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Inhibiting NF-κB During Cytokine Storm in COVID-19: Potential Role of Natural Products as a Promising Therapeutic Approach

Running title: Inhibiting NF-κB During Cytokine Storm in COVID-19

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Abstract

Many inflammatory mechanisms are involved in the pathophysiology of COVID-19 infection. COVID-19 inhibits IFN antiviral responses, so we should expect an out-of-control viral replication. “Cytokine storms” occur due to the over-production of pro-inflammatory cytokines after an influx of neutrophils and monocytes/macrophages and may be responsible for the immunopathology of the lung involvement. Several cascades have been reported in the activation process of NF-κB. In this paper, to find new therapeutic options for COVID-19 infection, we reviewed some natural products that could potentially

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inhibit the NF-κB pathway. We found that sevoflurane, quercetin, resveratrol, curcumin, KIOM-C, bergenin, garcinia kola, shenfu, piperlongumine, wogonin, oroxylin, plantamajoside, naringin, ginseng, kaempferol, allium sativum L, illicium henryi, isoliquiritigenin, lianhua qingwen, magnoflorine, and ma Huang Tang might be effective in inhibiting the NF-KB pathway. These natural products could be helpful in the control of COVID-19 infections. However, larger clinical trials are needed to ascertain the efficacy of these products fully.

Keywords: COVID-19, Pandemic, Natural Products, NF-KB.

1. Introduction

During a SARS-CoV infection, the viral antigen is recognized by the pathogen-associated molecular patterns (PAMPs) of the innate immune cells (1). Then PAMPs are identified by TLR-3, TLR-7, endosomal RNA receptors, and RIG-I/MDA5 (the cytosolic RNA sensor). When the viral antigens have been identified via PAMPs, downstream signaling pathways like NF-κB and IFR3 get triggered. Activation of these pathways contributes to the hyper-production of several pro-inflammatory cytokines. This situation is commonly known as a cytokine storm (2, 3). NF-κB is an upstream regulator of molecules such as IL-6, IL-8, TNF-α, MMP, and ICAM-1 (4-6). Based on the recent reports about the SARS-CoV and MERS-CoV viruses, preventing the activation of these signaling pathways could significantly decrease the probability of cytokine storms. Moreover, frequent studies have emphasized the part of NF-κB in the pathogenesis of COVID-19 (7, 8). Chinese traditional medicine has a broad spectrum of therapeutic ranges. Recent studies have reported the anti-inflammatory role of some Chinese herbal medicines. Some of these natural products have the potency to reduce the inflammation caused by the NF-κB pathway. The inhibition of the NF-κB pathway by these herbs raises the possibility of them being effective as potential therapeutic options for COVID-19 infection.

1.1. Virus Classification and Immune Response

After the emergence of a new coronavirus in China in early 2020, a pandemic outbreak was announced by the World Health Organization (WHO) (9-13). Members of the Coronaviridae family, including SARS-CoV-2, are enveloped by single-stranded RNA, positive-sense viruses (1, 14-17).

SARS-CoV-2 is composed of different structural and functional proteins. Structural proteins found on the SARS-CoV-2 membrane are E protein (envelope protein), M protein (membrane protein), and S protein (spike protein). The essential functional proteins in coronaviruses include helicase, RdRp protein, PLpro protein, and 3-CLpro protein. Both structural and functional proteins and some proteases are exclusively involved in the infection process, including intracellular virion transportation, proliferation, and assembling of the virions in host cells (18, 19). SARS-CoV-2 spikes allow it to stick firmly to ACE2. In addition, it is probably essential for inter-individual transmission (2).

The virus may diminish IFN antiviral responses causing an uncontrolled viral replication. Cytokine storms occur due to the over-production of pro-inflammatory cytokines after an influx of neutrophils and monocytes/macrophages and may be responsible for the immunopathology of the lung involvement. Th1/Th17 cell responses may also arise, leading to an aggravated inflammatory response in the patients. SARS-CoV-2 seems to share the entry receptor of ACE2, expressed by Type 2 alveolar cells and monocytes/macrophages in the lungs (4, 20-22).

Innate immune system cells identify the viruses invading the body by PAMPs. As mentioned earlier PAMPs are recognized by TLR-3, TLR-7, phagosomal RNA receptors, and RIG-I/MDA5 (the cytosolic

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RNA sensor). The identification of PAMPs by these receptors activates the downstream signaling pathways, such as NF-κB and IRF3, and their nuclear translocation. As the opening phase of defense in the case of COVID-19, the expression of Type-I IFNs and the other pro-inflammatory cytokines is elevated (3, 20). The JAK-STAT pathway, in turn, is activated by type I IFNs through IFNAR. So STAT1 and STAT2 are phosphorylated by the JAK-1 and TYK-2 kinases. The phosphorylated STAT1 and STAT2 are embedded in a complex with IRF9. This complex enters the nucleus of the cell to induce the transcription of ISGs within the limits of promoters of the ISRE. An acceptable ascent of the Type-I IFN response could probably inhibit the viral replication and its progression in the body at the start point (20, 23, 24).

1.2.Virus complications

Several complications have been reported due to SARS-CoV-2 infection, including fever, cough, and sore throat. Cases such as diarrhea, chest pain, and nausea also were observed in some patients (25). Moreover, some organ damages like acute kidney injury, cardiac injury, and lung injury were reported (26).

1.3. ALI and ARDS

During ALI, lung capillaries become permeable leading to inflammation. This condition occurs due to endotoxemia (27). A severe ALI condition also is called ARDS, takes place despite an endotoxin shock (28). In both of these conditions, the pro-inflammatory cytokines increase because the immune system is over-activated. Thus therapies in which the immune system is being suppressed are particularly essential (6).

1.4. NF-κB pathway

NF-κB is a nuclear transcriptional factor. It possesses many structural proteins which form both homo- and heterodimers. The Rel/NFkB dimer is composed of p50-RelA (p65) and is the most typical dimer in mammals (5). NF-κB potentially cooperates to regulate lots of effector genes that encode the cytokines and adhesion molecules like TNF-α, IL-6, IL-8, MMP-9, and ICAM-1 (29, 30). Figure 1 illustrates the NF-κB signaling pathway precisely.

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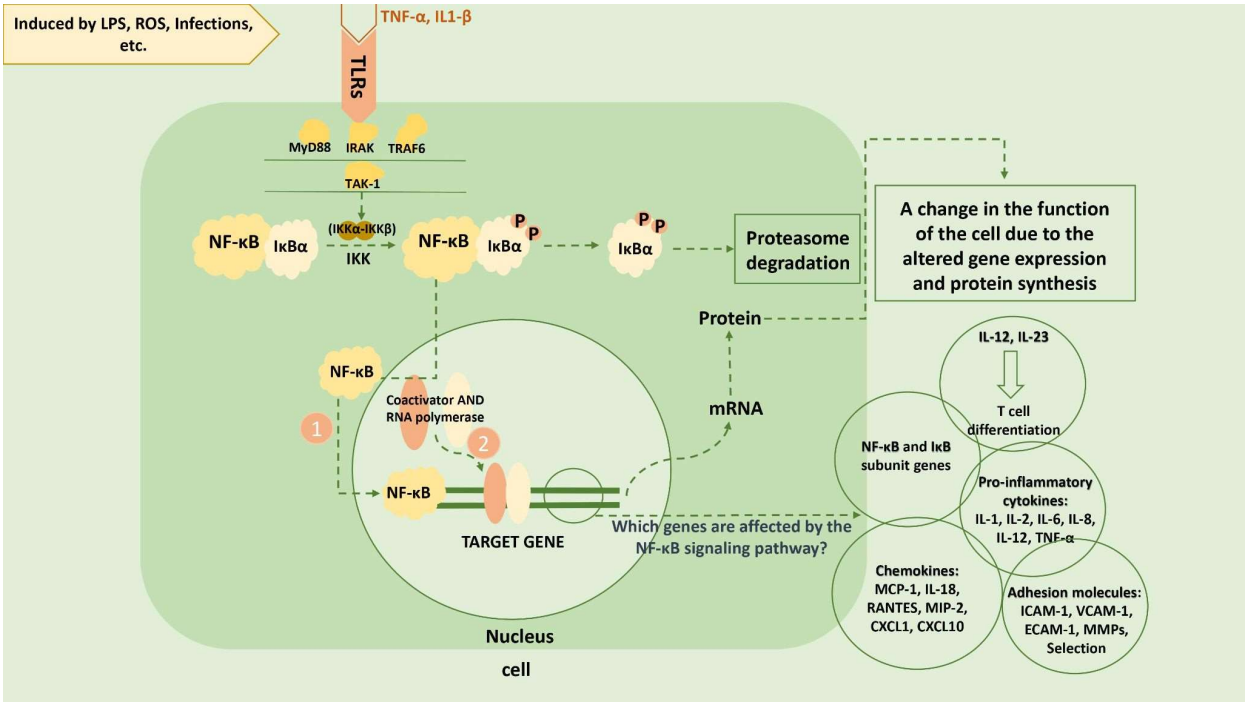

