Review Article

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Cytokine Storm Management in Severe COVID-19: Exploring Four Effective Medicinal Plants as Potential Interventions

Mina Shafiee[1];PharmD, Samira Sadat Abolmaali[1,2*];PhD, Mohsen Salmanpour[1,3] PhD, Ehsan Amiri-Ardekani[4,5,6] PhD$_{student}$, Ali Mohammad Tamaddon[1];PhD

[1]Center for Nanotechnology in Drug Delivery, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
[2]Department of pharmaceutical nanotechnology, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
[3]Cellular and Molecular Biology Research Center, Larestan University of Medical Sciences, Larestan, Iran
[4]Department of Phytopharmaceuticals (Traditional Pharmacy), Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[5]Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[6]Scientific Association of Indigenous Knowledge, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

COVID-19, caused by the SARS-CoV-2 virus, has emerged as a global health threat. Due to coronovirus mutations and genetic variations, effective treatments remain elusive. Currently, the primary strategy for disease management revolves around coronovirus vaccines, representing the sole avenue for disease control. A prominent factor in the pathogenesis of COVID-19 is the severe inflammation triggered by a phenomenon known as cytokine storm. This review delves into the pivotal role of interleukin-6 (IL-6) in orchestrating the cytokine storm and explores the intricate network of signaling pathways and inhibitors, including phytochemicals. Numerous clinical trials have explored the potential of anti-cytokine agents and medicinal plants with cytokine-modulating attributes in COVID-19 patients. According to various studies investigating the effects of medicinal plants on COVID-19, four specific plants—Silybum marianum L., Tanacetum parthenium L., Curcuma longa L., and Zingiber officinale Rosc.—have exhibited significant anti-IL-6 signaling properties. However, further rigorous clinical data are needed to establish their prophylactic or therapeutic efficacy. Overall, both in-vivo and clinical studies suggest that the aforementioned medicinal plants, endowed with proven anti-inflammatory and immune-modulatory properties, particularly through IL-6 reduction, could make valuable contributions to the management of COVID-19.

Keywords: COVID-19, Cytokine storm, Interleukin-6, Herbal medicine.

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1. Introduction

Coronaviruses (CoVs) are a well-known group of positive single-strand RNA viruses that can infect humans and animals. They can cause respiratory, enteric, hepatic, and neurological problems(1, 2). The clinical significance of human coronaviruses (HCoVs) was recognized during the outbreaks of the severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), which are two types of HCoVs that cause a range of disease symptoms from flulike symptoms to acute respiratory distress syndrome (ARDS) (2). Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the SARS coronavirus 2 (SARS-CoV-2) that has been declared a global health emergency (3). A group of patients with clinical respiratory disorders was

Corresponding Author: Amir Savardashtaki, Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
Email: dashtaki63@gmail.com

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reported in Wuhan, China, in December 2019. SARS-CoV-2, a novel coronavirus, manifested in various symptoms, ranging from a self-limiting upper respiratory tract illness to severe pneumonia, multi-organ failure, and even death(3-5). The World Health Organization declared COVID-19 as the sixth public health emergency of international concern on January 30, 2020 (6). It quickly spread worldwide, and the World Health Organization declared it a pandemic in March 2020. Since then, it has been a major public health issue that has posed challenges to medicine and health care worldwide (3-5). As COVID-19's spread has disrupted many aspects of human life worldwide, several studies have been conducted to understand the origin, functions, treatments, and preventions of SARS-CoV-2 (7). Until now, existing therapies have failed to control the disease, mostly due to its high morbidity as well as mortality rates and rapid transmission (8, 9).

