Biotechnology Reports 35 (2022) e00749

Contents lists available at ScienceDirect

Biotechnology Reports

journal homepage: www.elsevier.com/locate/btre

Review

Can natural products modulate cytokine storm in SARS-CoV2 patients?

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ARTICLE INFO

Keywords:
Cytokine storm
Immunomodulation
Natural products
SARS-CoV2

ABSTRACT

Currently, the number of cases and deaths of SARS-CoV2, especially among the chronic disease groups, due to aggressive SARS-CoV2 infection is increasing day by day. Various infections, particularly viral ones, cause a cytokine storm resulting in shortness of breath, bleeding, hypotension, and ultimately multi-organ failure due to over-expression of certain cytokines and necrosis factors. The most prominent clinical feature of SARS-CoV2 is the presence of elevated proinflammatory cytokines in the serum of patients with SARS-CoV2. Severe cases exhibit higher levels of cytokines, leading to a "cytokine storm" that further increases disease severity and causes acute respiratory distress syndrome, multiple organ failure, and death. Therefore, targeted cytokine production could be a potential therapeutic option for patients severely infected with SARS-CoV2.

Given the current scenario, great scientific progress has been made in understanding the disease and its forms of treatment. Because of natural ingredients properties, they have the potential to be used as potential agents with the ability to modulate immune responses. Moreover, they can be used safely because they have no toxic effects, are biodegradable and biocompatible. However, these natural substances can continue to be used in the development of new therapies and vaccines.

Finally, the aim and approach of this review article is to highlight current research on the possible use of natural products with promising potential as immune response activators. Moreover, consider the expected use of natural products when developing potential therapies and vaccines.

1. Introduction

Infection with SARS-CoV2, the virus that causes SARS-CoV2, is characterized by binding to the angiotensin-converting enzyme 2 (ACE2) and viral spike protein [1]. Activation of spike proteins is mediated by TMPRSS2, which play an vital role in the infection [2]. After onset and subsequent endocytosis, SARS-CoV2 infection causes an increase in a kinase that mediates pneumonia (PAK1), pulmonary fibrosis, and other critical lung damage factors. Elevated levels of PAK1 also reduce adaptive immune response and facilitate viral replication [3]. SARS-CoV2 infection has been associated with increased levels of activated proinflammatory chemokines and cytokines, causing atypical pneumonia with rapid respiratory impairment and lung failure [4]. Cytokine release has been shown to be important in the spectrum of SARS-CoV2 infection. This mechanism is more related to organ dysfunction than viral load [5]. In this line, a retrospective observational study found higher serum levels of proinflammatory cytokines such as TNF, IL-1, andIL-6 in patients with severe SARS-CoV2 [6].

It has been reported that SARS-CoV2 has a higher lung damage rate of about 3.7% than influenza with a lung damage rate of >1% (WHO, 2020). Some scientific evidence suggests that some groups of severe SARS-CoV2 cases may have cytokine storm syndrome and respiratory failure due to cytokin storm, which are the leading causes of death [7]. Therefore, molecules that can modulate this unregulated response may be an effective drug useful in treating the cytokine storm syndrome associated with SARS-CoV2 infection [8].

SARS-CoV2 infection causes abnormal release of cytokines and proinflammatory molecules is closely associated with lung damage [9, 10]. Uncontrolled release of cytokines such as IL-1β, IL-6 and Monocyte Chemo-attractant Protein (MCP)-1, in combination with a reduction in natural killer cell numbers, can cause the so-called "cytokine storm" [11, 12] (Fig. 1).

Therefore, the use of antiviral drugs alone until a specific vaccine is available may not be sufficient to stop cytokine storm and shortness of breath in critically SARS-CoV2 patients. To reduce all-cause lung damage, it is important to identify new therapies that can prevent or reduce cytokine storms and their aftermath. Immunomodulators of natural origin can be useful as preventive and therapeutic tools in reducing cytokine storms and their associated effects. Therefore, available approaches emphasize this cascade for reduced inflammation and immune

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https://doi.org/10.1016/j.btre.2022.e00749
Received 4 April 2022; Received in revised form 24 May 2022; Accepted 8 June 2022
Available online 9 June 2022

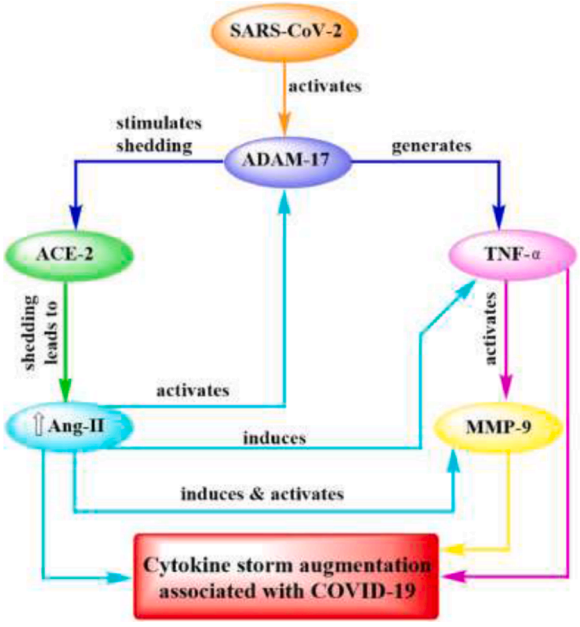

Fig. 1. Possible mechanism of action of SARS-CoV2.

modulation. Many research projects are underway in the biotechnology and academic fields to find new drugs and vaccines against cytokine storm.

SARS-CoV2 infection causes inflammation by activating inflammatory lung damage pathways of the immune system. A growing number of indications show that apart from viral damage and uncontrolled inflammation due to an unregulated immune response of the host contributes to disease severity and death ([13–17]; Geng et al., 2020).

Consistent with this hypothesis, patients with severe SARS-CoV2 showed significant increases in serum levels of proinflammatory molecules (inflammatory cytokines, D-dimer, ferritin, and C-reactive protein), liver dysfunction, disseminated intravascular coagulation, and thrombotic tendencies that indicate the occurrence of immunological complications such as cytokine storm. Due to the hyperactive nature of the immune response in severe SARS-CoV2, the reorientation of some disease-modifying anti-inflammatory drugs, such as baricitinib (JAK inhibitor) and tocilizumab (IL-6 receptor inhibitor) possible treatment for SARS-CoV2 ([13–17]; Geng et al., 2020) (Fig. 2).

The most critical cases of SARS-CoV2, which require intensive ventilation care and often result in prolonged ventilation dependence and death, are the result of an exaggerated inflammatory response to infection (England et al., 2020). SARS-CoV2 infection has been associated with increased levels of activated proinflammatory chemokines and cytokines, causing atypical pneumonia with rapid respiratory impairment and lung failure [4].

Cytokine storm have been shown to be important factors in lung damage from SARS-CoV2 infection. In patients with severe SARS-CoV2, higher serum levels of proinflammatory cytokines were found compared to patients with mild disease [6]. The molecular mechanism involved in this immune process is the target of various synthetic drugs being tested in patients, including ciclesonide, hydroxychloroquine, ivermectin, and ketorolac, which are PAK1 blockers (Maruta et al., 2020). PAK1 is overexpressed in the lung in response to SARS-CoV2 infection and is an important mediator of cytokine storm, which frequently causes death in hospitlung damagezed patients (Maruta et al., 2020).

In general, although no specific drug has been reported, studies have shown that various administrations and dosing regimens inhibit the release of inflammatory cytokines, thereby increasing whiteness levels. Blood cell count and histologic examination increase ([18]; Park 2020). These results are encouraging as the potential of this molecule for early treatment of SARS-CoV2 patients SARS-CoV2 could be further investigated.

Among the many therapeutic options that need to be explored, bioactive molecules have received a lot of attention due to the increasing use of their immunomodulatory, antioxidant, and anti-inflammatory properties.

Given the current scenario, using foods rich in natural immunomodulators is a vital option to enhance immunity and reduce the risk of SARS-CoV2 contamination. Moreover, although the use of natural products as a therapeutic strategy has not yet become a lung damage, based on all the scientific evidence for the immunomodulatory potential of these bioactive molecules, the use of dietary supplements is a rational choice [19].