Fig 1. NF-κB signaling pathway. TNF-α, IL1-β, which are over-secreted induced by COVID-19 infection, are recognized by TLRs. Then IKK gets activated by the mediation of MyD88, IRAK, TRAF6 and TAK-1. IKK phosphorylates IκBα which is bonded to NF-κB, and this leads to the NF-κB activation. Later NF-κB enters the nucleus and activates coactivator and RNA polymerase to express specific genes, as shown in the figure.

Several cascades have been reported that get triggered by the activation of NF-κB. One of these cascades starts with the binding of TNF-α to its receptors (TNFR1 /TNFR2) (31, 32) which requires TRAF2, RIP, and NIK, all of them trimerized (33). NIK then both phosphorylates and starts-up IkB kinase (IKK) (34), which subsequently targets IkBa to attach it to ubiquitin and move it towards the proteasome in order to get it degraded. Another cascade occurs through the activation of PI3K by TNFR1 and its downstream target, Akt kinase (protein kinase B), which mediates the activation of NF-κB by promoting TNF-α (35).

HMGB1 protein is notorious for causing inflammation and cell damage. This protein is secreted to the extracellular matrix by stimulating inflammatory factors like LPS (36). It could take part as a DAMP (37), a perpetual part of many clinical conditions, such as ALI/ARDS, sepsis, asthma, and cancers (38, 39).

HMGB1 protein activates the inflammation-related signaling pathways through binding to a receptor for AGE's and the TLR-2/4. NF-κB and MAPK are two of these pathways that are flourished by overproduction of the downstream pro-inflammatory mediators, TNF-α, IL-1β, and IL-8 (40). There is some evidence that better therapy results could be achieved in LPS-induced ALI/ARDS by prohibiting the HMGB1-mediated TLR4/NF-κB signaling pathway (7, 8).

Some studies have introduced NF-κB as a significant factor in the pathogenesis of coronaviruses. A study by Dediego et al., also demonstrated the crucial role of NF-κB in the pathogenesis of SARS-CoV-2 due to different cytokines expression and inflammation. This study suggested that the inhibition of this pathway might be a viable solution to reduce inflammation caused by SARS-CoV-2 and the other coronaviruses (41).

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Gupegui et al., also showed the role of this pathway in MRES-CoV pathogenicity (42). Sallenave et al., introduced NF-κB as a crucial factor in new coronavirus pathogenesis and suggested that inhibition of this pathway might be helpful in the treatment of COVID-19 (43). A recent research revealed the efficiency of some natural products to inhibit the NF-κB pathway (44).

APCs can activate the NF-κB signaling pathway in different ways. Presentation of the SARS-CoV-2 antigens to CD4 plus T-helper cells through MHC class I molecules and recognition by APCs, is one way to activate the NF-κB signaling pathway. Viral antigens also can cause the release of IL-12 and subsequently motivate the activation of Th1 cells. As stated before, the activation of NF-κB induces the hyper-production of some pro-inflammatory cytokines. Among them, elevated levels of IL-17 have been observed the most in SARS-CoV-2 infection. These cytokines can mostly absorb neutrophils and monocyte to the site of infection; and activate some other chemokines and pro-inflammatory cytokines, namely IL-1, IL-6, IL-8 IL-21, TNF-β, and MCP-1 (45-48).

Moreover, APCs can distinguish the protein spike of SARS-CoV-2 by TLR-4. This differentiation leads to stimulation of the NF-κB and MAPKs pathways through Myd88`s mediation which can cause the production of inflammatory proteins. On the other hand, diagnosis of ssRNA or dsRNA genome of the coronavirus through the activation of TLR7/8 and TLR3 can recruit TRIF adaptor proteins which in turn activate IRF3 and NF-κB transcription factors and stimulates the production of pro-inflammatory cytokines such as TNF-β and IFN-α (20, 45, 46, 49). Overexpression of different cytokines can lead to a cytokine storm, which may gradually turn to ARDS. This information can be observed at a glance in figure 2. Given this background and prior research, we aimed to investigate potentially beneficial Chinese herbs that play a promising role in inhibiting the NF-κB pathway. If proven to behave as predicted, they could be a possible candidate for the management of ALI (50-52).

1.5. Summary of herbs

1.5.1. Sevoflurane:

Sevoflurane is an inhaled, sweet-smelling, methyl isopropyl widely used in general anesthesia. Inhalation of sevoflurane has anti-inflammatory and protective effects in some inflammatory processes such as sepsis or ischemia/reperfusion of blood flow in the heart, brain, kidneys, and liver (53, 54). It could also prevent ALI and liver ischemia/reperfusion (IR) (55, 56). The inhibitory effect of sevoflurane on LPS has been shown both in vivo and in vitro studies (55, 57, 58).

Sevoflurane improves resistance cytokine storms by lowering serum levels of IL-1 and -6, IFN-γ, and TNF-β. Moreover, sevoflurane has been shown to reduce NF-κB expression by increasing miR-9-5p expression and decreasing p56 factor expression; therefore, it helps protect the liver from IR damage (56).

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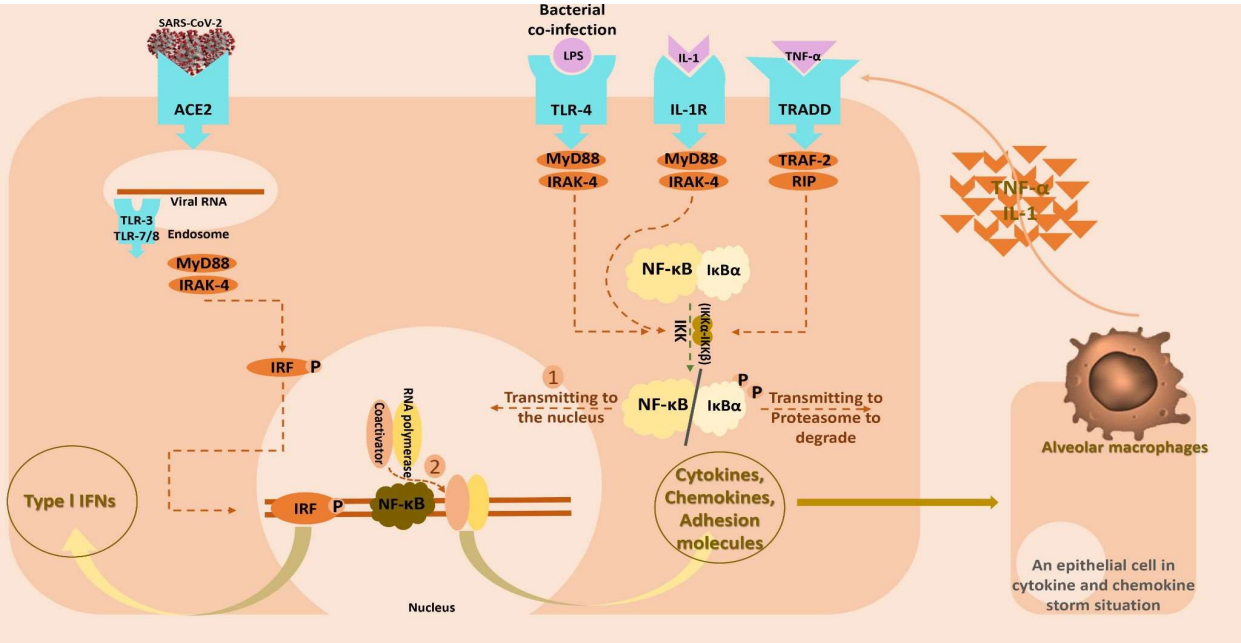

Fig 2. The correlation between cytokine storms induced by COVID-19 infection and NF-κB signaling pathway. SARS-CoV-2 can bind to ACE2 receptors as an entry point to the cell. Viral RNA in the endosome through TLR-3/7/8 and by the mediation of MyD-88 and IRAK-4 phosphorylates IRF. Then phosphorylated IRF in the nucleus induces the type I IFNs gene expression. The over-secretion of TNF-α and IL1-β by cells such as alveolar macrophages NF-κB pathway gets activated.

