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REVIEW

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Flavonoids as potential phytotherapeutics to combat cytokine storm in SARS-CoV-2

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Emergence of severe acute respiratory syndrome *coronavirus*-2 (SARS-CoV-2) infection, COVID-19, has become the global panic since December 2019, which urges the global healthcare professionals to identify novel therapeutics to counteract this pandemic. So far, there is no approved treatment available to control this public health issue; however, a few antiviral agents and repurposed drugs support the patients under medical supervision by compromising their adverse effects, especially in emergency conditions. Only a few vaccines have been approved to date. In this context, several plant natural products-based research studies are evidenced to play a crucial role in immunomodulation that can prevent the chances of infection as well as combat the cytokine release storm (CRS) generated during COVID-19 infection. In this present review, we have focused on flavonoids, especially epicatechin, epigallocatechin gallate, hesperidin, naringenin, quercetin, rutin, luteolin, baicalin, diosmin, ge nistein, biochanin A, and silymarin, which can counteract the virus-mediated elevated levels of inflammatory cytokines leading to multiple organ failure. In addition, a comprehensive discussion on available in silico, in vitro, and in vivo findings with critical analysis has also been evaluated, which might pave the way for further development of phytotherapeutics to identify the potential lead candidatetoward effective and safe management of the SARS-CoV-2 disease.

KEYWORDS
COVID-19, Flavonoids, Inflammatory cytokines, Cytokine storm, Immunomodulation, Phytotherapeutics

Abbreviations: ACE2, angiotensin-converting enzyme 2; AP-1, activator protein-1; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; COPD, chronic obstructive pulmonary disease; COX-2, Cyclooxygenase-2; COVID-19, coronavirus disease 2019; CRS, cytokine release storm; EGCG, epigallocatechin gallate; ERK, Extracellular signal-regulated kinases; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HMC, human mast cell; HMGB1, high mobility group box 1; HO-1, Heme oxygenase-1; HUVEC, human umbilical vein endothelial cells; ICU, intensive care units; ICAM-1, Intracellular adhesive molecule-1; IFN-γ, interferon-gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; IP-10, inducible protein-10; JAK-STAT, Janus kinase/signal transducers and activators of transcription; JNK, c-Jun N-terminal kinases; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage-colony stimulating factor; MD-2, Myeloid differentiation factor; MIP 1-α, macrophage inflammatory protein 1-alpha; NF-κB, nuclear factor-kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NO, nitrite oxide; Nrf2, Nuclear factor erythroid 2-related factor 2; PHA, phytohemagglutinin; PI3K, phosphatidylinositol-3-kinase; PMAC1, phorbol 12-myristate 13-acetate and calcium ionophore; PPAR-γ, Peroxisome proliferator-activated receptor gamma; RBC, red blood cells; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIRT1, Sirtuin 1; Smad, Small mothers against decapentaplegic; TGF-β, Transforming growth factor-beta; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; TRPC6, Transient receptor potential C6 Ion channel gene; WHO, World Health Organization.