Here we review the literature the possible use of natural substances obtained from medicinal plants as cytokine storm inhibitors (Fig. 3). We highlight some natural products with promising potential. However, the focus is on naturally extracted substances. Therefore, the implications of the specific molecular properties of natural products that can be used for promising therapeutic interventions are discussed in detail. We also discuss how natural molecules generate critical adaptive immune responses to influence antibody development, and detail the basic

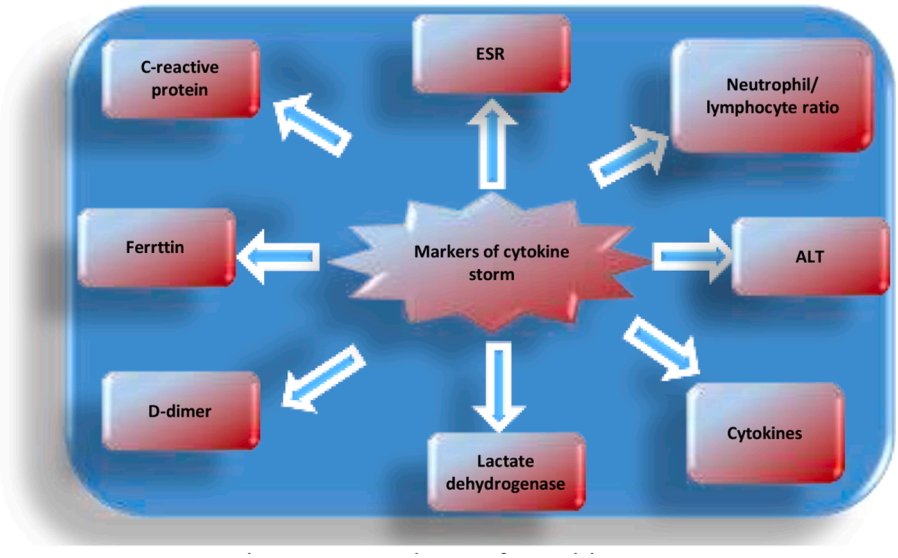

Fig. 2. Markers of cytokine storm.

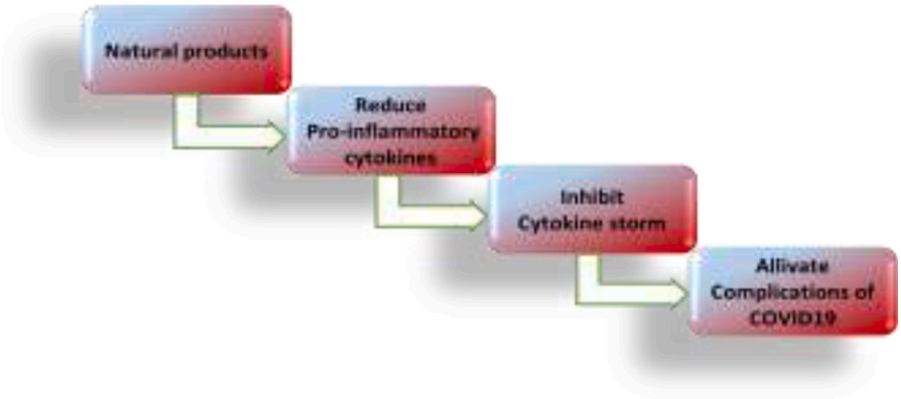

Fig. 3. Natural products as a cytokine storm inhibitors.

mechanisms that modulate the immune system. Finally, a contextual dialog will be opened about the potential of natural products as an effective and safe platform in the development of vaccines and potential therapies to strengthen immunity.

This comprehensive review provides important updates on a number of natural products that have promise potential for SARS-CoV2 treatment. However, as much of the research on the antiviral effects of bioactive products and Chinese medicine in this area is only preliminary, in-depth *in-vivo* studies on appropriate animal models are needed to uncover the underlying cellular and molecular mechanisms. There are several promising pharmacokinetic studies of natural products and should be carried out to obtain a pharmacokinetic profile, including absorption, distribution, metabolism and excretion parameters. Moreover, clinical studies are needed to test the effectiveness and safety of antiSARS-CoV2 in humans. More importantly, studies should be conducted to examine potential interactions between TCM or natural products and available antiviral agents for antiSARS-CoV2 effects. Optimizing some of the above-mentioned lead molecules with known or novel mechanisms of action could lead to the possible development of new therapies for SARS-CoV2.

2. TCM in treating cytokine storm in COVID19

As TCM has the characteristics of a multicomponent, multipurpose, and reusable pathway to treat disease, it has great potential to treat SARS-CoV2. In this review, many medicinal plants and natural products have demonstrated promising anti-SARS-CoV2 activity through a variety of targeted approaches and could be further developed into therapeutic guides. Although natural bioactive products have shown potential to treat SARS-CoV2, there is still a long way to go before they can be used in the clinic. One of the main limitations in the development of natural bioactive products in medicine is their solubility and bioavailability. The high cost and complexity of clinical trials are other barriers to the development of new anti-SARS-CoV2 from bioactive products. Pharmaceutical industries face a number of regulatory challenges, such as more stringent test designs and increased safety requirements for drug approval.

Plant extracts are widely used for their potential to treat COVID19 symptoms. Popular TCM have been used not only via the anti-inflammatory route but also in a wider range of biological activities, such as antiviral, being considered [18].

Licorice can significantly reduce levels of proinflammatory cytokines. Moreover, licoricehas specific goals related to immune response, inflammation, bacterial protection, endotoxin response, glucocorticoid response, antipyretic, sweating, etc. Each relationship, each time through a common goal for intergroup relations, shows different goals for materials and synergies paths (Han et al., 2019).

Further studies were carried out with decoctions of rhubarb, a plant widely used as a food ingredient, has been studied for its potential to affect extravascular lung water in cytokin storm case. Therefore, this bioactive product can be used effectively in the early treatment of respiratory distress patients [20]. Similary, Xuanbai Chengqi has been used traditionally in China since the late 18th century. This natural product decoction has been tested for the treatment of COVID19. A clinical study found that pulmonary compliance, whether static or dynamic, was significantly higher in patients treated with the decoction than in the control group. Moreover, lung damage was lower in the treated patients (Mao et al., 2016). Details of some medicinal plants studies are given in Table 1.

2.1. Propolis

In preclinical studies, propolis upregulated the immune regulation of proinflammatory cytokines. This immune regulation includes macrophages, monocytes, and inflammatory pathways, reducing the risk of cytokine storm. Moreover, propolis holds promisingagent in treating some very dangerous co-morbidities in patients with SARS-CoV2, including respiratory diseases, high blood pressure, diabetes, and cancer. Given the current state of the SARS-CoV2 pandemic and limited therapeutic options, propolis is presented as a suitable and promising therapeutic option that is safe, available and easy to administer orally [28].

Propolis increase the production of antibodies against SARS-CoV2, reduce anchoring ACE2and TMPRSS2expression and limits entry of the virus. Moreover, propolis promotes NF-KB and monocyte/macrophage immunomodulation, reduce proinflammatory cytokine overproduction, and reduce PAK1 activation [28]. Propolis extract inhibits NF-B activation [29]. Induces Ca2+ lung damage in dendritic cells in Peyer's patches and enhances immune response [30]. Attenuates inflammatory reactions via intracellular levels of ROS and NO with decreased IL-1 expression and IL-6 [31]. Regulates the cytokines IFN-γ, IL-6 and IL-10 in an experimental asthma model [32]. Increases TGF-β. and IL-10, which contributes to the regulation of the inflammatory process in acute pneumonia [33].

Caffeic acid phenethyl ester (CPE) is considereda strong inhibitor of NF-kB activation in myelo-monocyte cells. Ansorge et al. [34] demonstrated that propolis, CPE, hesperidin, andquercetin,can inhibit cytokine production. Moreover, CPE can reduce oxidation and inflammation by decreasing JAK2/STAT3 lung damage [35], also CPE inhibits phosphorylation of STAT3 and IL-6, which are responsible for the development of proinflammatory Th17 [36].CPE, a component of propolis, is also known as an immunomodulatory agent [37] and should be considered as an alternative to reduce excessive inflammatory reactions. In a mouse model, propolis has an immunomodulatory effect on the expression of toll-like receptors and on the production of proinflammatory cytokines *in vivo* [38].

Table 1
Medicinal plants with potential activity to reduce cytokine storm.

Medicinal plants	Mechanism	Refs.
Xuanbai Chengqi	Increase lung compliance Reduce plateau pressure Reduce incidence rate and the fat lung damage rate of complications Reduce end-expiratory pressure Increase dynamic lung compliance	Mao et al., 2016
Lianqinjiedu	Reduce body temperature Reduce TNF-α, and IL-6levels Reduce lung injuries	[21]
Physlung damages alkekengi	Reduce TNF-α expression Reduce oxidation products accumulation Reduce COX-2, caspase-3, p53, ERK, JNK and NF-κBlevels Enhance Nrf2 translocation from the cytoplasm to the nucleus Reduce inflammation Reduce apoptosis Reduce oxidative stress	[18]
Rhubarb	Increase oxygenation index Reduce pulmonary vascular and permeability index levels	[20]
Portulaca oleracea	Reduce the lung wet-to-dry ratio Reduce IL-β, IL-6, TNF-α, PGE2, and TGF-β levels Reduce interstitial edema index Increase of IL-10 level Improvement of MDA, MPO and SOD level in white blood cells Increase CAT activities	[22]
Cordyceps sinensis	Reduce histopathological injury degree Reduce MPO activity Inhibit neutrophils and macrophages count in BALF Reduce IL-6, IL-1β, NOandTNF-α levels Reduce NF-κB, COX-2 and iNOS DNA binding ability Reduce wet-to-dry weight ratio	[23]
Aster tataricus	Repair of vascular endothelial Inhibit inflammatory cytokines release	[24]
Ulmus davidiana	Reduce nitrite/nitrate, LDH and TNF-α levels in BALF Ameliorate TNF-α expression and nitrite levels Ameliorate IL-1β mRNA expression	[25]
Ilex kaushue	Pulmonary protection Reduce superoxide generation Inhibit human neutrophil elastase activity	[26]
Sini	Ameliorate lung injury Reduce MPO activity Reduce inflammatory factors in lung tissue Reduce of ACE expression Activate ACE2 angiotensin pathway	[27]
Licorice	Reduce levels of proinflammatory cytokines Enhance immune response Reduce inflammation Bacterial protection Glucocorticoid response Antipyretic	Han et al., 2019