Recent research based on the western-blot technique shows that sevoflurane could improve the damages caused by inflammatory responses via blocking miR-27a, TLR4, MyD88, and NF-κB signaling pathway in airway smooth muscle cells (59). As a result, the lungs are protected from ALI (55, 60). It also increases the synthesis of PGE2 by COX-2 in peritoneal macrophages, which attenuates the severity of ALI (3, 54). So, it could be effective in COVID-19 infection.

1.5. 2. Quercetin:

Quercetin is a plant flavonol from the flavonoid group of polyphenols. Both in vivo and in vitro studies demonstrated anti-inflammatory, antiviral, anti-microbial, antitumor, and antioxidant effects of quercetin. It also reduces the risk of cardiovascular disease (23, 24). Previous studies have shown that quercetin downregulates NF-κB signaling pathways, leading to some anti-inflammatory impacts (61-64). Quercetin notably blocks LPS-induced production of NO, IL-1, iNOS, COX-2 (65) and inhibits the release of IL-6, CXCL10, MCP-1, RANTES, TNF-α, G-CSF, GM-CSF, LIX, VEGF, and LIF as well as calcium release in dsRNA induced with polyinosinic-polycytidylic acid (66).

Quercetin restricts LPS-induced inflammation through the blockage of Src- and Syk-mediated PI3K-(p85) tyrosine phosphorylation and also blockage of ensuing complex formation of TLR4, MyD88 AND PI3K. The complex downscales the activation of downstream signaling pathways. It also promotes the function of HO-1 in a dose and time-dependent manner. The phosphorylation of IKB, translocation of NF-κB, binding of NF-κB to AP-1, and transcriptional reporters are also suppressed by quercetin (65). It has been demonstrated that quercetin could reduce ICAM-1, both mRNA and protein levels, and also MCP-1 dose-dependently. Reduction of ICAM and MCP-1 is achieved by inhibiting the inflammatory signaling pathways, phosphorylation of MAPKs, an inhibitor of (IKK)α/β, and activating ATF2, which eventually

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leads to blockage of the NF-κB p65 transmission to the core (62). Due to Quercetin's inhibitory and suppressor effects on the inflammation and cytokine storms (67, 68), it can be a potential therapeutic option for the COVID-19 infection.

1.5. 3. Resveratrol:

Resveratrol is a stilbenoid, and a phytoalexin generated in several plants when they get hurt or some pathogens such as bacteria or fungi attack them. It has been found the most in the red grapes (69). Resveratrol has antioxidant (70), antitumor (71) and anti-inflammation (72) properties. Resveratrol therapy significantly diminishes the permeability of the pulmonary arteries. It also lowers the probability of cytokine storms caused by staphylococcal enterotoxin B and the resulting inflammation. This cytokine storm usually occurs after an increase in the caspase-8-dependent apoptosis in the SEB activated T cells. Resveratrol therapy significantly regulates myeloid Cd11b and Gr1 suppressor cells, thereby inhibiting the activation of SEB-mediated T cells under laboratory conditions. In addition, resveratrol therapy is associated with SIRT1 regulation and NF- κB down-regulation in the inflamed lung cells (73, 74). In another study, the administration of resveratrol significantly reduced spinal cord injury and also induced pulmonary edema (39).

Also, Resveratrol significantly reduces the neutrophils penetration and the inflammatory mediator's production. Resveratrol treatment was associated with careful regulation of SIRT1 expression and suppressing NF-κB activity in the lung tissue. Based on this evidence, resveratrol might be useful in treating COVID-19 infection (75, 76).

1.5. 4. Curcumin:

Curcumin is a lemon-yellow chemical is synthesized by Curcuma longa plants. It is the main curcuminoid of turmeric, a member of the ginger family, Zingiberaceae. This substance has anti-inflammatory, antimicrobial, antiviral, and antioxidant properties (77-79) partly because it influences the activity of COX-2, lipoxygenase, and iNOS enzymes. It cooperates to inhibit the production of inflammatory cytokines such as TNF-α, MCP-1, IL-1, IL-2, IL-6, IL-8, and IL-12 (80).

Administration of curcumin to minimize the lung involvement induced by intestinal ischemia-reperfusion injury (IIR) attenuated the inflammatory indicators such as MPO activity, IL-6, and ICAM-1 level. Attenuating these levels subsequently leads to the inhibition of the NF-κB pathway, in parallel reducing the SOD activity. Thus it has been shown that the NF-κB pathway gets inhibited through the anti-inflammatory and antioxidant effects of Curcumin (81).

Another study showed that curcumin could affect the immune system by changing the IL-1β, IL-4, and VEGF in the blood (82). In one study, curcumin was used to control liver toxicity caused by the oral administration of CCl4. Using CCl4 increases the levels of inflammatory mediators involved in liver damage such as TNF-α, IL-1β, and IL-6, which were dramatically suppressed by curcumin. CCl4 transmits NF-κB to the nucleus and the NF-κB DNA is prevented from binding to CCl4 by using curcumin (83). In a study on the effects of curcumin on Cardiac Ischemia/Reperfusion during cardiopulmonary bypass (CPB), levels of IL -8, IL-10, TNF-α, and cardiac troponin I, which increases due to heart damage, were significantly lower in the group receiving curcumin. In addition, apoptotic cardiomyocytes have been shown to decrease in those patients. Myocardial neutrophil activation, which is measured using myocardial MPO activity, was significantly reduced as well. In comparison, the group that did not receive curcumin saw a significant increase in the fracture fragments associated with apoptosis from Caspase 3 and poly-ADP-ADP-ribose polymerase. As a result, curcumin prevents NF-κB

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inhibition, increases inflammatory cytokines during CPB, and reduces the incidence of cardiomyocyte apoptosis after cardiac ischemia/reperfusion injury (84).

Another study found that curcumin inhibits NF-κB transport to the nucleus by inhibiting IKKβ, contributing to the stabilization of NF-κB inhibitor, IkBa, in the prostate cancer cells, PC-3. Controlling NF-κB activity reduces CXCL1 and -2 expression and eliminates the autocrine/paracrine ring that binds two chemotherapeutic compounds to NF-κB. Finally, curcumin reduces the formation of metastases in vivo by inhibiting NF-κB signaling and disrupting this feedback loop (85). Due to the anti-inflammatory and antioxidant activities of curcumin in the heart (86), lungs (87), liver (88), and kidneys (89), it might help the treatment of COVID-19 disease quite well.

1.5. 5. KIOM-C:

KIOM-C is a combination of several herbal medicines, including Platycodon grandiflorum, Angelicae Gigantis, Radix Glycyrrhizae, Radix, Zingiber officinale, Radix Paeoniae Alba, Radix Scutellariae, and Lonicera japonica Thunb. It possesses anti-H1N1 influenza effects (90-92).

An array of studies have shown that pigs grow better by consuming KIOM-C. It also protects their bodies against PCVAD (93).

