, C., & Liu, L. (2020). First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. *Infection*, 48(5), 773–777. <https://doi.org/10.1007/s15010-020-01424-5>
- Zeng, M., Li, L., & Wu, Z. (2020). Traditional Chinese Medicine Lianhua Qingwen Treating corona Virus Disease 2019(COVID-19): Meta-Analysis of Randomized Controlled Trials. *PLoS One*, 15 (9), e0238828. doi: [10.1371/journal.pone.0238828](https://doi.org/10.1371/journal.pone.0238828)
- Zhang, F., Liu, W., Huang, J., Chen, Q., Wang, D., Zou, L., Zhao, Y., Zhang, W., Xu, J., Chen, H., & Ge, G. (2022). Inhibition of drug-metabolizing enzymes by Jingyin granules: implications of herb–drug interactions in antiviral therapy. *Acta Pharmacologica Sinica*, 43(4), 1072–1081. <https://doi.org/10.1038/s41401-021-00697-2>
- Zhang, J., Litvinova, M., Wang, W., Wang, Y., Deng, X., Chen, X., Li, M., Zheng, W., Yi, L., Chen, X., Wu,

- Q., Liang, Y., Wang, X., Yang, J., Sun, K., Longini, I. M., Halloran, M. E., Wu, P., Cowling, B. J., ... Yu, H. (2020). Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study. *The Lancet Infectious Diseases*, 20(7), 793–802. [https://doi.org/10.1016/S1473-3099\(20\)30230-9](https://doi.org/10.1016/S1473-3099(20)30230-9)
- Zhang, M., Yan, X., Shi, M., Li, R., Pi, Z., Ren, X., Wang, Y., Yan, S., Wang, Y., Jin, Y., & Wang, X. (2022). Safety and efficiency of stem cell therapy for COVID-19: a systematic review and meta-analysis. *Global health research and policy*, 7(1), 19. <https://doi.org/10.1186/s41256-022-00251-5>
- Zhang, S., Yang, Z., Chen, Z.-L., Li, Z.-N., Yue, S.-J., Li, J.-J., & Tang, Y.-P. (2022). Efficacy and Safety of “Three Chinese Patent Medicines and Three TCM Prescriptions” for COVID-19: A Systematic Review and Network Meta-Analysis. *Evidence-Based Complementary and Alternative Medicine*, 2022, 1–16. <https://doi.org/10.1155/2022/4654793>
- Zhang, Y., Xie, H., Li, Y., Li, T., Yuan, H., Fu, X., & Xie, C. (2020). Qingfei Paidu decoction for treating COVID-19: A protocol for a meta-analysis and systematic review of randomized controlled trials. *Medicine*, 99(36), e22040. <https://doi.org/10.1097/MD.00000000000022040>
- Zhao, J., Tian, S., Lu, D., Yang, J., Zeng, H., Zhang, F., Tu, D., Ge, G., Zheng, Y., Shi, T., Xu, X., Zhao, S., Yang, Y., & Zhang, W. (2021). Systems pharmacological study illustrates the immune regulation, anti-infection, anti-inflammation, and multi-organ protection mechanism of Qing-Fei-Pai-Du decoction in the treatment of COVID-19. *Phytomedicine*, 85, 153315. <https://doi.org/10.1016/j.phymed.2020.153315>
- Zhao, Z. H., Zhou, Y., Li, W. H., Huang, Q. S., Tang, Z. H., & Li, H. (2020). Analysis of Traditional Chinese Medicine Diagnosis and Treatment Strategies for COVID-19 Based on "The Diagnosis and Treatment Program for Coronavirus Disease-2019" from Chinese Authority. *The American journal of Chinese medicine*, 48(5), 1035–1049. <https://doi.org/10.1142/S0192415X20500500>
- Zheng, E. X., & Navarro, V. J. (2015). Liver Injury from Herbal, Dietary, and Weight Loss Supplements: a Review. *Journal of clinical and translational hepatology*, 3(2), 93–98. <https://doi.org/10.14218/JCTH.2015.00006>
- Zhong, L. L. D., Lam, W. C., Yang, W., Chan, K. W., Sze, S. C. W., Miao, J., Yung, K. K. L., Bian, Z., & Wong, V. T. (2020). Potential Targets for Treatment of Coronavirus Disease 2019 (COVID-19): A Review of Qing-Fei-Pai-Du-Tang and Its Major Herbs. *The American Journal of Chinese Medicine*, 48(05), 1051–1071. <https://doi.org/10.1142/s0192415x20500512>
- Zhong, Y., Zhou, J., Liang, N., Liu, B., Lu, R., He, Y., Liang, C., Wu, J., Zhou, Y., Hu, M., & Zhou, J. (2017). Effect of Maxing Shigan Tang on H1N1 Influenza A Virus-Associated Acute Lung Injury in Mice. *Intervirology*, 59(5–6), 267–274.
- Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., Zheng, X. S., ... Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798), 270–273. <https://doi.org/10.1038/s41586-020-2012-7>
- Zhou, Z., Zhao, N., Shu, Y., Han, S., Chen, B., & Shu, X. (2020). Effect of Gastrointestinal Symptoms in Patients With COVID-19. *Gastroenterology*, 158(8), 2294–2297. <https://doi.org/10.1053/j.gastro.2020.03.020>
- Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., & Tan, W. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, 382(8), 727–733. <https://doi.org/10.1056/nejmoa2001017>
- Zhuang, J., Dai, X., Wu, Q., Cai, H., Fu, X., Zhang, W., & Chen, B. (2021). A meta-analysis for Lianhua Qingwen on the treatment of Coronavirus disease 2019 (COVID-19). *Complementary therapies in medicine*, 60, 102754. <https://doi.org/10.1016/j.ctim.2021.102754>