Propolis can reduce and ameliorate inflammatory diseases ([39]; Pineros et al., 2020) and has immunomodulatory properties [34]. However, these properties may vary depending on the plant of origin of the propolis as well as the extractionprocess and inflammation protocol used (cell culture, animal models, lipopolysaccharide induction) when testing propolis extracts [40]. Animal model studies have shown that propolis can reduce levels of TNF and IL-6, and can increase levels of IL-10 [33]. Kaempferol, a component of propolis, reduces VEGF (vascular endothelial growth factor), IL-6, and TNF-alpha [41]. Propolis also inhibits the production of IL-1 beta, an important component in diseases such as lupus, rheumatoid arthritis and other autoimmune diseases (Ramos et al., 2007). Although its mechanism of action is not well understood, this component of propolis has potential as an additive in the prevention of chronic inflammatory disease (Tozser et al., 2016). Older people are more likely to develop cytokine storm that may contribute to the development of cytokine storms, one of the leading causes of SARS-CoV2 death [42].The study, using aqueous propolis extract, demonstrated a reduction in key proinflammatory cytokines. Prostaglandin and leukotriene D4 levels were significantly reduced [43].

2.2. Natural ingredients

The use of natural ingredients for the treatment of cytokine storm has been reported (Fig. 4). However, as noted above, current treatments for SARS-CoV2-associated cytokine storm are also to treat symptoms, particularly respiratory disease, caused by inflammatory mediators. Therefore, several herbal supplements, isolated ingredients have been reported to modulate the expression of many inflammatory factors [44].

2.3. Alkaloids

Alkaloids deserve special mention. They exhibit multiple pharmacological activities *in vivo*. Berberine is the main alkaloid in the rhizome of *Coptis chinensis* [45]. These alkaloids have been studied for their effect on the integrity of the endothelial glycocalyx because these structures are known to be damaged under cytokin storm. Berberine can reduce damage and improve the condition of the glycocalyx by inhibiting factors such as ROS. Yu et al. [46] reported that the potential of tetrahydroberberberubine against LPS-induced lung damage. This study found that administration of this alkaloid decreasedthe ratio of wet to dry lung. Moreover, coagulation, inflammatory cell infiltration and pulmonary edema are reduced by these alkaloids [46].

Tabersonin, inhibits pro-inflammatory mediators and enhancing anti-inflammatory mediators, it can be concluded that these bioactive molecules hold promise for early treatment of SARS-CoV2 [47]. Details of individual alkaloids studies are given in Table 2.

2.4. Flavonoids

Flavonoids are a broad class of molecules that have anti-inflammatory effects. These bioactive ingredients are known to improve health and slow several diseases (Ramawat and Merillon, [169]; [134,135]; [51–55]; [56,57]; [58]). In fact, computer studies of its antiinflammatory effect have shown that phospholipase A2 can be inhibited by flavonoids (Lattig et al., 2007). Moreover, flavonoids can prevent mast cell degranulation and immunoglobulin E (IgE) synthesis [59]. Due to its wide use in respiratory diseases, a diet high in flavonoids in cytokin storm patients may show useful results that could be further investigated to prevent the development of the syndrome in patients with SARS-CoV2.

Acacetin is a flavonoid that occurs naturally in several plants ([60]; Hu and Huang; 2018; [61, 50]). These O-methylated molecules were investigated as potential candidates for cytokin storm treatment. Sonne et al. (2018) reported that the potential for this connection through two different mechanisms [50,60]. Sonne et al. (2018) found that this bioactive molecule can reduce lung damage and swelling by reducing MPO activity and inflammatory cells [61]. Moreover, this compound is able to regulate heme oxygenase-1, SOD, COX-2 and iNOS. On the other hand, Wu et al., [50] investigated the mechanism and came to the conclusion that this molecule is able to increase HO-1 levels and Nrf-2 activity, while increasing TNF-α.

Astilbine, is a flavonol molecule that has been tested for potency *in vivo* and *in vitro* against cytokin storm [62]. This compound was used to treat LPS-induced lung damage in mice and LPS-induced inflammation in human umbilical vein endothelial cells. In fact, astilbin was able to suppress the activity of MDA and MPO and reduce the expression of IL-6 and TNF-α. In general, these molecules attenuate histopathological changes in the lung and neutrophil infiltration.

Similar results were observed in an *in vitro* study with lung damage [63]. This type of plant is rich in flavonoids. Ryu et al. [63], produced

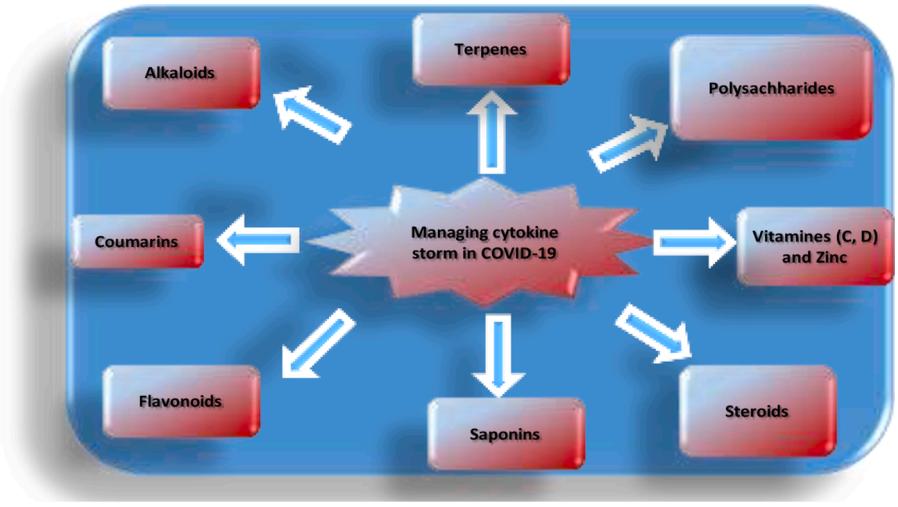

Fig. 4. managing of cytokine storm in COVID-19.

Table 2
Alkaloids with potential activity to reduce cytokine storm.

Alkaloid	Mechanism	Refs.
Berberine	Inhibit syndecan-1 shedding and heparan sulfate Reduce pro-inflammatory cytokines InhibitNF-κB lung damage pathway	[45]
Total alkaloids from *Dendrobium crepidatum*	Inhibit NO production Downregulate lung damage pathway of Mitogen-activated protein kinase	[48]
Protostemonine	Reduce pro-inflammatory cytokinesproduction Reduce iNOS expression	[49]
Protostemonine	Inflammatory cell infiltration attenuation Reduce Pro-inflammatory cytokine Eliminate lung edema Inhibit MPO activity Suppress p38 MAPK, iNOS expression Supress NO production	[50]
Tetrahydroberberrubine	Reduce Edema and inflammatory cells infiltration Reduce nitrate/nitrite content in BALF. Reduce TNF-α Reduce myeloperoxidase activity Reduce inflammatory markers in cells.	[46]
Tabersoninefrom Catharanthus roseus	Attenuation of pathological lung injury Inhibit neutrophil infiltration Inhibit IL-6 , IL-1β, andTNF-αexpression Inhibit MPO activity Suppress NF-κB	[47]

lung damage methanol extract which was able to increase NO production, iNOS expression, and inhibit IL-6 and TNF-α levels.

Emodin, a flavonoid isolated from Rhei Radix, was able to block SARS-CoV2 by interfering with the interaction of S-protein and ACE2. It also exhibits anti-inflammatory, antiproliferative, and anti-cancer properties. Dose-dependent emodin reduces asthmatic airway inflammation by inhibiting activated macrophage polarization and STAT6 phosphorylation.

Scutellarein, another vegetable flavonoid, has anti-inflammatory effects by inhibiting COX-2 expression and inducing NOS by inhibiting the NF-κB pathway. The flavonoids of Lonicerae Japonicae, glycyrrhizin and resveratrol are also said to have anti-inflammatory effects. A high-profile study published in Science reports that desaminothyrosine, a microbial metabolite, can protect the host from influenza by suppressing type I interferon lung damage and enhancing pulmonary immunopathology. Desaminothyrosine can be produced by human intestinal bacteria from the metabolism of flavonoids and amino acids. Moreover, desaminothyrosine is also a flavonoid decomposition product that is rich in certain foods and some Chinese medicines.

Hydroxysafflor yellow A [64], hesperetin [65] and silibinin [66] were able to reduce LPS-induced cytokin storm in mice, while silymarin reduced puerarin-induced pulmonary changes in rabbits ([60]; Hu and Huang; 2018; [61,50,67]). In general, it could be concluded that the flavonoid have possible use against cytokin storm act to reduce inflammatory mediators associated with increased symptoms of cytokin storm. Animals treated with the molecule not only exhibited changes in these mediators, but also reduced pathological changes in pneumonia and improved abnormal lung tissue morphology. From these *in vivo* studies it can be assumed that suitable phytotherapy dosage forms based on these molecules are promising for clinical studies for the treatment of cytokin storm in COVID19 patients.