In an in vitro study on mice by Talactac et al., antiviral activities of KIOM-C against H1N1 influenza (PR8), vesicular stomatitis virus, and Newcastle disease virus (94) were demonstrated. These effects are through the induction of protein phosphorylation (IRF3, p65, STAT1, TBK1, p38, and ERK), IFN type I and ISGs, and also the regulation of inflammatory cytokines (TNF-α, IL-6, IL-12) (RAW264.7). In an in vivo study, a BALB/c mouse treated with KIOM-C could survive longer and had lower viral titers against H5N2, H1N1, H7N3, or H9N2 in comparison to the untreated group (95).

Another study examined how KIOM-C influences the metastatic potential of HT1080 and B16F10 cells and whether it decreases the pace of tumors getting metastatic. Using KIOM-C to inactivate NF-κB reduces the activity of MMP-9 in the resting and stimulating state of PMA dose-dependently in HT1080 cells. Frequent oral administration of KIOM-C efficiently reduced lung metastasis to B16F10 cells (96). In the EH Kim study, oral administration of KIOM-C has been shown to boost the production of antiviral cytokines, such as IFN-γ and TNF-α, reduce the levels of inflammatory cytokines like IL-6, and also chemokines like MCP-1 in mice infected with H1N1 flu BAL (90). Therefore, this drug might be helpful in the treatment of COVID-19 infection.

1.5. 6. Bergenin:

Bergenin, which is also called Cuscutin, is a trihydroxy benzoic acid glycoside. It is the C-glycoside of 4-O-methyl gallic acid. It has an O-demethylated derivative known asnorbergenin and shows a potent immunomodulatory effect (97-99). In the Yang study, Bergenin reduced inflammatory cells and produced IL-1β and IL-6 in BALF through the expression of MyD88 protein and the inhibition of NF-κB P65 phosphorylation and nuclear translocation in Raw264.7 cell lung tissue. It also produced TNF-α, IL-1β, and IL-6 in the serum of mice dealing with ALI caused by LPS (100).

As a PPAR-γ agonist, Bergenin reduces TNF-α and IL-6 expression by improving the presentation of SIRT1 and inhibiting NF-κB-mediated macrophage activation (101). In a study by X Gao et al., Bergenin suppressed the expression of NO, IL-1β, TNF-α and IL-6 by getting NF-κB and MAPKs signaling pathways inactivated. This may introduce a new therapeutic option for reducing inflammation of the lung tissue caused by LPS (102). Thus, Bergenin might be helpful to the treatment of COVID-19.

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1.5. 7. Kolaviron

Kolaviron is mainly obtained from Garcinia kola extract (103), a species of Angiosperms in the Clusiaceae family (104, 105). It possesses antihepatotoxic (106), antioxidant, and antiseptic properties (107). In Abarikwu et al. (2014), when pre-treated macrophages with Kolaviron (Kol-V) were stimulated by LPS, phosphorylation of MAPK11, pc-JUN, Akt, ERK1/2, IκBα, and NFκB (p65) was blocked. However, Kol-V failed to block the phosphorylation of CREB. In addition, Kol-V inhibited the expression of CXCL10 mRNA but did not affect LPS-induced reduction in cytokines expressions such as IL-1α, IL-1β, IL-33 and IFNβ1-1. Kol-v also showed some protective effects on phosphorylation of LPS kinase protein activated by MAPK, a member of the JNK family. In all Kol-V concentrations, there were no effects induced by Kol-v on LPS-induced TNF-α inflammatory cytokine secretion. Still, inhibition of Kol-v concentration was observed in IL-6 secretion. Kolaviron reduced pulmonary expression of IL-1b, RANTES, IL-10, MCP-1, NF-κB, iNOS, and COX-2 (108). Therefore, it might have a potential role in treating COVID-19 due to its antioxidant properties and the potential to suppress cytokine storms.

1.5. 8. Shenfu:

Shenfu is a traditional Chinese natural product. It has been approved by the Chinese State Food and Drug Administration. It originates from Ginseng Radix et Rhizoma Rubra and Aconiti Lateralis Radix Praeparata. The anti-inflammatory effects of Shenfu are well-known in China. Shenfu injection is approved in treating septic shock (109). Shenfu can raise superoxide dismutase activity and has some antioxidant effects by removing oxygen free radicals and inactivating xanthine oxidase (110). Shenfu also has a Ca2+ regulating effect which is achieved through blocking the intracellular Ca2+ channel and preventing intracellular Ca2+ overload (111).

In vivo studies convey that Shenfu might inhibit the generation of pro-inflammatory cytokines such as TNF-α and IL-6 beyond the dose and also prevent their production in the lungs. Besides, Shenfu can suppress their gene regulator, NF-κB (112). A Shenfu injection could significantly reduce complement components like C3, C4, and C5b-9 as well (113).

Shenfu reduces neutrophil accumulation into the lung tissue through its apparent suppression of NF-κB and other pro-inflammatory cytokines. Thus, it has a protective effect against pulmonary edema (112). In addition, Shenfu could prevent translocation of NF-κB, but it's unable to prevent the production of TNF-α in the lungs. This is because though NF-κB is the key upstream regulator of TNF-α, it is not the only one. Secondly, it is partially inhibited by the anti-NF-κB pathway (114).

1.5.9. Piperlongumine:

Piperlongumine (PL) is an active dihydropyridine alkaloid (115). It is extracted from Piper Longum and long pepper plants (116). It has insecticidal, antibacterial, anticarcinogenic, antidiabetic, anti-platelet aggregation, and anti-fungal properties (115, 117-121).

PL acts via ROS-dependent apoptotic pathways mediated by H2O2 and NO (122). In vitro studies showed that administration of PL could attenuate TNF-α levels. In addition, it significantly blocked the nuclear translocation of p50 and p65 (122). PL not only attenuated NF-κB translocation but also attenuated ph-Akt and its downstream targets (123). IL-6, IL-8, ICAM-1, and MMP-9 also decreased significantly by using PL due to attenuated activation of NF-κB (124). Several in-vitro studies have shown the anti-inflammatory impacts of PL, which acts through inhibition of LPS-induced inflammation, collagen-induced arthritis, and neuroinflammation (125-127). Robust evidence indicates that PL exerts its anti-inflammatory effects through the down-regulation of NF-κB (128, 129).

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1.5.10. Wogonin:

Wogonin is a component obtained from nature belonging to the bioflavonoids and extracted from the roots of Scutellaria baicalensis Georgi (130-132). Wogonin inactivates the NF-κB pathway, which leads to suppression of LPS-induced expression of iNOS, NO, TNF-α, and IL-1β (133, 134).

In vivo studies demonstrated that Wogonin turns off IL-6 and IL-8 gene expression; it also stops NF-κB binding to the DNA, contributing to down-regulation of inflammation-associated protein COX-2 production and preventing the inflammation. Available data show that Wogonin could be beneficial to treat inflammatory diseases, including COVID-19 infection (135).

Furthermore, Wogonin can inactivate TLR4 adaptors (MyD88 and TAK1) in LPS-induced inflamed cells (136). Also, in vitro studies showed promising evidence that Wogonin can inhibit LPS-induced inflammation via inhibition of the TLR4/ NF-κB pathway and reduce IL-6, IL-8, IL-1β, TNF-α, COX-2, and iNOS gene expression (137). Other studies also revealed that Wogonin could reduce pro-inflammatory mediators in LPS-induced inflammations, including COX-2, iNOS, IL-1B, IL-6, and TNF-α through the inhibition of NF-κB and MAPKs signaling pathways (138).

1.5.11. Oroxylin A:

Oroxylin A (OroA) is an active Polyphenol compound extracted from Scutellariae radix. This compound has anti-inflammatory, antipyretic, analgesic, and antitumor properties (139, 140).

In vivo studies on rodents demonstrated that OroA significantly lowers the lung inflammation severity and the mortality rate of LPS-induced ALI. OroA profitably suppresses the NF-κB signaling pathway, which contributes to lessening the inflammation severity and probability. It significantly obstructs the elevated circulating TNF-α levels and NO release of the nuclear HMGB1 into the cytoplasm. OroA also prevents the accretion of macrophages and neutrophils in the tissue space. Furthermore, OroA restrains the intra-alveolar septa of the lungs from thickening (141).