There are several anti-COVID-19 vaccines in various stages of development in academia, industry, and the market. They are considered as the most promising approach for the termination of COVID-19 pandemic and returning to normal life (10) . Besides vaccination as an active immunization approach, pharmacotherapy of COVID-19 has been also taken into account. Despite clinical trials on various antiviral drugs for SARS-COV-2 management, only few of them have been approved for COVID-19 treatment so far (5, 11, 12). As a result, it is critical to develop therapeutic approaches based on the pathophysiological mechanisms of the disease. Huang et al. reported that patients with COVID-19 who are critically ill have an elevated cytokine profile, which is similar to the overstate immune response seen in SARS and MERS, two pneumonia-causing CoVs (13). This excessive and uncontrolled load of proinflammatory cytokines in COVID-19 causes activation and release of inflammatory cytokines in a pathogen-triggered inflammation positive feedback loop, resulting in a hyperinflammatory state known as "cytokine storm"(5). Cytokine storm affects various tissues, primarily causing acute lung injuries of varying severity, and is a cause of patients rapidly progressing with ARDS and septic shock, followed by multiple organ failure and death (3, 5). Overall, cytokine storm plays a critical role in SARS-CoV-2 morbidity and mortality and there is currently no proven treatment to combat this systemic response (5, 11, 14). This minireview addresses inflammation signaling pathways and suggests medicinal plants with the potential to serve as complementary agents for the management of COVID-19.

2. Cytokine Storm and IL-6 Signaling

Initial investigations into patients afflicted by COVID-19 unveiled that inflammatory agents play a notable role in the development of the disease and can harm the heart, liver, and kidneys, leading to conditions like shock, respiratory insufficiency, and multiple organ failure (11). This disease causes an increase in serum levels of interleukins (ILs) such as IL-1, IL-2, IL-6, IL-7, IL-8, IL-10, and IL-17, as well as interferon-γ (IFN-γ), IFN-inducible protein 10, monocyte chemoattractant protein 1, tumor necrosis factor-alpha (TNF-α), macrophage inflammatory protein 1α and granulocyte-macrophage colony-stimulating factor, and also other proinflammatory chemokines, including CC chemokine ligand 2 and 3 and chemokine ligand 10 CXC (4, 5, 11, 13). Interestingly, severely affected COVID-19 patients display systemic cytokine profiles that bear a striking resemblance to those found in sepsis, a condition characterized by an excessive release of cytokines known as a "cytokine storm" (4, 13). Moreover, COVID-19 shares certain similarities with sepsis, such as (a) the occurrence of pyroptosis, an inflammatory type of programmed cell death prevalent during infections, and (b) the identification of nonspecific C-reactive protein as an indicator of inflammation. The abnormal activation of a broad array of hyper-inflammatory factors associated with COVID-19 has given rise to the idea that it could lead to sepsis and septic shock. Essentially, the heightened levels of inflammatory cytokines and chemokines involved in inflammatory processes have been associated with both the severity of COVID-19 and a high mortality rate.(4). According to Quirch et al., patients who required Intensive Care Unit (ICU) admission had higher levels of granulocyte colony-stimulating factor, IFN-inducible protein 10, monocyte chemoattractant protein 1, TNF-α, and macrophage inflammatory protein 1(5). Consequently, it seems advantageous to employ anti-cytokine treatment in severe COVID-19 cases to mitigate its mortality rate (11).

IL-6 stands out as a significant cytokine

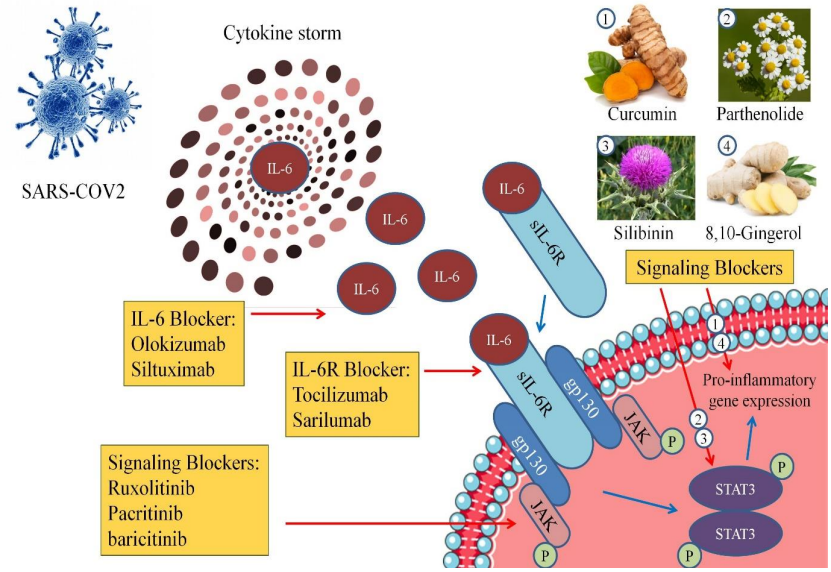

Figure 1. IL-6 signaling pathway in COVID-19 and the inhibitors, including phytochemicals.