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1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak has created a pandemic, which has turned out to be a major public health crisis worldwide (Hamid, Mir, & Rohela, 2020). This global outbreak of SARS-CoV-2, also termed coronavirus disease 2019 (COVID-19), was initially considered to be spread through zoonotic transmission connected with the seafood market in the Wuhan area of China (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Soon after, it was acknowledged that human-to-human transmission played a significant role in the consequent outbreak, thus transmitted to the rest of the world through rapid pulsatile movement (Yuki, Fujiogi, & Koutsogiannaki, 2020). World Health Organization (WHO) declared it as a pandemic with an average mortality rate of 2.9% around the world (Cucinotta & Vanelli, 2020; Shereen, Khan, Kazmi, Bashir, & Siddique, 2020; Sohrabi et al., 2020). Adults within the age range of 35–55 years are prone to this infection than children, where males are accounted for 59–68% of total cases (Hamid et al., 2020; Q. Li et al., 2020). Moreover, older people with a median age of 75 years (48–89 years) and associated with a poor immune system, chronic comorbidities, surgery history, and under immunosuppressive drugs are more likely to casualty (Wang, Tang, & Wei, 2020). Several antiviral drugs (e.g., lopinavir, ritonavir, ribavirin, remdesivir, favipiravir, umifenovir, and danoprevir), antibiotics (e.g., azithromycin, ivermectin, and doxycycline), repurposed drugs (e.g., corticosteroids, chloroquine, hydroxychloroquine, camostat, darunavir, cobicistat, duvelisib, decitabine, aspirin, clopidogrel, rivaroxaban, disulfiram, nitazoxanide, isotretinoin, infliximab, pamrevlumab, levilimab, ruxolitinib, tocilizumab, sirolimus, dexamethasone, prednisone, methylprednisolone, colchicine, aviptadil, and indomethacin) as alone or in combination are at different stages of investigation in multiple clinical trials globally for prophylactic as well as treatment of this disease (Chibber, Haq, Ahmed, Andrabi, & Singh, 2020; Horby et al., 2020; Luo et al., 2020; Million et al., 2020; Rabby, 2020; M. A. Rahman et al., 2020; Scavone et al., 2020). However, there is no approved therapy available to date to selectively counteract this disease prevalence. Moreover, consumption of the above-mentioned drugs is associated with serious adverse effects, including cardiotoxicity, hepatotoxicity, gastrointestinal toxicity, renal toxicity, reduced red blood cells (RBC) level, etc. (Falcão, de Góes Cavalcanti, Filgueiras Filho, & de Brito, 2020; Funck-Brentano, Nguyen, & Salem, 2020; Million et al., 2020; Sacks et al., 2018; Sardana, Sinha, & Sachdeva, 2020). Alternatively, Comirnaty (mRNA-based vaccine), Moderna COVID-19 vaccine (mRNA-based vaccine), CoronaVac (inactivated vaccine), Covishield (Adenovirus vaccine), Sputnik V (non-replicating viral vector), BBIBP-CorV (inactivated vaccine), EpiVacCorona (peptide vaccine), and Covaxin (inactivated vaccine) are recently approved vaccines, whereas several others are at different stages of research (https://www.clinicaltrials.gov). There is a growing awareness among the people toward boosting immunity to prevent SARS-CoV-2 infection and to recover infected cases.

Under these circumstances, natural products have immense potential to heighten the immunity status of the people. Moreover, pathophysiological investigation of the COVID-19 patients showed a crucial role of cytokine storm in the severity and complexity of the disease (Nile et al., 2020; Q. Ye, Wang, & Mao, 2020; Ming Zhao, 2020). Currently, supplementation therapy with zinc, vitamin C, vitamin D, deferoxamine, lactoferrin, omega-3-fatty acids, glycine, and probiotics has also been prescribed to minimize the likelihood of infection (http://ctri.nic.in; https://www.clinicaltrials.gov). In this direction, biological activities like immunomodulatory, antiviral, anti-inflammatory, and so on are crucial to prevent the chances of infection as well as combat the cytokine release storm (CRS) generated during this viral infection (Boozari & Hosseinzadeh, 2020; Islam et al., 2020; Yang, Zhang, et al., 2020). Natural products are well known for these above-mentioned pharmacological actions because a large proportion of marketed drugs are indirectly or directly obtained from natural origin. Currently, several research works are also ongoing under this purview as there are quite a few reported evidences in the literature. Plants species like *Allium*, *Piper*, *Boswellia*, *Curcuma*, *Echinacea*, *Glycyrrhiza*, etc., are known to have immunomodulatory and anti-inflammatory effects for treating COVID-19 patients (Brendler et al., 2020; Yang, Zhang, et al., 2020). Similarly, cannabidiol-rich extract of *Cannabis sativa* had shown to modulate the expression of ACE2 and serine protease, TMPRSS2 (Wang, Kovalchuk, et al., 2020). The extract also reported possessing an anti-inflammatory activity to regulate the cytokine storm during COVID-19 infection (Onaivi & Sharma, 2020). Additionally, plant-based natural products like homoharringtonine, silvestrol, tylophorine, 7-methoxycryptopleurine, and so on are reported for their potent antiviral activity (Islam et al., 2020). Based on the ADMET profile of different natural bioactive compounds, Abd El-Mageed et al. (2021) reported that caulerpin could be considered as a potential candidate to target SARS-CoV-2 spike protein, SARS-CoV-2,3-chymotrypsin-like protease, and a host target human angiotensin-converting-enzyme 2 (ACE2) receptor. Methyl tanshinonate, sugiol, α-cadinol, 8-β-hydroxyabieta-9,13-dien-12-one, dehydroabieta-7-one, and tanshinone-I are plant-based terpenes or their derivatives exhibited activity against SARS-CoV-2 protease (Alrasheid, Babiker, & Awad, 2021; Diniz, Perez-Castillo, Elshabrawy, & de Sousa, 2021). Rhein, an active metabolite of diacerein (anthraquinone derivative), is known to inhibit cytokine storm and viral replication as well as inhibits SARS-CoV-2 spike protein and ACE2 activity (de Oliveira et al., 2020). Concurrently, studies on ayurvedic preparations or traditional plant-based medicines are ongoing in different parts of the world to prevent chances of infection as well as for improving the immunity of a person to combat this disease (Iqubal, Iqubal, Ahmed, & Haque, 2021). A few examples include *Tinospora cordifolia*, *Glycyrrhiza glabra*, *Cocculus hirsutus*, *Withania somnifera*, *Ocimum sanctum*, *Bryonia alba*, *Curcuma longa*, Brazilian green propolis, resistant starch, ayurvedic kadha, shanshamani vati plus, etc. (http://ctri.nic.in; https://www.clinicaltrials.gov). Despite the unprecedented advancement of the modern system of medicine, a high percentage of marketed drugs are evidenced from natural origin, especially plant-based products (Gurnani, Mehta, Gupta, &