Evidence shows that OroA could attenuate the formation of pulmonary edema by protecting endothelial function to alleviate neutrophil sequestration. Although the overproduction of NO and TNF-α causes injury to vascular endothelial cells and an increase in permeability of lung vessels, OroA could alleviate vascular damage by reducing these mediators (142).

iNOS and two other enzymes generate NO, a potent lung vasodilator, from L-arginine in the alveolar macrophages. OroA restrains iNOS gene expression, so it stops the alveolar macrophages producing NO and reduces inflammation in the lungs (143).

OroA reduces the cytokine release during and following the inflammation and prevents the irremediable damages caused by the release of HMGB1. Also, since OroA has anti-NF-κB properties, it blocks the release of LPS-induced NO (143). In vivo studies reported that OroA has a dramatic potency to ameliorate asthma by inhibiting ovalbumin (OVA)-induced lung histopathologic changes mediated by NF-κB activation, AHR, the levels of OVA-specific IgE in serum, and Th2 cytokines in BALF (144). OroA also could act against human tumor cells through inducing apoptosis and cell cycle arrest and through the anti-invasion function (145).

1.5.12. Plantamajoside:

Plantamajoside (PMS) is a unique compound identified as a phenylpropanoid glycoside (146). It is a principal constituent extracted from Plantago asiatica L. (Plantaginaceae) and has been recognized for its broad bioactivities such as antioxidant, anti-proliferative, antitumor, antiviral, diuretic, and anti-

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inflammatory properties (146-150). PMS could exert anti-inflammatory influences (150), and no adverse effects were reported induced by the oral administration until 90 days (151).

The distinct character of LPS-induced lung inflammation is pulmonary edema (152). The infiltration of the activated neutrophils into the lungs and the production of the MPO (153, 154), which is the main ingredient of neutrophils cytoplasmic granules, is always observed in the ALI inflammatory response (155). IL-6, IL-1β, and TNF-α are some predictive markers in ALI, and let us know if the ALI will respond to the treatment by PMS or not (75).

PMS showed an anti-inflammatory potency in vivo by reducing IL-6, IL-1β, TNF-α and also increasing IL-10 dose-dependently (156). This dramatic effect is achieved by inhibiting NF-κB and MAPKs phosphorylation in LPS-induced ALI (157). PMS could efficiently protect advanced glycation end-product-induced endothelial cells (AGEs) against inflammatory cellular dysfunction (158). Thus, PMS can protect the body against many respiratory inflammatory diseases, namely asthma and chronic obstructive pulmonary disease (COPD) (159).

1.5.13. Naringin:

Naringin is a flavanone glycoside mostly found in grapes and citrus fruits. It has antioxidant, antibacterial, anti-atherosclerosis, anti-inflammatory, and anti-hyperlipidemic properties and could efficiently lower blood glucose levels (160-166).

In vitro and in vivo studies have asserted that Naringin attenuates the effects of ALI through alleviating pathological lung changes and facilitating the LPS-induced sepsis model via inhibition of the NF-κB signaling pathway (167, 168). Naringin could reduce the release of TNF-α and HMGB1 from the macrophages stimulated by LPS (169). Moreover, it elevates the anti-inflammatory IL-10 and decreases the release of pro-inflammatory cytokines such as IL-6 and neutrophils MPO (163, 170).

Flavonoids, a class of polyphenolic secondary metabolites in plants, possess antiviral properties (171). In a vast majority of COVID-19 patients who show increased levels of TNF-α, IL-1β, and IFN-γ, cytokine storms have been observed. LPS is the main constituent of the outer membrane of all Gram-negative bacteria. It induces an increase in cytokines such as TNF-α, IL-1β, IL-6, IFN-γ, and MCP-,1, leading to a cytokine storm (172). It is concluded that Naringin (at concentrations of 10, 20, 40 μg/mL) has the potency to reduce inflammatory cytokines such as IL-1β, and IL-6, and subsequently COX-2, iNOS via the inhibition of p38 MAPK and HMGB-1 signaling pathways (173). Several studies on 2019-nCoV binding sites showed that this virus has a high affinity to the human ACE2, which is widely expressed in the kidneys, lung, brain, and digestive tract (174).

Results demonstrated that Naringin might have the highest binding activity to the ACE2 among citruses, close to chloroquine docking energy. This restrains the virus from attaching to the ACE2 and blocking it (173, 175). Several studies have demonstrated that increased levels of TNF-α could lower the survival of osteoblast cells and differentiation from its precursors, even though it is reported that Naringin at a high dose can alleviate the TNF-α-associated osteoporosis via inhibition of the NF-κB signaling pathway (176, 177). Sometimes, the activation of the NF-κB signaling pathway could be due to free radicals, which would subsequently cause inflammation. At a dosage of 100mg/kg, Naringin could significantly reduce oxidative stress and decrease the levels of oxidative enzymes. Also, it could decrease the MPO levels, NF-κB-DNA-binding activities, and pro-inflammatory cytokines, such as IL-6 and TNF-α, which lead to inflammation suppression (178).

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1.5.14. Ginsenoside:

Ginseng is the root of the Panax ginseng C.A. Meyer plant. Studies have shown that the Re and Rg6 types are effective in the immune system as an anti-inflammatory drug (179, 180).

Ginsenoside can inhibit IKK-β phosphorylation, NF-κB activation, and the expression of inflammatory cytokines like TNF-α and IL-1β, LPS induced IRAK-1 phosphorylation and degradation of IRAK-1 and IRAK-4 in the LPS-stimulated peritoneal macrophages. However, it still does not act on TNF-α or PG-stimulated peritoneal macrophages (179, 181-183). In addition, Ginsenoside blocks the binding of LPS to TLR4 on peritoneal macrophages in the inflammatory processes.

Studies have shown that oral administration of Ginsenoside significantly inhibits the expression of IL-1β and TNF-α in LPS-induced systemic inflammation and TNBS-induced colitis (179, 184-186). An in vivo study demonstrated that Ginsenoside down-regulates the NF-κB pathway in TNBS-treated mice (179).

Ginsenoside Rg6 is a rare type of Ginsenoside that can regulate inflammation reactions, reduce neutrophil infiltration, expression of TNF-α and increase serum levels of IL-10. Rg6 inhibits inflammatory signals like NF-κB activator and MAPKs (180, 182, 185, 187, 188). Additionally, Rg6 induces an operator of miRNA called miR-146a as an anti-inflammation substance (180). Ginsenoside can have some magnificent anti-inflammatory effects that might be helpful in the COVID-19 therapy.

1.5.15. Kaempferol:

Kaempferol contains flavonoid compounds that can effectively prevent lung inflammatory diseases like influenza and ALI. Based on recent studies, this substance has reduced the production of ROS and MDA. Also, this natural drug decreases the production of inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, helping to the down-regulation of the lung tissue inflammation (189-193). In the inflammatory pathways, Kaempferol upregulates TLR4, MyD88, and NF-κB p65 DNA binding activity (194). Also, it can suppress the MAPKs level (195).

A recent study regarding Kaempferol on H9N2 influenza virus demonstrated that Kaempferol produces an effect that protects the body from the virus invasion and the subsequent inflammation through TLR4/MyD88 suppression and also the NF-κB and MAPKs pathways (195).

Another investigation assessed the effects of Kaempferol on LPS induced ALI in vivo (196). It showed that Kaempferol suppresses the MAPKs and NF-κB signaling pathways, which probably are responsible for tissue oxidative injury and inflammation reactions of the lungs (196, 197). Therefore, Kaempferol might help inhibit pulmonary inflammation, one of the most critical obstacles in treating the COVID-19 infection.

1.5.16. Allium sativum L.:

Allium sativum L. is the scientific name of garlic. Garlic possesses anti-carcinogenic and anti-infection properties and is protective against cardiovascular disease (198-202). The chemical substance extracted from garlic is called methyl 3-formyl-4methykpentanoate (SMFM), potentially inhibiting lung inflammation. It also inhibits NO, PGE, TNF-α, IL-6, and IL-1β as inflammatory factors in LPS-induced infections (24, 203-206).