linked to COVID-19 due to its ability to anticipate the severeness of clinical outcomes (11, 14, 15). It as a dual-purpose cytokine, capable of exerting both proinflammatory and anti-inflammatory effects (16, 17). Signaling pathways driven by Signal Transducer and Activator of Transcription 3 (STAT3) are responsible for mediating the anti-inflammatory responses of IL-6 (18). Conversely, IL-6's proinflammatory functions involve the recruitment of monocytes to areas of inflammation, as seen in chronic inflammatory conditions such as rheumatoid arthritis (18, 19). Various cell types, including neutrophils, macrophages, natural killer cells, and hepatocytes, express the IL-6 receptor (14). Activation of the IL-6 signaling pathway, implicated in the cytokine storm's development, can have diverse impacts on immune cells through the actions of Janus Kinases (JAK) and STAT. Consequently, strategies to inhibit IL-6 signaling and its downstream effects could hold promise as treatments for COVID-19 patients (20). The depiction of IL-6 signaling pathways and the potential roles of chemical inhibitors and herbal remedies in COVID-19 treatment can be seen in Figure 1.

Novel treatments are being developed to address the inflammation associated with severe cases of COVID-19, including drugs that target the IL-6-JAK-STAT signaling pathway like tocilizumab and ruxolitinib (14, 21). Some monoclonal antibodies, such as siltuximab, which target IL-6, and drugs like tocilizumab and sarilumab, which target IL-6 receptors, have been approved for clinical use in different diseases (22). Clinical trials are also evaluating the efficacy of JAK inhibitors like pacritinib and baricitinib, which not only aim to counteract the inflammatory state of COVID-19, but might also possess antiviral properties per se (21).

3. Herbal therapy in COVID-19

The role of herbal therapy for COVID-19 treatment mostly lies in the potential of natural compounds to contribute to comprehensive healthcare strategies. Herbal remedies, steeped in historical and traditional use, offer a rich source of bioactive constituents that possess antiviral, anti-inflammatory, and immune-modulating properties. These natural compounds have the potential to address a range of symptoms associated with COVID-19, offering relief from respiratory distress, fever, and immune system dysregulation (14). Bahrami et al. recently reported and reviewed the immunosuppressive and anti-inflammatory properties of natural products derived from herbal medicines that can be used against inflammatory mediators (11). several clinical trials have investigated the inhibition of IL-6 signaling as a therapeutic approach for addressing severe cases of COVID-19 (22). This encourages us to review numerous articles and focus on four herbs that might impact IL-6 signaling pathways, including Silybum marianum L., Tanacetum parthenium L., Curcuma longa L., and Zingiber officinale Rosc.