Mehta, 2014). Among these herbal components, flavonoids are known to be useful to combat against overproduction of cytokines and/or boosting the immune system based on their several key pharmacological properties (A. Agrawal, 2011; García-Lafuente, Guillamón, Villares, Rostagno, & Martínez, 2009; Havsteen, 1983; Serafini, Peluso, & Raguzzini, 2010; Tripoli, La Guardia, Giammanco, Di Majo, & Giammanco, 2007). Additionally, flavonoids are also found to be beneficial to protect drug-induced toxicity in major organs as evidenced in COVID-19 patients (Dillard & German, 2000; Sadzuka, Sugiyama, Shimoi, Kinae, & Hirota, 1997; Shahbazi, Dashti-Khavidaki, Khalili, & Lessan-Pezeshki, 2012). Therefore, we had explored the available literature on flavonoids for their inhibitory effect on important cytokines, particularly interleukins (ILs) like IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), including the pathways of action based on in vitro as well as an in vivo platforms. Most of the reported preclinical efficacy by the flavonoids was evaluated under the lung injury model, which could be closely in line with the SARS-CoV-2 infection. Available reports on flavonoids based antiviral effects as well as in silico molecular docking studies to predict the binding of SARS-CoV-2 with flavonoids are also described. Being the first of a kind, to the best of our knowledge, this comprehensive information of flavonoids can be handy for the researchers toward the development of phytotherapeutics for the prevention as well as symptomatic management of COVID-19.

2 | ROLE OF CYTOKINES IN IMMUNO-PATHOPHYSIOLOGY OF SARS-COV-2 INFECTION

The pathophysiological mechanism of SARS-CoV-2 infection involves invasion of the virus within the cell through ACE2 receptor, primarily via the toll-like receptor-4 (TLR-4) (Ekaidem, Moses, & Tatfeng, 2020; Liu, Xiao, et al., 2020). Thereafter, this virus-mediated infection stimulates the immune response by recruiting the macrophages as well as monocytes, cytokines, and adaptive B and T cell immune responses in the microenvironment of the lung cells. Viral infection and replication of SARS-CoV-2 in the airway epithelial cells induce elevated virus-mediated pyroptosis (programmed cell death due to viral infection) with vascular leakage, which triggers the subsequent inflammatory responses (I.-Y. Chen, Moriyama, Chang, & Ichinohe, 2019; Fink & Cookson, 2005; Zhang, Zhou, et al., 2020). IL-1β, the major inflammatory cytokine, is released during pyroptosis and additionally increased during SARS-CoV-2 infection (Figure 1) (Huang, Wang, et al., 2020). The pathogen-associated molecular patterns (e.g., viral RNA) and damage-associated molecular patterns (e.g., ATP, nucleic acid and, ASC oligomers) by a variety of pattern-recognition receptors, alveolar macrophages, and alveolar epithelial cells were reported. After confirmation of COVID-19, proinflammatory cytokines and chemokines such as IL-6, interferon-gamma (IFN-γ), monocyte chemoattractant protein-1(MCP1), and inducible protein (IP-10) were reported to be