In a study on Cecal ligation and puncture (CLP), an experimental polymicrobial sepsis model in mice, SMFM decreased bacterial peritoneal fluid infections and inhibited the production of pro-inflammatory cytokines. Moreover, lymphocyte apoptosis decreased in the spleen (24). In another in vitro study, macrophages survived using SMFM substance in LPS-induced inflammation. The findings included the

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inhibition of NO, PGE, TNF-α, IL-1β, COX-2, and NF-κB protein expression and transcription (206). As previously noted, inhibition of NF-κB signaling can help to treat COVID-19 infection.

1.5.17. Illicium henryi:

Illicium henryi is a medical plant used in traditional medicine, especially in eastern Asia and China (207). Studies report that this plant possesses antioxidative and antiviral properties, especially against HBV and HIV (208). This root contains flavonoids like quercetin, neolignans, sesquiterpene, ligans, and glycosides, which are the origins of the antioxidant and anti-inflammatory properties (209-211).

Two recent in vivo studies confirmed the effects of the Ethanol extract (EEIH) of Illicium henryi (EEIH) on LPS-induced acute liver and kidney injury and acute kidney injury in mice (185, 186, 212). The first study, which has focused on LPS-induced AKI in mice, showed that EEIH significantly decreased serum creatinine and blood urea nitrogen rates in mice. EEIH restrained the expression of TNF-α, IL-1β, and IL-6 and the production of COX-2 by downregulating TLR4 and NF-κB phosphorylation dose-proportional manner during inflammation (213).

The other observed effects were reducing NO, MDA, and glutathione and decreased SOD levels (185, 214, 215). The second study evaluated EEIH effects on LPS-induced ALI. They showed that EEIH reduced the expression of pro-inflammatory factors, including TNF-α, IL-1β, IL-6, and COX-2, based on the exact mechanism employed by the other investigation. Like the former study, NO, MDA levels decreased, and a reduction in SOD levels was observed. Upregulation of Nrf2 was observed as well (185, 216). According to these studies showing the suppression effects of this drug on the TLR4/NF-κB pathway, it can treat inflammation, and therefore might be useful in treating COVID-19 infections.

1.5.18. Isoliquiritigenin:

Natural flavonoid Isoliquiritigenin (ILG) is a chemical substance extracted from the roots of the Glycyrrhiza species. It inhibits the activation and phosphorylation of NF-κB in LPS stimulated macrophages that subsequently causes the down-regulation of the pro-inflammatory molecules, including PGE2, TNF-α, and IL-6 (217).

Also, in endothelial cells treated with TNF-α, ILG can inhibit the transcription and expression of the adhesion molecules like VCAM-1 and E-selectin (218). ILG is effective against the influenza virus as well. It activates the expression of antioxidant enzymes via the transcription factors for Nrf2 (219, 220). A recent study assessed the effects of ILG on improving inflammation and viral replication in human bronchial epithelial cells (187).

It is found that ILG inhibits the release of inflammatory factors from infected cells. This anti-inflammatory function is achieved through the activation of the PPARɣ signaling pathway (221). ILG also reduced the expression of cytokine proteins, and subsequently, inflammation in the patient's lung tissue (222, 223). Moreover, by using ILG, the inflammatory cells, especially T cells infiltration, has been attenuated in mice. Based on these findings and the anti-inflammatory effects of ILG in the lung cells, this substance might effectively treat COVID-19 infections.

1.5.19. Lianhua Qingwen:

Lianhua Qingwen (LHQW) is a traditional Chinese medicine with anti-inflammatory and immune regulatory effects (224, 225). LHQW suppressed IL-8, IL-6, TNF-α, CCL-2, CXCL-10, MCP-1, and NF-κB activation in a dose-proportional manner. LHQW suppresses many factors that contribute to worsening a viral infection. Therefore it has some antiviral functions (188, 224, 226).

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A recent in vivo study evaluated the effects of LHQW on A-type influenza. Phosphorylation of NF-κB, expression of IL-8, IL-6, TNF-α, CXCL10, and MCP-1 was found to be suppressed by this substance (188). Also, the antiviral activity of LHQW against SARS-CoV-2 has been reported in vitro. Data suggest a significant reduction of IL-6, TNF-α, CCL-2, CXCL-10, and MCP-1 expression following LHQW. The SARS-CoV-2 replication was inhibited as well (227).

Research performed by Liang Dong et al., about treatment with LHQW in acute exacerbation of chronic obstructive pulmonary disease showed a reduction in the expression of IL-8, IL-17, IL-23, and TNF-α after the treatment in the patients (190). In another research, LHQW down-regulated the MCP-1 serum levels in LPS-induced ALI in mice (191). Based on these and other studies, the anti-inflammatory properties of LHQW might help treat COVID-19 infections (228, 229).

1.5.20. Magnoflorine:

Magnoflorine (MAG) is an alkaloid that is extracted from Tinospora species. It has antioxidative, anti-anxiety, anticancer, anti-cancer and anti-inflammatory properties (230). In Chinese herbal medicine, it is used to treat coughs, headaches, allergic diseases, and psychological disorders like depression. It also helps to lower the blood pressure (231-234).

In general, MAG inhibits the expression of IL-1β, TNF-α, IL-6, phosphorylation of p65, p38, ERK and IκBα. Besides, it suppresses NF-κB, related factors and cytokines. A study using LPS-induced models found that MAG inhibits the TLR4/NF-κB signaling pathway in vitro and also decreases the expression of IL-1β, IL-6, IL-8, and TNF-α (192).

A recent study evaluated the NF-κB signaling pathway activity in the macrophages in vitro. Findings showed that TNF-α, IL-1β, and PGE2 were upregulated by MAG (193). Another recent in vivo study on mice demonstrated the anti-inflammatory effects of MAG in LPS induced acute lung injury. They demonstrated that MAG inhibits the TLR4/NF-κB signaling pathway and also reduces the production of the MAPK and NF-κB signaling pathway-related proteins as well as pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6 (194). Therefore, due to the promising anti-inflammatory properties of MAG, it might prove valuable in the treatment of COVID-19 infections.

1.5.21. Ma Huang Tang:

Ma Huang Tang (MHT) is a classic Chinese herbal medicine usually used for upper respiratory tract infections like influenza, bronchitis, asthma, and fever and headaches (235, 236). Some investigations have shown that MHT decreases lung index, TNF-α, IL-4, IL-5, IL-1β, CD3+/CD8+ T cell rates, protein expression of TLR4, TLR7, MyD88, and NF-κB. It also increases IL-10, IFN-γ, IL-2, and CD4+/CD8+ T cell rates.

Anti-inflammatory properties of MHT are related to inhibiting the MYD88-dependent pathway of TLR4 (196, 237). Three recent studies performed by Wenyang Wei et al., evaluated the effects of MHT in Influenza A-induced viral infections. In vitro studies showed some effective antiviral functions for MHT. The results also represented a reduction of IL-4, IL-5, and an increase in IL-2, IFN-γ due to the inhibition of the TLR4 pathway, MYD88-dependently (237). Another study investigated the effects of MHT in Influenza A-induced viral infections in vitro and in vivo. They found a reduction in IL-1β, TNF-α, and NF-κB (196).

In another investigation on Influenza-infected cells, a reduction of TLR4, TLR7, MYD88, and TRAF6 expression was found. The mechanism of this reduction was the inhibition of the TLR4 signaling pathway by MHT. Based on these studies and the reported anti-inflammatory properties of MHT, it might help treat COVID-19 infections (237).

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2. Conclusion

In conclusion, sevoflurane, quercetin, resveratrol, curcumin, KIOM-C, bergenin, garcinia kola, shenfu, piperlongumine, wogonin, oroxylin, plantamajoside, naringin, ginseng, kaempferol, allium sativum L, illicium henryi, isoliquiritigenin, lianhua Qingwen, magnoflorine and ma Huang Tang were all found to be effective to inhibit NF-κB pathway which in turn reduces the probability of cytokine storms. Therefore, these natural products could prove helpful in the control of COVID-19 infections. However, more extensive comprehensive studies and clinical trials will be required to demonstrate these effects beyond doubt, especially if they are to be used as a form of approved treatment.