Several flavonols, including kaempferol, fizetin, rutin, and myricetin, can inhibit cytokine expression and synthesis (Higa et al., 2003). Quercetin has an immunosuppressive effect; this molecule inhibits cytokine production (Zaragozá et al., 2020) and induces suppression of pyrindome containing 3 which is inflammatory activation (Owona et al. , 2020). Moreover, the simultaneous administration of quercetin induces immunomodulatory regulation and enhances the antiviral response (Colunga Biancatel [68]). Its positive effect on acute lung injury has been reported through the inhibition of inflammation containing pyrindome-3 (Tianzhu et al., 2014). Details of individual flavonoids studies are given in Table 3.

2.5. Polyphenols

Polyphenols are derived either from the phenylpropanoid route or from the acetate/malonic polyketide route in plant biochemistry. Several groups of certain phenolic molecules have been known, such as flavonoids, xanthones, bergenine, lignans, coumarins,curcumin and caffeic acidare obtained from various fruits and vegetables [69–71].

In fact, curcumin is the most important curcuminoidin terms of pharmacological action. Studies have shown that curcumin can effectively suppress the increase in cytokines production. Abi et al. and Jains et al. reported that curcumin inhibits the release of cytokines such as TNFα, IL8, and IL1β. Moreover, secretion of IL8 in human esophageal epithelial cells and IL6 in rheumatoid synovial fibroblasts are controlled by curcumin [71–74]. Therefore, curcumin haspotential to prevent cytokine storm in SARS-CoV2 patients.

Zhang et al. [71] stated that this molecule can reduce lung damage, inflammation and lung damage by decreasing NF-kB, IFN-β, TNF-, and

Table 3
Flavonoids with potential activity to reduce cytokine storm.

Flavonoid	Mechanism	Refs.
Acacetin	Suppress NO production Reduce inflammatory and edema Increase Nrf-2 activity Reduce IL-1β and TNF-α levels in lung tissues.	[50]
Puerarin	Upregulation of caspase 3 Downregulation of TGF-β1and Bcl-2 Increase IL-10 levels Reduce IL-1, IL-2 and IL-4 production Reduce wet-to-dry ratio of lung tissue Reduce abnormal changes in lung tissue morphology	Hu et al., 2019 [60]
Acacetin	Reduce MPO activity. Reduce lung edema. Regulate COX-2, iNOS,HO-1andSODs. Reduce inflammatory cytokine concentration. Reduce infiltrated inflammatory cell number in BALF.	[61]
Astilbin	Inhibit MAPK pathways and heparanase. Attenuate neutrophil infiltration. Reduce TNF-α and IL-6 expression. Reduce lung wet-to-dry weight ratios. Reduce heparan sulfate production. Suppress MPO and MDA activities.	[62]
Gnaphlung damageum affine methanolic extract	Inhibit iNOS, IL-6 and TNF-α production. Inhibithuman neutrophil elastase (HNE).	[63]
.Hydroxysafflor yellow A	Increase of slight collagen deposition. Reduce body weight loss and pathologic changes in pulmonary inflammation. Reduce IL-6, IL-1β,TNF-α Expression. Reduce protein levels. Inhibitnuclear factor NF-κB and α-SMA.	[64]
Hesperetin	Reduce MPO activity. InhibitMAPK activation. Regulation of IκB degradation. Lung protective effect.	[65]
Silymarin	Reduce the inflammation Ameliorate lung histological changes and pulmonary function Reduce neutrophils infiltration lymphocytes and macrophages Mitigate protein level in BALF	[67]
Silibinin	Inhibit inflammatory cytokines production in BALF. Suppress NF-κB activation Supress pyrindomain-containing 3 inflammasome expression.	[66]

other inflammatory factors. Similarly, bergenine and phenethyl ester of caffeic acid reduced edema by reducing levels of MPO, IL-6, TNF-, activity, and other inflammatory factors.

Moreover, several studies indicate that plants rich in polyphenols have been tested for their therapeutic benefits in preventing cytokin storm (Fig. 5). Rosmarinic acid [75] was investigated for various models of inflammation in mice. The results showed that polyphenolreduced markers of liver, kidney and lung dysfunction by modulating NF-κB and metalloproteinase. Similarly, Chen et al. [26] showed that Ilex Kaushue aqueous extract and 3,5-dicapheoylquinic acid inhibited neutrophil elastase activity and superoxide formation and reduced lung damage in mice. This extract also enhances lung protection [26]. Details of individual polyphenol studies are given in Table 4.

2.6. Coumarin

Coumarins are phenolic molecules consisting of a benzene ring and a -pyrone. Isofraxidine, a coumarin, isolated from Sarcandra glabra and Acanthopanax senticosus, is said to have an anti-inflammatory effect. Niu et al. [76] showed that this molecule reduced lung damage in mice from lung injury after intraperitoneal injection to 15 mg/kg. The authors observed an inhibitory effect on histopathological changes in the lung and COX-2 expression. Moreover, the levels of inflammatory cytokines are also reduced. Similar anti-inflammatory and promising *in vivo* results from a mouse model with lung damage were obtained from the study by Li et al. [37] and Wang et al. [9]. Details of individual coumarin studies are given in Table 5.

2.7. Glucoside

Glucoside is assigned to compounds related to glucose. These molecules can be identified by the presence of intermolecular glucosidic bonds (Ramawat and Mérillon [169]). Fraxin, is a glucoside with several biological andpharmacological effects [77]. This connection was also investigated in an LPS-induced lung damage model in mice. He succeeded in reducing the pathological changes in the lung tissue of the animals examined. Moreover, the pulmonary inflammatory response is reduced because the production of IL-6, TNF- and IL-1β is inhibited. On the other hand, polydatin, has been shown to be useful in LPS-induced cytokin storm by inhibiting apoptosis in mice [37].

Liu et al. [78] conducted a similar study on forsythosideand its effect oninflammation in RAW macrophages 264.7. This molecule is a phenyletanoside, found in some plants, and has been known to have neuroprotective, antibacterial, and antioxidant properties. The authors examined the anti-inflammatory properties of this molecule and found that initial treatment with this molecule could reduce histopathological changes in the lungs and edema, inhibit inflammatory cytokines, and reduce infiltration of inflammatory cells into the lungs. Similar results by Lu et al. [79] who showed that this glucoside is also capable of reducing histologic changes in the lung and inhibiting inflammatory cytokines.

2.8. Terpenes

Terpenoids are the most abundant bioactive compounds among herbs and plants (Ramawat and Mérillon [169]). Bisabolol and bisabolol nanoparticles have been reported to decrease lungdamage by suppressing proinflammatory mediators in a mouse model of acute lung injury. Despite their different chemical structures, similar results were obtained for picfeltarraenin, dehydrocostus lactone, bigelovii A, isoalantolatone and bardoxolone are responsible for the reduction in COX2 and IL-8expression and PGE2 production.

It has been reported that cucurbitacin is an antiproliferative agent by inhibiting the activation of components of STAT3andJAK2 [80]. Inhibition of the JAK/STAT pathway increases p21WAF1 expression independently of p53 activity, thereby leading to stop the accumulation and proliferationof T lymphocytes and inhibiting cytokines production [81, 82]. Moreover, cucurbitacins have been shown to inhibit the expression of CD69 and CD25 [83]. Cucurbitacins can inhibit the JAK/STAT3 pathway. Interestingly, cucurbitacins inhibit of COX-2, TNFexpression and pro-inflammatory mediators (Bernard et al., 2010; [84]). Such a strategy could be used to limit the growth of cytokine production in SARS-CoV2patients.