3.1. Silybum marianum L.

Silybum marianum L., commonly known as milk thistle, has emerged as a potential candidate for COVID-19 management due to its multifaceted therapeutic properties. The active compound within milk thistle, known as silibinin, has demonstrated antioxidant, anti-inflammatory, antiviral, and immunomodulatory effects. In the context of COVID-19, where an overactive immune response and inflammation can lead to severe outcomes, the immunomodulatory properties of silibinin are of particular interest. Silibinin has been shown to modulate inflammatory pathways, potentially mitigating the cytokine storm associated with severe cases of COVID-19 (23-25). Interestingly, an examination of the molecular mechanisms has revealed that silibinin has the potential to counteract the hyperactivation of STAT3-induced lung damage caused by excessive IL-6 production. As a direct STAT3 inhibitor, silibinin has been demonstrated to regulate the responses of reactive reparative cells (such as macrophages and astrocytes) to damaged tissues (24). Son et al. investigated an animal model of radiation-induced lung injury that partially mimicked the late-phase inflammation and end-stage pulmonary fibrosis associated with ARDS in severe COVID-19. Their findings suggest that silibinin can reduce inflammation and fibrosis, increase survival time, and decrease the number and infiltration of inflammatory cells in bronchoalveolar lavage fluid, and also the respiratory tract (26). Tian et al. utilized silibinin to inhibit inflammatory responses in mice afflicted with acute lung injury. Their findings unveiled a marked reduction in the activation of airway inflammatory cells such as macrophages, T-cells, and neutrophils, alongside diminished production of specific proinflammatory cytokines (27). Moreover, an in-silico screening study predicted that silibinin could effectively target the RNA-dependent RNA polymerase/nsp12 machinery crucial for coronaviral replication/translation. Consequently, it emerges as a promising phytochemical with potential antiviral properties. The Catalan Institute of Oncology in Catalonia, Spain, undertaking translational research titled "SIL-COVID-19" to assess the therapeutic efficacy of silibinin in preventing moderate-to-severe COVID-19 in onco-hematological patients, by considering silibinin's dual functionality in targeting the cytokine storm and the virus's RNA replication machinery Currently, a randomized, phase II multicentric clinical trial is underway (24). Additionally, Musazadeh and colleagues conducted a review outlining the positive impacts of silymarin on oxidative stress and inflammation. They concluded that silymarin could potentially offer therapeutic benefits in combating COVID-19 by interacting with specific proteins targeted by SARS-CoV-2, ultimately hindering viral replication (28).

3.2. Tanacetum parthenium L.

Tanacetum parthenium L., commonly referred to as feverfew, offers a potential avenue for COVID-19 management due to its historically recognized therapeutic properties. With a history of use dating back to Greek and European herbal traditions, feverfew has gained attention for its potential anti-inflammatory and immune-modulating effects. The active ingredient parthenolide, found within the plant, holds promise for its ability to inhibit proinflammatory cytokines and pathways, which are implicated in the cytokine storm seen in severe COVID-19 cases (29). Within feverfew, active components include flavonoid glycosides, monoterpenes, sesquiterpenes, and sesquiterpene lactones(11). The primary active ingredient, parthenolide, recognized for its substantial analgesic, anti-inflammatory, and antipyretic properties, is predominantly found in the plant's leaves and flower heads (29). Moreover, in vitro studies have unveiled parthenolide's capability to notably curtail IL-1, IL-2, IL-6, IL-8, and TNF-α signaling pathways in various human cell lines encompassing monocytes, macrophages, and neutrophils. Experimental evidence has demonstrated parthenolide's efficacy in significantly diminishing hyperalgesia and edema responses in mice and rats (30). Bahrami et al. suggest that parthenolide could be a viable candidate for COVID-19 treatments due to its potent inhibitory effect on proinflammatory pathways. This is noteworthy as the employment of monoclonal antibodies constitutes a principal therapeutic approach for managing cytokine storms in the context of this disease (11).

3.3. Curcuma longa L.

Curcumin, a natural polyphenol found in turmeric (Curcuma longa L.), has gained attention for its potential role in COVID-19 management.