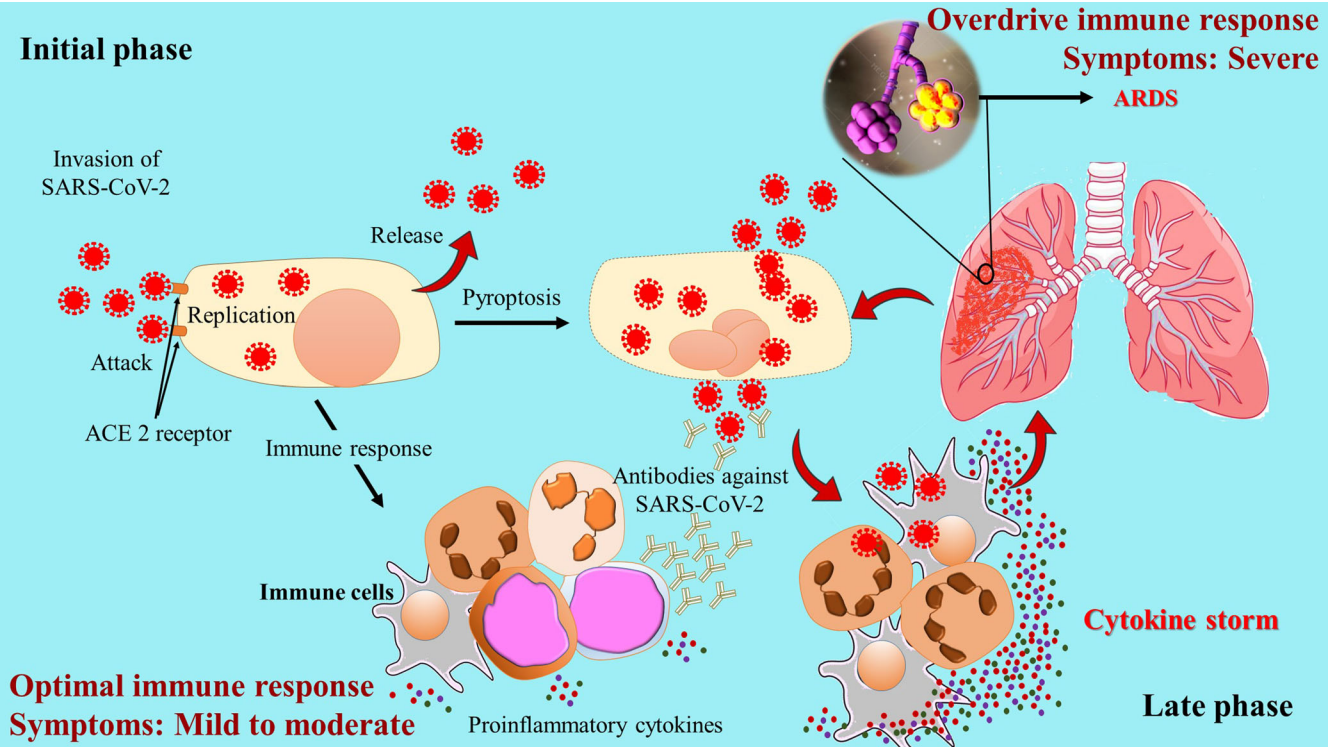

FIGURE 1 A schematic overview of SARS-CoV-2 invasion into the lung cells via ACE 2 receptor and generation of cytokine storm to adversely affect the lungs alveoli to ARDS [Colour figure can be viewed at wileyonlinelibrary.com]