Saponins are compounds that have surfactant activity due to their amphiphilic nature caused by the presence of terpene groups and sugars. These molecules are mostly present in various plant species and are also triterpenoid glucoside molecules (Ramawat and Mérillon [169]). Studies on the effect of glycyrrhizic acid on lung damage were carried out in this group. A mouse model of induced sepsis was developed by Zhao et al. [85] who found these saponins reduced lung damage and reduced the ratio of wet to dry lungs. Moreover, these compounds were able to reduce many inflammatory mediators [85]. Moreover, ginseng or ginsenosides, a class of molecules represents most of the therapeutic activity of ginseng (Ramawat and Mérillon, [169]). Ginsenoside Rb1,

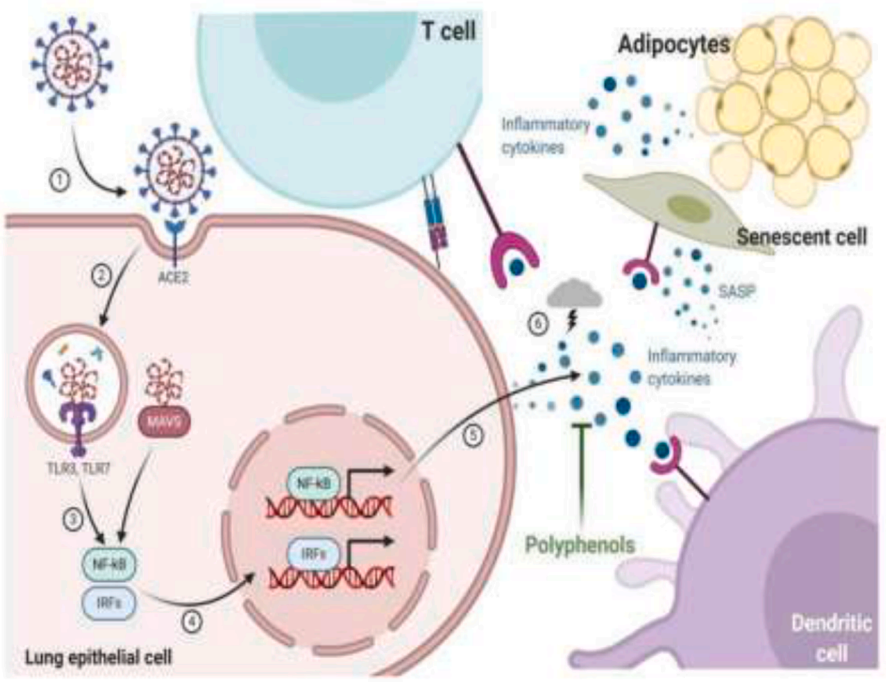

Fig. 5. Possible proposed effect of polyphenols on cytokin storm.

Table 4
Phenolic molecules with potential activity to reduce cytokine storm.

Phenolic molecule	Mechanism	Refs.
Bergenin	TNF-α and IL-6 production in serum. Improve histological changes. Reduce pulmonary edema. Reduce IL-6 andIL-1β production InhibitNF-κB p65 phosphorylation Inhibit the expression of MyD88. Reduce MPO activity.	[70]
Caffeic acid phenethyl ester	Reduce MPO activity Prevention of LPS/MD-2/TLR4 complex formation. Reduce TNF-α, IL-6 levels	[69]
Curcumin	Reduce inflammation and injury Improvement of cell survival. Reduce IFN-β; TNF-α	[71]
Rosmarinicacid	Reduce paw edema Reduce AST, ALT and LDH. Reduce multiorgan dysfunction markers Modulate mettaloproteinase-9and NF-κB	[75]

Table 5
Coumarins with potential activity to reduce cytokine storm.

Coumarin	Mechanism	Refs.
Imperatorin	InhibitNF-κBand JAK/STAT. Reduce COX-2 and iNOSexpression. Reduce immune cell infiltration and edema. reduce TNF-α and IL-6 production.	[37]
Umbelliferone	Attenuation of inflammatory cell infiltration in lung tissue. Reduce MDA and MPO activity Increase SOD activity. Reduce monocyteIL-1β, IL-6, MCP-1,and TNF-α in BALF. reduce wet-to-dry lung weight ratio.	[9]
Isofraxidin	Reduce lung wet-to-dry weight Reduce macrophages and neutrophilscount in MPO and in BALF activity. Reduce TNF-α, BALF, PGE2 and IL-6levels InhibitCOX-2 expression and lung histopathological changes	[76]

one of the most important ginseng molecules, attenuates histopathological variations in lung damage in mice. Like the saponins that have been mentioned, these molecules reduce inflammatory mediator's expression [86].

Sun et al., [87] found that ginsenosides enhance lung permeability index, oxygenation index, and ancillary outcomes associated with the development of lung damage.

Glycyrrhizic Acid reduce of lung wet-to-dry weight and ratio, alleviate lung injury,reduce IL-6 andIL-1β levels and also reduce MPO activity, nhibit iNOS expressionand NO production, attenuate MDA production, preserveSOD activity, mitigate p-IκB-α expression [85].

Carotenoids are a type of tetraterpenoids, they are called pigments. They are derived from two diterpenes and have a conjugated polyene chromophore. Therefore,. These compounds are often found in chromoplasts of plants (Ramawat and Mérillon [169]).

Zhang et al. [88] investigated that crocin was able to increase pulmonary vascular permeability in mice by inhibiting inflammatory lung damage pathways and improving pulmonary vascular permeability, regulating the expression of inflammation-associated proteins, inhibiting inflammatorypathways, nuclear factor κB, heparinase, mitogen-activated protein kinase, cathepsin Land MMP-9 expression, and protecting endothelial glycocalyx heparan sulfate degradation [88].

Limonin supplements have also been shown to reduce IL-6 in healthy adults (PA et al., 2013). Limonin acts as a ligand for adenosine A receptors. The adenosine A receptor has been shown to have an antiinflammatory effect in a mouse model of acute lung injury (F-d-P et al., 2012). This suggests that limonin may have a protective effect on lung function by mediating the release of inflammatory mediators and reducing lung resistance and elasticity. Overall, limonin may be important in combating acute lung damage in SARS-CoV2.

Limonin attenuates proinflammatory cytokines (Fig. 6), increases antioxidant levels, including glutathione (MB et al., 2017). Limonin has shown a protective effect on the epithelial barrier and reduces intestinal inflammation by inhibiting TNF-induced NF-B translocation (PA et al., 2013), as well as the NOS, COX-2, LOX, PGE2, TGF-β and ERK1/2 pathways. It also enhances antioxidant and mucosal protection. Moreover, it attenuates pro-inflammatory cytokines such as NF-B and reduces neutrophil infiltration (DS et al., 2019). The progression and

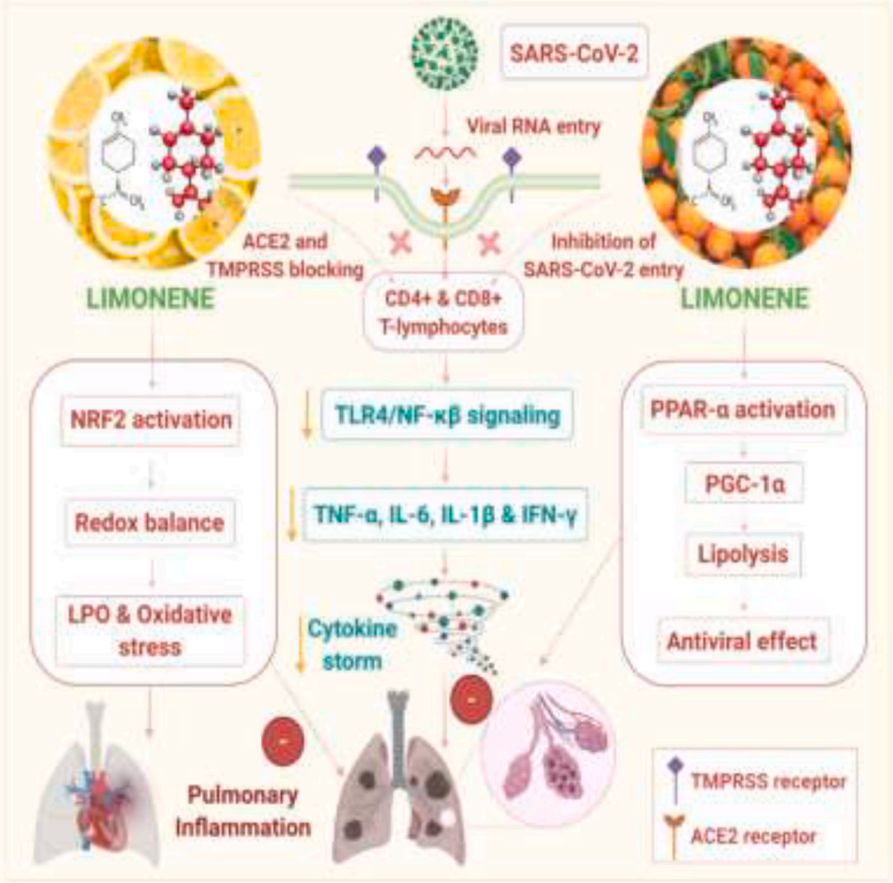

Fig. 6. Possible proposed effect of limonene on cytokin storm.

complications of SARS-CoV2 include cytokine storms;therefore, Moreover to their organ-protective effects, they inhibit potentially proinflammatory cytokines and chemokines. Therefore, in view of limonin multiple tissue remodeling and protective effects, limonin may be a research candidate for possible use in combating SARS-CoV2 infection.

Terpenes could be future source of antiinflammatory agents for severe viral infections. Details of individual terpene studies are given in Table 6.

2.9. Quinone

Quinone comes from aromatic molecules. 2-Hydroxymethylanthraquinone induces the suppression of many proinflammatory mediators such asIL-6,IL-1β, TNFandNO. Moreover, NF-B is activated and TLR4 expression is downregulated.reduces pulmonary edema after LPS-induced lung injury [97]. Shikonin, a molecule that inhibits TLR4 activation, modulates several inflammatory mediators and reduces inflammatory cell infiltration Zhang et al. [47]. Details of individual quinones studies are given in Table 7.