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Table 1. In vivo studies investigating the role of NF-κB pathway to inhibit cytokine storm

Studies	Natural Product	Dose	Inflammatory Agent	Effect	
				Signaling Pathway	Cytokines
(54)	***Sevoflurane***	3.4%	LPS	Induce PGE2	Increase IL-10 & Reduce IFN- γ
(84)		3%	LPS	Blocking miR-27a /TLR4/ MyD88/NF-κB	Decrease TNF-α, (IL)-1β & IL-6
(24)	***Quercetin***	2 mg/ml and 4 mg/ml	Radiation-induced lung injury (RILI)	Decrease NF-κB/MAPK & JNK/SAPK, p38 and p44/p42	Decrease TNF-α, (IL)-1β IL-8 & IL-6
(84)	***Resveratrol***	100 mg/kg	Spinal cord injury	Up-regulation of expression of SIRT1 and suppression of NF-κB activity	Increase IL-10 & Reduce IL-1 & IL-6
(73)		100 mg/kg	Staphylococcal enterotoxin B	up-regulation of expression of SIRT1 and suppression of NF-κB activity	Increase cd11b+ and gr1+
(81)	***Curcumin***	1 mg/kg and 5 mg/kg	Intestinal ischemia-reperfusion injury (IIR)	Inhibiting NF-κB	Decrease IL-6
(83)		200 mg/kg, p.o.	CCl4	inhibiting NF-κB	Decrease TNF-α, IL-1β, and IL-6
(84)		70 μM/kg	Cardiac Ischemia/Reperfusion	inhibiting NF-κB	Decrease IL-8, IL-10 &TNF-α
(85)		15 μM	Prostate cancer metastasis	inhibition loop between NFκB and CXCL1/-2	Decrease CXCL1 and -2
(84)	***KIOM-C***	150 μM(0.163 mg/L)	H1N1 flu	IFN type I	Increases TNF-α & decrease IL-6, IL-10 MCP-1
(238)	***Kolaviron***	15, 25, 50 and 100 μM	LPS	Inhibition ERK1/2, NF-κB, p38, Akt, p-c-JUN and JNK	Inhibition of IL-6 secretion
(84)		400 mg / kg	A/H3N2/ Pert/16.09	Reduces pulmonary expression of NF-κB	Reduces IL-1b, RANTES, IL-10, MCP-1
(7)	***Shenfu***	0.1 mg aconitine and 0.5 mg ginsenoside per milliliter	LPS	Abolished NF-κB	Decreased IL-6
(239)					
(84)		1 mg/mL Panax ginseng C. A. Mey. and 2 mg/mL	Epinephrine	Ischemia accompanying cardiac arrest	Decreased IL-6, IL-8 and TNF-α

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		Radix Aconitum Carmichaeli.			Decreased C3, C4 and C5b-9 Increased IL-4 and IL-10
		10, 100 mg/kg	LPS	Reduced NF-κB	Inhibited TNF-α and IL-6
(84)	***Piperlongumine***	10 mg/kg	Ovalbumin	Inhibiting NF‑κB	Reduced the serum IgE level, TNF‑α and IL‑6
(129)		10-30 mg/kg	LPS	Inhibited NF-κB signaling cascade	Reduced IL-1β, IL- 6, TNF-α, IL-17, IL-22, and (TGF)-β
(84)		50 and 100 μM	LPS	Inhibition of NF-κB–Akt–AP-1– p38/ERK1/2-JNK MAPK signaling pathways	Reduced IL-6
(69)	***Oroxylin A***	15 mg/KG	LPS	Abolished NF-κB	Blockade of TNF, NO, HMGB1
(84)		15, 30, and 60 mg/kg	Ovalbumin	Inhibited NF-κB	Reduced IL-4, IL-5, IL-13, and serum IgE
(156)	***Plantamajoside***	25, 50 and 100 mg/kg	LPS	Inhibition of the NF-κB and MAPK	Reduction in IL-1β, IL-6, and TNF-α and elevation in the IL-10
(84)	***Naringin***	30 or 60 mg/ kg	LPS	Inhibition of NF-κB	Decreased IL-6, TNF-α, and HMGB-1 Elevated IL-10
(178)		100 mg/kg	Gentamycin	Inhibition of NF-κB	Decreased TNF-α and IL-6
(84)	***Ginsenoside***	20 mg/kg	LPS PG	Blockage of binding of LPS to TLR4	Inhibition of IL-1β, NF-κB and TNF
(183)	***Kaempferol***	100 mg/kg	LPS	Blockage of MAPKs and NF-κB signaling pathway	Decreasing inflammatory factors like TNF-α, IL-1β, and IL-6
(84)	***Allium sativum L.***	15 mg/kg	LPS	Blockage of cytokine storm/ enhancing microbial killing	Inhibition of HL-1β and TNF-α
(185)	***Illicium henryi***	1.25 – 5 mg/kg	LPS	Suppression of NF-κB/TLR4 pathway/ upregulating Nrf2	Decreasing inflammatory factors like TNF-α, IL-1β, and IL-6
(84)		1.25 – 5 mg/kg	LPS	Suppression of NF-κB/TLR4 pathway/	Decreasing inflammatory factors like TNF-α,

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				upregulating Nrf2	IL-1β, and IL-6
(187)	***Isoliquiritigenin***	10 mg/kg	Influenza A (H1N1 strain)	Activation of the peroxisome proliferator-activated receptor-gamma (PPARϒ) pathway/ inhibits activation of NF-κB	Decreasing inflammatory factors like TNF-α, PGE2, and IL-6
(84)	***Lianhuaqingwen***	0.35 – 2 mg/ ml	Influenza A	Suppression of NF-κB activation	Reduction of IL-8, IL-6, TNF-α, IP-10, and MCP-1
(190)			AECOPD patients	Suppression of IL-8 and TNF-α (important mediators in AECOPD)	Reduction of IL-8, IL-17, IL-23, and TNF-α
(84)		300 – 1200 mg/kg	LPS	Decreasing MCP-1 serum level	Reduction of TNF-α
(194)	***Magnoflorine***	5, 10, and 20 mg/kg	LPS	Inhibition of the TLR4- NF-κB signaling pathway	Reduction of IL-1β, TNF-α, IL-6

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Table 2. In vitro studies investigating the role of the NF-κB pathway to inhibit cytokine storm

Studies	Natural Product	Dose	Inflammatory Agent	Effect	
				Signaling Pathway	Cytokines
(66)	***Quercetin***	>50 μM	Polyinosinic-Polycytidylic Acid	Blocking calcium-STAT	Decrease IL-6, MCP-1, IP-10, RANTES, GM-CSF, G-CSF, TNF- α, LIF, LIX, and VEGF
(84)		5-20 μM 98%	LPS	Inhibit tyrosine-phosphorylated phosphatidylinositol 3-kinase and myeloid differentiation factor-88 association and inhibit MAPK/AP-1 and IKK/NF-κB	Decrease TNF-α, (IL)‑1β IL-6 & GM-CSF
(62)		2.5-20 μM	(IL)‑1β	Blocking of MAPK and NF-κB	Decrease IL-8, IL-6, MCP-1 &TNF-α
(84)	***Resveratrol***	1 mg/mL	LPS	Blocking MAPK, NF-κB & TLR negative regulator	Decrease TNF-α, IL-6, IL-1β, and IL-12p70, IRAK-1
(101)	***Bergenin***	20, 50 mg/kg with the purity>98%	Dextran sulfate sodium (DSS)	Regulating PPAR-γ /SIRT1/NF-kB-p65 pathway	Reduces TNF-α and IL-6 expression
(84)	***Piperlongumine***	NA	NA	Attenuate NF-κB	Reduced IL-6, IL-8, MMP-9, and ICAM-1
(121)		3μM	LPS	NA	NA
(84)	***Wogonin***	0‑50 μM	LPS	TLR4/NF-κB signaling pathway	Inhibition of IL‑1β, IL‑6, IL‑8, COX‑2, iNOS, and TNF‑α
(138)		0–100 μM	LPS	TLR4–MyD88–TAK1-Mediated NF-κB and MAPK Signaling Pathway	Inhibition of expressions of iNOS, COX-2, TNF-a, IL-1b, and IL-6
(84)		10 and 50 μM	LPS	TLR4-MyD88-TAK1-mediated NF-κB pathway	Decreased IL-1b, IL-6, IL-8, COX-2, and iNOS
(145)	***Oroxylin A***	100 μM	LPS	Inhibited NF-κB	Reduced IL-6