Curcumin is known for its antioxidant, anti-inflammatory, and immune-modulating properties. These properties are particularly relevant in the context of COVID-19, where excessive inflammation and immune response can contribute to disease severity. Curcumin has been studied for its ability to inhibit various proinflammatory pathways and cytokines, including IL-6 and TNF-α, which are implicated in the cytokine storm observed in cases of severe COVID-19 (31, 32). Avasarala et al. investigated a murine model of viral-induced ARDS and observed that curcumin substantially diminished the infiltration of inflammatory cells into the interstitial and interalveolar spaces, thereby impeding subsequent fibrosis. This compound was also found to reduce levels of inflammatory markers, such as IL6, IL10, and IFN, as well as markers associated with fibrosis, including tenascin-C, smooth muscle actin, and E-cadherin (33). Thota et al. recognized turmeric as a potential agent for addressing lung disorders in COVID-19 patients, encompassing lung dysfunction, acute lung injury, pulmonary fibrosis, and ARDS (32). Furthermore, a double-blind, randomized clinical trial with 76 COVID-19 patients admitted to Ali-Asghar Hospital between December 2021 and March 2022 revealed that the combination of nanocurcumin with standard COVID-19 treatment exhibited an enhanced anti-inflammatory impact. This combination was observed to contribute to the recovery from the acute inflammatory phase in hospitalized patients with mild-to-moderate disease severity (34). On the other hand, Nugraha et al. demonstrated that SARS-CoV-2's cellular entry is substantially linked to the angiotensin-converting enzyme II (ACE2) receptor. They cautioned that further clinical trials are warranted to ascertain curcumin's prophylactic and therapeutic effects on COVID-19, considering its potential to elevate ACE2 expression and production, which might potentially exacerbate the disease's progression (35).

3.4. Zingiber officinale Rosc.

Zingiber officinale Rosc., commonly known as ginger, presents itself as a potential component in COVID-19 management due to its multifaceted therapeutic attributes. Ginger contains bioactive compounds such as 6-gingerol and 6-shogaol that confer antioxidant, anti-inflammatory, and immunomodulatory properties. These qualities hold significant relevance in the context of COVID-19, where an excessive inflammatory response can lead to severe outcomes. Notably, ginger has been investigated for its ability to inhibit proinflammatory cytokines and pathways, including IL-1β, IL-6, and TNF-α (36). In a 21-day randomized clinical trial involving 32 patients with ARDS, ginger extract was introduced into their enteral diet (120 mg per day in three divided doses). Remarkably, in comparison to the placebo group, these participants demonstrated significantly reduced serum levels of inflammatory markers, including IL-1, IL-6, and TNF-α (37). Furthermore, the group receiving ginger treatment exhibited improved oxygenation, reduced duration of mechanical ventilation, and shorter stays in the ICU compared to the control cohort. However, the rates of organ failure and mortality between the ginger-treated and placebo groups remained comparable (37). Likewise, Silveira et al. proposed that ginger's anti-inflammatory properties could potentially offer benefits in alleviating respiratory symptoms associated with conditions like COVID-19 (36). Interestingly, Magzoub et al. advocated for incorporating ginger juice into daily routines for COVID-19 prevention and treatment, emphasizing ginger's potential to positively modulate the immune system and reduce levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [36]. The *in silico* study by Rajagopal et al. highlighted significant activities of ginger constituents (such as 8-Gingerol and 10-Gingerol) against COVID-19 (38). Additionally, in a randomized controlled exploratory trial conducted by Singh and colleagues at a designated COVID-19 care center in India, involving 60 participants with mild or moderate COVID-19, it was shown that ginger could efficiently shorten the duration of clinical recovery and enhance the time required for viral clearance in cases of mild and moderate COVID-19 (39).

4. Conclusion

In severely ill COVID-19 cases, the inflammation triggered by a cytokine storm plays a crucial role in both the morbidity and mortality of affected patients. Consequently, there has been an exploration of the potential effectiveness of mitigating this cytokine storm through anti-cytokine

therapies, with a particular focus on those targeting IL-6. Numerous clinical trials have been conducted on anti-IL-6 monoclonal antibodies like siltuximab, sarilumab, tocilizumab, and olokizumab. This mini-review aims to elucidate the prospective role of four specific notable medicinal plants—Silybum marianum L., Tanacetum parthenium L., Curcuma longa L., and Zingiber officinale Rosc.—in reducing IL-6 levels in COVID-19 patients. Silymarin and ginger show promise due to their potential anti-cytokine properties, but further clinical investigations are essential to validate their efficacy in preventing and treating COVID-19. Conversely, additional studies are required to explore the limitations of using these plants, including safety, drug interactions, and bioavailability. Furthermore, future research needs to assess novel delivery systems for co-administering drugs and phytochemicals with limited water solubility and oral bioavailability.

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Conflict of Interest

The authors declare no conflict of interest.

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