2.10. Glycoprotein

Glycoproteins are molecules that show proteins in their amino acid side chains that are covalently bound to oligosaccharide chains. With respect to this molecule, two manuscripts represent isolated glycoprotein studies against lung damage. Wang et al. [98] used ulinastatin (ginsenosides) in rats increasing the likelihood of using this compounds due to its potential to reduce lung edema in animal model [98]. In various ways, histidine-rich glycoproteins were able to enhance mouse viability, inhibit ROS production and other phenomena in sepsis-induced models [99]. These studies underscore the tremendous potential of glycoproteins to improve lung function. Details of individual glycoproteins studies are given in Table 8.

2.11. Polysaccharides

Polysaccharides have been studied for their potential in the prevention and treatment of cytokin storm. In general, studies have used models of rat lung damage caused by LPS to determine whether the proposed treatment improve animal health. Polysaccharide of Lycium barbarum [69], Oudemansiella radicata polysaccharides [100] Oudemansiella radicata polysachharides [101], and Kochia scoparia fruit polysaccharides [102] showed positive results in improving induced mice. Among the most notable results, these polysaccharides appear to reduce lung damage by reducing oxidative stress, regulating inflammatory pathways and reducing neutrophil infiltration. Details of individual polysaccharides studies are given in Table 9.

2.12. Lipids

Lipid-derived compounds and lipids have been studied in detail for their modulation of inflammatory pathways [103]. Oleic acid, a naturally occurring fatty acid in plants widely used as a dietary supplement, shows promise against cytokin storm. This compound reduces neutrophil accumulation and lung damage. Moreover, these molecules also regulate inflammatory cytokines [104].

Mena et al. [105] confirmed that Acrocomia crispa fruit lipid extract reduces pulmonary edema after LPS-induced lung damage in mice. Spengler et al. (2017) found that surfactants phospholipids have anti-inflammatory activity and significantly improved the overall condition of the lungs by improving ventilation and oxygenation efficiency. Moreover, demonstrated suppression of inflammation, inhibition of

Table 6
Terpenes with potential activity to reduce cytokine storm.

Terpenes	Mechanism	Refs.
Bigelovii A	Reduce inflammatory mediators Alleviate lung injury Reduce lung permeability, and neutrophil infiltration. Attenuate NF-κ B activation Inhibitp38 MAPK phosphorylation Reduce MCP-1, MIP-2 andIL-6levels	[89]
Bisabolol	Reduce histological changes BlockNF-κB activationpathway Suppress IL-6, IL-1β and TNF-α,levels in BALF Reduce NO production in lung tissue Inhibit IκB-α degradation Reduce MPO activity	[90]
Euphorbia factor L2	Reduce TNF-α,IL-6,IL-8 andIL-1βlevels Reduce MPOactivity Attenuate pathological changes Inhibit NF-κB lung damage activation Downregulate IκB-αandIKKα/β Suppressp65 translocation Suppress DNAbinding activity	[47]
HJB-1–17-Hydroxy-Jolkinolide B	Alleviate pulmonary histological changes Suppress the degradation of IκB-α Reduce the accumulation of NF-κB p65 subunit Reduce lung edema Suppress MAPK phosphorylation Reduce TNF-α, IL-6 and IL-1β expression in BALF	[91]
Picfeltarraenin IA	InhibitPGE2 production Suppress IL-8 and COX2 expression	[92]
Bardoxolone	Induce Nrf2 Reduce neutrophil infiltration Improvement of SOD and GSH activities Reduce MPO levels Improve ROS production Ameliorate histopathological changes Improve TNF-α, IL-6 and IL-1β release Improve the expression of COX2and iNOS SuppressNF-kB Ameliorate p38, extracellular signal-regulated kinase 1/2 (ERK1/2) and JNK activation	[93]
α-bisabolol nanocapsules	Reduce airway hyperreactivity, neutrophil infiltration, MPO activity, chemokine levelsand tissue lung injury. Reduce p38 andJNKphosphorylation	[94]
Cucurbitacine	Inhibit the activation of components of STAT3 Inhibitcytokine production by inhibiting JAK/STAT pathway Immunosuppressants and anti-inflammatory effects Inhibit CD69 expressionand CD25 Inhibit pro-inflammatory and TNFexpressions Inhibit NO synthase-2 Inhibit COX-2-mediated NO production.	[83] [82]
Isoalantolactone	SuppressIL-6, IL-1β, TNF-α, and NO expression Suppresspulmonary permeability and neutrophil infiltration Suppress Akt, ERK, andNF-κBactivation	[95]
Dehydrocostus Lactone	Attenuate pathological injury Suppress NF-κB activity *via* p38 MAPK/MK2 and Akt lung damageInhibit TNF-α, NO, iNOS, IL-1β, IL-6and IL-12 expression	[96]
Limonin	Reduce IL-6 in healthy adults Mediate the release of inflammatory mediators Reduce lung resistance and elasticity Attenuate proinflammatory cytokines Increaselevels of antioxidants Inhibit TNF-induced NF-B translocation Inhibit NOS, COX-2, LOX, PGE2, TGF-β and ERK1/2 pathways Enhance mucosal protection	PA et al., 2013 d-P et al., 2012 MB et al., 2017 DS et al., 2019

Table 6 (*continued*)

Terpenes	Mechanism	Refs.
	Attenuate proinflammatory cytokines such as NF-B Reduceneutrophil infiltration Inhibit potentially proinflammatory cytokines and chemokines	

Table 7
Quinones with potential activity to reduce cytokine storm.

Quinone	Mechanism	Refs.
Shikonin	InhibitNF-κBand MAPK activation. InhibitCOX2, TNF-α, IL-6, and IL-1β, expressions. Reduce inflammatory cell infiltration. Promote interferences in the TLR4 activation.	[47]
2-Hydroxymethyl anthraquinone from *Hedyotis diffusa* Willd	Antagonizate NF-κBactivation Reduce MDA level in serum Suppress NO,IL-1β, IL-6, and TNF-α, expression. Increase GSH andSODlevels Attenuate MPO activity, and pulmonary edema	[97]

Table 8
Glycoprotein with potential activity to reduce cytokine storm.

Glycoprotein	Mechanism	Refs.
Histidine-rich Glycoprotein	Preserve neutrophils permeation Inhibit ROS production Inhibit hypercytokinemia and lung inflammation Improve mice survival	[99]
Ulinastatin	Attenuate vascular permeability and pulmonary edema Inhibit endothelial glycocalyx destruction Reduce heparin sulfate production Reduce the activity of heparanase	[98]

polymorphonuclear leukocyte activity and reduction of cellular apoptosis. Details of individual Lipids studies are given in Table 10.

2.13. Steroids

Steroids are terpenoid with four rings that differ by changing the carbon atoms number, side chain and type of functional group. Steroids are of a special class due to their chemical properties and endocrine function. Liu et al. [106] and Wu et al., [107] confirmed that ruscogenin and senegenin have anti-inflammatory effects on lung damage by reducing cellular apoptosis, modulating leukocyte activity, and inhibiting inflammatory mediators (Fig. 7). Details of individual steroids studies are given in Table 11.

3. Cannabidiol

Phytocannabinoids are a structural class of diverse naturally occurring chemicals found in several species of the cannabis plant, including Echinacea angustifolia, Echinacea purpurea, Acmella oleracea, Echinacea pallida, Radula marginata, and Helichrysum umbraculigerum. Cannabidiol is a phytocannabinoid that regulates immune responses in a number of experimental disease models, including laboratory work demonstrating post-injury benefits similar to acute respiratory distress syndrome in mice. Support the therapeutic use of cannabidiol in patients infected with COVID-19. Although a number of mechanisms have been

Table 9
Polysaccharides with potential activity to reduce cytokine storm.

Polysaccharides	Mechanism	Refs.
Polysaccharides of Kochia scoparia fruits	Inhibit human neutrophil elastase Reduce elastase activity Reduce neutrophil infiltration Reduce IL-6 and TNF-α levels	[102]
Polysaccharides of *Oudemansiella radicata*	Downregulation of MDA and LPO content. Reduce hs-CRP level in serum Reduce MPO activity. Increase of CAT and SOD values Reduce IL-1β, IL-6andTNF-α, levels	[100]
Polysaccharides of *Oudemansiella radicata*	Reduce IL-6, IL-1β, and TNF-α levels in BALF. Increase pulmonary activities of SOD, CAT andGSH-Px Reduce C3, CRP and GGT levels in serum Downregulate LPO and MDA contents Alleviate lung injury	Gao et al., 2018
Polysaccharides of *Lycium barbarum*	SuppressNF-κB activation Increase cell viability Reverse endothelial cells migrationdysfunction Reduce oxidative stress and apoptosis Attenuate lung inflammation and pulmonary edema Inhibit ROS production and caspase-3 activation	[69]

Table 10
Lipids with potential activity to reduce cytokine storm.

Lipids	Mechanism	Refs.
Acrocomia crispa fruit lipid extract	Reduce histological score Reduce lung edema, lung weight/body weight ratio	[105]
Oleic acid	Reduce lung damage Mitigate IL-6 and TNF-α, expression and MPO activity Suppress superoxide anion and elastase	[104]

postulated to mediate the antiviral benefits of cannabidiol, including down regulation of SARS-CoV-2 receptors on the human epithelium and inhibition of proinflammatory cytokine production such as IL-1β, IL-6, TNF-α. Cannabidiol also improves lung structure and has a strong anti-inflammatory effect after experimental acute respiratory distress syndrome. The beneficial effects of cannabidiol are related to the regulation of apelin, an endogenous peptide with a protective effect on lung tissue.