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(84)	***Plantamajoside***	20 or 40 μg/ml	LPS	Inhibit PI3K/Akt and NF-κB Signaling	Decreased IL-1β, IL-6, TNF-α, and MCP-1
(150)		0, 10, 20, 40, 80, 160, and 320 μg/ml	LPS	Inhibition of NF-κB signaling	Decrease IL-6
(84)	***Naringin***	10, 20, 40 μg/mL	LPS	Inhibition of p38 MPK and HMGB-1	Decreased COX-2, iNOS, IL-1β, and IL-6
(177)		20 ng/ml	NA	Inhibition of NF-κB	Decreased TNF-α
(84)	***Kaempferol***	5 – 50 μmol/ml	By chemical substances	Inhibit the iNOS and COX-2	Increasing VCAM-1 and ICAM-1
(184)	***Allium sativum L.***	5 – 30 μg/ml	LPS	Inhibition of NF-κB and subsequent suppression of inflammatory factors	Inhibition of TNF-α, NO, PGE and IL-1β
(84)	***Lianhuaqingwen***	24 mg/ml	SARS-Cov-2	Blockage of virus replications	Reduction of IL-6, TNF-α, IP-10, CCL-2, CXCL-10, MCP-1
(192)	***Magnoflorine***	0–60 μg/ml	LPS	Inhibition of the TLR4- NF-κB signaling pathway	Reduction of IL-1β, TNF-α, IL-6, IL-8
(84)		***	LPS	Enhancing NF-κB signaling pathway	Upregulating of TNF-α, IL-1β, and PGE2
(197)	***Mahuang Tang***	5 g/l	Influenza A	Inhibition of TLR4 signaling pathway	Reduction of TLR4, TLR7, MYD88, and TRAF6 expression

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Table 3. Studies investigating role of NF-κB pathway to inhibit cytokine storm through both in vivo and in vitro experiments

Studies	Natural Product	Dose	Inflammatory Agent	Effect	
				Signaling Pathway	Cytokines
(55)	***Sevoflurane***	3%	LPS	Decrease TLR4/NF-κB	Decrease TNF-α, IL‑1 & IL‑6
(84)		3%	Ligating the hepatic artery (Liver ischemia)	Reduce NF-κB	Decrease IL-1, IL-6 &TNF-α
(95)	***KIOM-C***	10 mg	Lung viruses	IFN type I and ISGs	Decreases TNF-α, IL-6, IL-12
(84)		50, 170&510 mg	Pulmonary metastasis	Inhibition of NF-κB activation and MMP-9 expression	***
(100)	***Bergenin***	50,100 and 200 mg / kg	LPS	Inhibition of NF-κB P65	Decreases IL-1β and IL-6 in BALF and produces IL-1β, TNF-α and IL-6 production in serum
(84)		100, 50, and 25 mg/kg with the purity>99.9%	LPS	Inhibition MAPK and NF-κB Signaling	Reduces the expression of, TNF-α, IL-1β, and IL-6
(181)	***Ginsenoside***	20 mg/kg	Influenza A (H1N1 strain)	Inducing the expression of miR-146a/ reduce neutrophil infiltration	Inhibition of TNF-α, NF-κB activation/ increasing of IL-10 expression
(84)	***Kaempferol***	15 mg/kg	Influenza A (H9N2 strain)	Suppressing of NF-κB/ upregulating TLR4	Decreasing inflammatory factors like TNF-α, IL-1β, and IL-6
(195)	***Mahuang Tang***	4-8 mg/kg	Influenza A	Inhibition MYD88-dependent pathway of TLR4	Reduction of IL-4, IL-5, and increase of IL-2, IFN-Ɣ
(84)		40 mg/kg	Influenza A	Inhibition of TLR4 signaling pathway	Reduction of IL-1β, TNF-α, and NF-κB

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Abbreviations

3-CLpro: 3-chymotrypsin-like protease

ACE-2: Angiotensin converting enzyme 2

AGE's: Advanced glycation end products

AHR: Airway hyperresponsiveness

Akt: Protein kinase B (PKB)

ALI: Acute lung injury

AP-1: Activator Protein1

APCs: Antigen-presenting cells

ARDS: Acute respiratory distress syndrome

ATF2: Activating transcription factor 2

BALF: Bronchoalveolar lavage fluid

CCL-2: C–C motif chemokine ligand 2

COX-2: Cyclooxygenase-2

CREB: cAMP-response element binding protein

CXCL-10: C-X-C motif chemokine ligand 10

DAMP: Damage-associated molecular pattern

ERK: Extracellular signal-regulated kinase

ERK1/2: Mitogen-activated protein kinase 1/2

G-CSF: Granulocyte colony-stimulating factor

GM-CSF: Granulocyte-macrophage colony-stimulating factor

HBV: Hepatitis B virus

HMGB1: High-mobility group box 1

HO-1: Heme oxygenase-1

ICAM-1: Intercellular Adhesion Molecule 1

IFN: Interferon

IFNAR: Interferon α/β receptor

IFR-3: Interferon regulatory factor 3

IKKβ: IkB-kinase

IL-1β: Interleukin 1 beta

IL-6: Interleukin-6

iNOS: Inducible nitric oxide synthase

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IRAK-1: Interleukin-1 receptor-associated kinase 1

ISGs: IFN-stimulated genes

ISRE: IFN-stimulated response element

IκBα: Inhibitory kappa B

LIF: Leukemia inhibitory factor

LIX: Phytoclock1

(IKK)α/β: Nuclear factor κ-B kinase

MAPK: Mitogen-activated protein kinase

MCP-1: Monocyte Chemoattractant Protein-1

MDA: Malondialdehyde

MDSCs: Myeloid-derived suppressor cells

MMP: Matrix metalloproteinase

MMP-9: Matrix metallopeptidase 9

MPO: Myeloperoxidase

Myd88: Myeloid differentiation factor 88

NIK: NF-κB inducing kinase

NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells

NO: Nitric Oxide

Nrf2: Nuclear factor erythroid 2 related factors 2

PCVAD: Porcine circovirus-associated disease

PMA: Phorbol myristate acetate

RANTES: Regulated upon activation, normal T cell expressed and presumably secreted

Rg: red ginseng

RIP: Receptor interacting protein-1

RdRp: RNA-dependent RNA polymerase

RP8: A/Puerto Rico/8/34

ROS: Reactive oxygen species

p65: Protein 65

p38: Protein 38

PAMPs: Pathogen-associated molecular patterns

PGE: Prostaglandin E

PGE2: Prostaglandin E2

PI3K: Phosphatidylinositol 3-kinase

PLpro: Papain-like protease

PPAR-γ: Peroxisome proliferator-activated receptor-gamma

SMFM: Methyl 3-formyl-4methykpentanoate

SOD: Superoxide dismutase

STAT1: Signal transducer and activator of transcription 1

TAK1: Transforming growth factor-β activated kinase 1

TBK1: TANK-binding kinase 1

TLR-3: Toll-like receptor-3

TNBS-induced colitis: 2,4,6-trinitrobenzenesulfonic acid-induced colitis

TNF-α: Tumor necrosis factor-alpha

TRAF2: TNF receptor-associated factor-2

TRAF6: Tumor necrosis factor receptor-associated factor 6

VEGF: Vascular endothelial growth factor

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