3.1. Vitamin

Vitamins are a group of substances causally linked to immune competence. Moreover to their defensive stimulatory activity, several vitamins may act directly on the inflammatory response [44].

3.2. Vitamin D (VitD)

VitD has been studied for the treatment of lung damage [108], who demonstrated that VitD3 could reduce lung damage by increasing the proliferation and migration of type II alveolar cells, inhibition of TGF-induced transient epithelial mesenchymal epitosis and epitope reduction induces cell apoptosis. These *in vivo* animal results promise to stimulate clinical studies of lung damage, as VitD is marketed as an available dietary supplement that would be a suitable alternative for preventive treatment and early treatment of COVID19 patients. VitD also inhibits the expression of proinflammatory cytokines, which are potentially important in infection and may counteract the cytokine storm (Fig. 8). However, VitD deficiency is a global health problem.

Table 11
Steroids with potential activity to reduce cytokine storm.

Steroids	Mechanism	Refs.
Senegenin	Inhibit NF-κB translocation Attenuate lung injury Reduce protein leak Reduce leukocytes infiltration Reduce lung wet-to-dry weight ratio Reduce MDA contents Reduce IL-1β and TNF-α levels Reduce MPO activity Increase GSH level and SOD activity	[106]
Ruscogenin	Attenuate pulmonary endothelial apoptosis. Inhibit TLR4/MYD88/NF-κB activation in pulmonary endothelium. Suppress TLR4 lung damage Ameliorate apoptosis	[107]

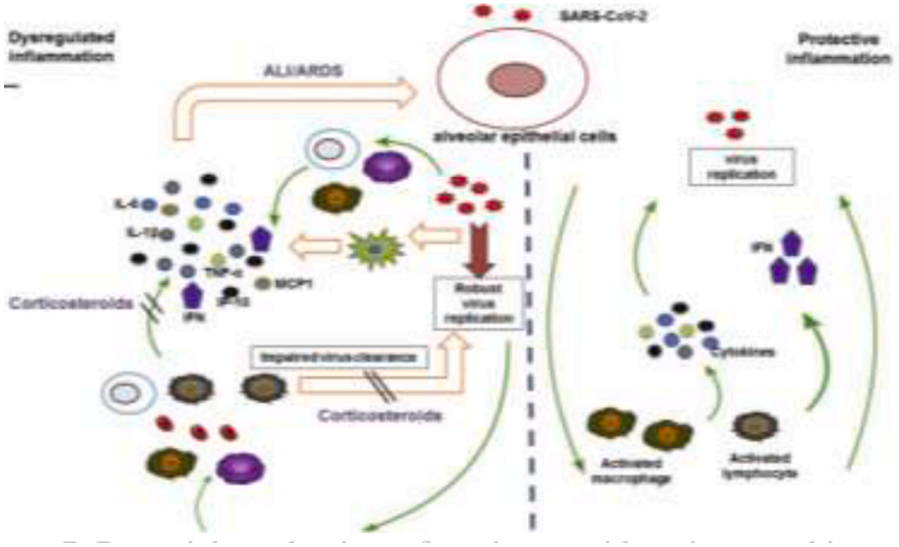

Fig. 7. Potential mechanism of corticosteroid against cytokin storm.

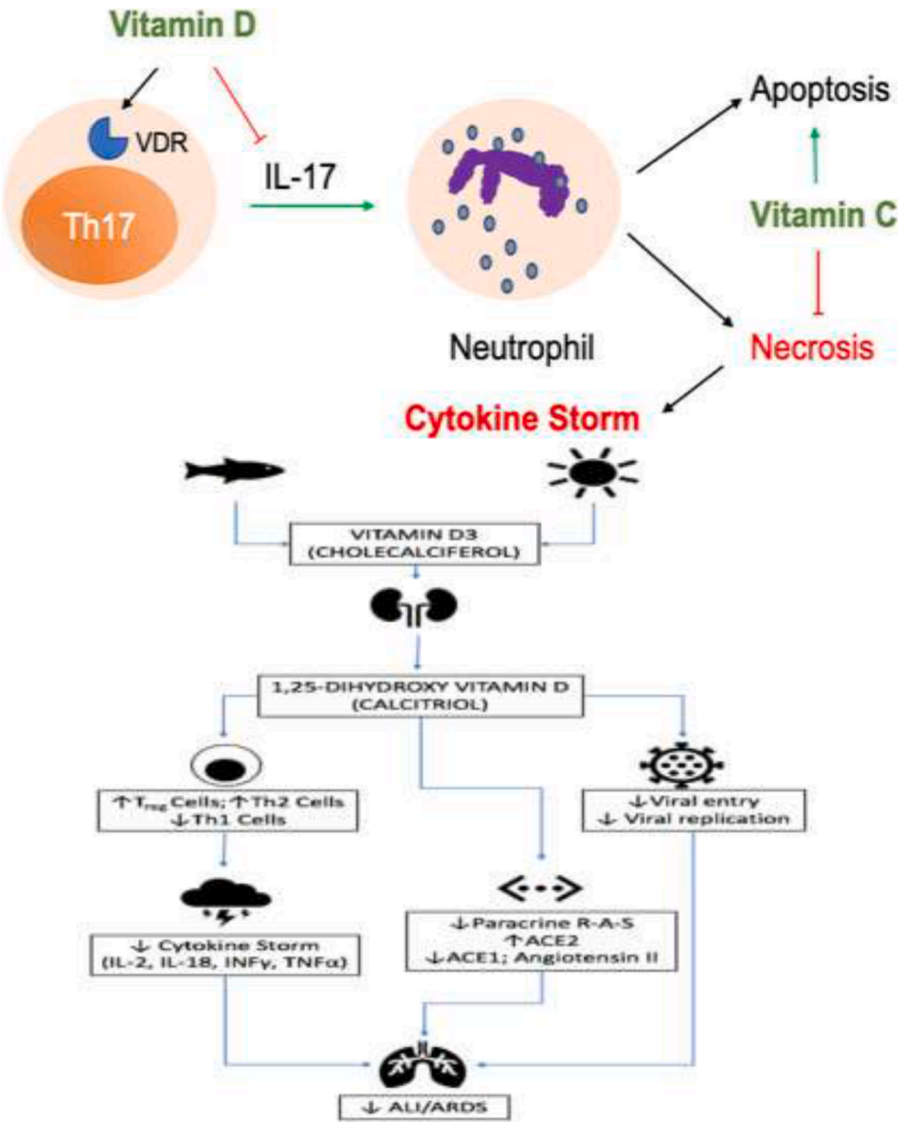

Fig. 8. Possible proposed effect of VitD on cytokin storm.

3.3. *Vitamin C (VitC)*

VitC helps develop a stronger immune system response by increasing antiviral activity and reducing cytokin storms. Perhaps reducing the cytokin storm in Covid19 infection is the primary use of VitC (Fig. 9).

SARS-CoV2 increase oxidative stress, which promotes cell failure and ultimately leads to organ failure.It helps to significantly increase oxidative stress through the formation of free radicals and cytokines. Uncontrolled inflammation, oxidative damage and destruction of the alveolar-capillary barrier are the main causes [109]. Severe oxidative stress causes lung damage and cytokin storm.

Cytokin storm are the key factors responsible for significantly higher morbidity ([110]; Hecker et al., 2018). An increase in C-reactive protein, an indicator of inflammation and oxidative stress, was observed in patients with Covid19 [111]. The transcription factor Nuclear Factor-Erythroid-2-Linked Factor 2 is an important regulator of cytoprotective protein expression, driven by antioxidant elements. Activation of the Nuclear Factor-Erythroid-2-Linked Factor 2 sign lung damage pathway is believed to play an important role in preventing cells and tissues from being exposed to oxidative stress.

The use of antioxidants in conjunction with conventional maintenance therapy has been shown to play an important role in controlling cytokine storm. VitC and other antioxidants are excellent remedies for respiratory distress. They can be used clinically. It is important that high doses of VitC are safe and effective. In this article we consider the use of high doses of VitC as an effective way to treat patients with cancer and infections. VitC's antiviral properties help reduce symptoms and death in children and adults (Khan et al., 2014; Hemilä et al., 2019). The antiviral activity of VitC is well known (Jungeblut et al., 1939). Moreover, the use of VitC as an important medical agent against various diseases is well established ([112]; 1953; 1974).

Clinically effective vaccines and specific antiviral agents, if available, may be effective. Given the current situation, the use of VitC as an antiviral agent should also be considered. In particular, VitC can be used alone or in combination with other available drugs to achieve a positive synergistic effect. Here we consider the main mechanism of action of VitC, which helps strengthen the immune system, reduces cytokine storm and inhibits oxidative processes.

3.4. *Zinc (Zn)*

Zn is considered important for fighting SARS-CoV2 infection because of its multiple effects. It prevents replication of the SARS-CoV2 RNA genome and also inhibits the translation process [113]. It also increases interferon-α production by enhancing immunity to viruses [114]. Since doxycycline can transport divalent cations such as zinc into infected host

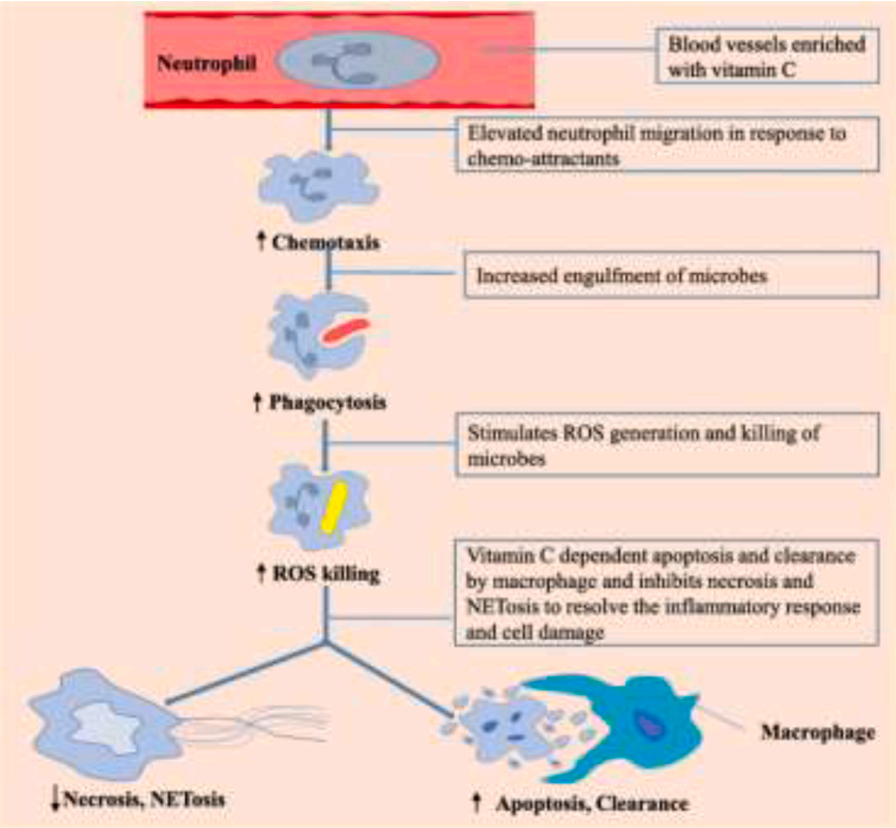

Fig. 9. Potential mechanism of VitC against cytokine storm.

cells, doxycycline exerts its therapeutic effect against SARS-CoV2 by increasing zinc transport, thereby preventing viral replication [115].

A recent study showed that Zn supplementation led to reduction in infection rates by reducing TNF production and increasing IFN-alpha [116].

Zn plays a vital role in receptor binding, cytokine response and IFNs release. Zn also inhibits the binding of IFN to the receptor and inhibits cytokine responses that prevent an IL6-mediated suprainflammatory and antiviral response (Yazar et al., 2016; [172]. Therefore, Zn may also be important in suppressing the exaggerated inflammatory response (Fig. 10).

Given the increase in Zn deficiency in the elderly and some chronic diseases, Zn replacement as part of routine treatment for these patients may appear to be a suitable option both to maintain a normal immune response and to benefit from antiviral effects. Zn deficiency affects both the innate and acquired immune systems, which can be amplified by Zn substitution [177].

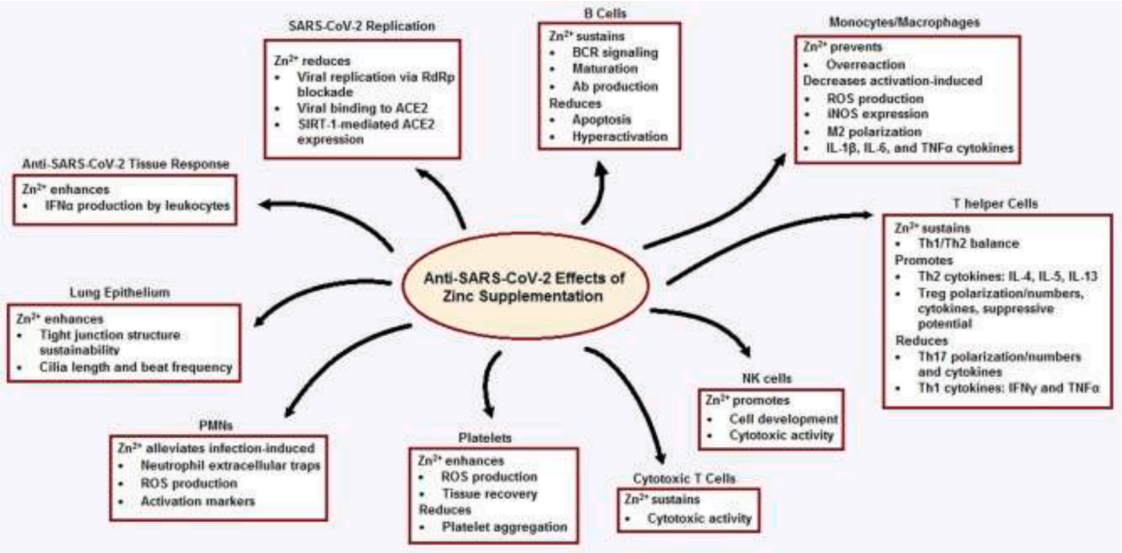

Fig. 10. Potential mechanism of Zn against COVID19.

4. Main results, final comments and conclusions

Cytokine storm caused by the SARS-CoV2 virus is a serious disorder with high lung damage rates. In a short time, SARS-CoV2 spreads through infected people all over the world, thereby increasing the spread of SARS-CoV2.

COVID19 has made major changes in the daily life of the world, destabilizing the global economy, and increasing lung damage rates. Although several studies, several advanced groups and worldwide research, have developed vaccines and drugs to treat SARS-CoV2, the disease continues to grow exponentially around the world. Therefore, new ways to prevent and stimulate an effective immune response need to be tested.

Despite the many difficulties in developing bioactive products in COVID19 drugs, there are increasing efforts to develop antiviral agents from bioactive products in clinical studies. The search for new antiviral agents made from natural ingredients remains a challenging but exciting task.

The conventional drugs can quickly treat the patient's main symptoms, but can cause serious side effects, while bioactive products have the benefit of safety. It is known that bioactive products can modulate the production of cytokines and immune cells. Proper immune response helps protecting the body from harmful substances and maintain immune system homeostasis. A systematic review and meta-analysis showed that integrated bioactive products had better effects and fewer side effects in patients with SARS-CoV2 than conventional drugs alone. Moreover, bioactive products have been reported to reduce side effects associated with conventional therapy in patients with SARS-CoV2. Therefore, further research is needed to determine the effectiveness and safety of bioactive products against COVID19.

Natural substances can play a decisive role in this. Based on several studies, we have come to the conclusion that bioactive products can be used as a platform for the manufacture of vaccines that act as coadjuvant, as they can easily bind to various cellular receptors.

In conclusion, we conclude that while using isolated bioactive ingredients is ideal due to their bioavailability, we emphasize that consuming a diet rich in biologically active natural products is also beneficial. Although its biological effects may not match those of isolated bioactive ingredients, it can still help people increase immunity and reducing cytokine storm when infected with SARS-CoV2.

Based on convincing evidence, it can be concluded that Natural products and its secondary metabolites have significant pharmacological bioactivity against cytokine storm in SARS-CoV2 patients. Its potent anti-inflammatory activity, including inhibition of macrophage infiltration and interactions with neutrophil endothelial cells, adhesion molecules, and cytokines, may be the main cause of inhibition in patients with SARS-CoV2. Natural product's potential as an immunomodulator, antioxidant to enhance its ability to inhibit ACE2 receptors, together with its antimicrobial activity can further help reduce symptoms and disease exacerbations, development of complications and death.

Overall, the antiviral, anti-inflammatory, and immunomodulatory properties of different secondary metabolites, together with its various pharmacological and molecular mechanisms, make it a promising therapeutic candidate against cytokine storm in COVID19. Moreover, bioactive product has safety status, molecular mechanisms, possible drug properties, and pharmacological effects, justify the use of Natural products as a nutrient against SARS-CoV2.

The information provided is based on the current state of research on the prevention, and elimination of lung damage, the mechanism of action of the presented natural products and their direct relationship to the cytokine storm. As shown in this review, plant extracts, and their bioactive ingredients are promising candidates for further research on their safety and effectiveness in preventing cytokin storm symptoms in SARS-CoV2 patients.

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The conventional drugs can quickly treat the patient's main symptoms, but can cause serious side effects, while bioactive products have the benefit of safety. It is known that bioactive products can modulate the production of cytokines and immune cells. Proper immune responses help protecting the body from harmful substances and maintain immune system homeostasis. A systematic review and meta-analysis showed that integrated bioactive products had better effects and fewer side effects in patients with SARS-CoV2 than conventional drugs alone. Moreover, bioactive products have been reported to reduce side effects associated with conventional therapy in patients with SARS-CoV2. Therefore, further research is needed to determine the effectiveness and safety of bioactive products against COVID19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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