elevated into the blood of infected patients (Huang, Wang, et al., 2020; Zhang, Dong, et al., 2020). These cytokines attract immune cells, particularly monocytes and T lymphocytes, from the blood to the site of infection (S. Tian et al., 2019; Xu, Shi, et al., 2020). The recruitment of immune cells and permeation of lymphocytes into the airways can elucidate the lymphopenia and elevated neutrophil–lymphocyte ratio in 80% of SARS- CoV-2 infected patients (Guan et al., 2020; S. Liu et al., 2016). Significant complications of lung occur mainly due to inflammation, which is again induced by interleukin and cytokine storm (Figure 1). Data on COVID-19 patients demonstrated that the elevated levels of serum cytokines, including IL-6, IL-10, IL-1β, TNF-α, IFN-γ, granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), MCP-1, and macrophage inflammatory protein 1-α (MIP 1-α) might increase hospitalization of the patients, particularly in the intensive care units (ICUs) (Huang, Wang, et al., 2020; Mehta et al., 2020; Zhou, Fu, Zheng, Wang, & Zhao, 2020). Actually, stimulation of interleukins (e.g., IL-6, IL-1β, and TNF-α) facilitates the production of specific cytotoxic CD8+ T cells followed by the stimulation of antigen-specific B cells and antibody via CD4+ helper T cells (Ahmadpoor & Rostaing, 2020). COVID-19 patients possessed average or reduced lymphopenia, and white cell counts, as well as patients with severe disease had demonstrated considerably augmented levels of neutrophils and urea in their blood (Liu, Du, et al., 2020; Tan et al., 2020). IL-6 level in COVID-19 patients had shown to increase constantly, which is positively connected with severity of the disease (critically ill patients > severely ill patients > ordinary patients). In addition, the level of IL-6 was reported to be relatively higher in non-survivors as compared to the survivors of COVID-19 (L. Chen et al., 2020a; Sinha, Matthay, & Calfee, 2020; Zhou, Yu, et al., 2020). Patients with severe diseased conditions exhibited a highly inflammatory monocyte-derived $FCN1^+$ macrophage population within the bronchoalveolar lavage fluid (BALF) (Liao et al., 2020). These patients demonstrated a considerably higher percentage of $CD14^+$ and $CD16^+$ inflammatory monocytes in peripheral blood (Y. Zhou, Fu, et al., 2020). These cells are known to produce inflammatory cytokines that could further contribute to the cytokine storm. Hyperproduction of cytokines possibly promotes edema, viral sepsis, and lung injury, which result in acute respiratory distress syndrome (ARDS) followed by hepatic, renal, and cardiovascular complications (Figure 1) (Costela-Ruiz, Illescas-Montes, Puerta-Puerta, Ruiz, & Melguizo-Rodríguez, 2020; Huang, Wang, et al., 2020; Luo et al., 2020; Moon, 2020; Prompetchara, Ketloy, & Palaga, 2020; Wang, He, & Wu, 2020).

3 | IMMUNO TARGETS FOR THE MANAGEMENT OF SARS-COV-2 INFECTION

During SARS-CoV-2 infection, the response elicited by the cytokines has been regarded as a decisive part of immunity and immune-pathophysiology (Channappanavar & Perlman, 2017). The augmented level of serum cytokines, including TNF-α, IL-6, IL-10, and IFN-γ, were linked with the severity of the disease and adverse clinical outcomes (Huang, Wang, et al., 2020; Liu, Zhang, et al., 2020). Among these, several cytokines exhibit different intracellular signaling pathway mediated by Janus kinase (JAK)-signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK), and *nuclear factor-kappa B* (NF-κB) (S. M. U. Ahmed, Luo, Namani, Wang, & Tang, 2017; Catanzaro et al., 2020; Dzobo, Chiririwa, Dandara, & Dzobo, 2021; J. S. Kim et al., 2021; Schwartz et al., 2017). It could be stated that the involvement of cytokines acts as a significant part in the CRS, triggers the JAK-STAT, MAPK, and NF-κB followed by stimulation of transcription signaling pathway to confer various biological functions, including lymphocyte growth and differentiation, immune regulation, oxidative stress, and so on (S. M. U. Ahmed et al., 2017; Catanzaro et al., 2020; Kang, Tanaka, Narazaki, & Kishimoto, 2019; Schwartz et al., 2017). Stimulation of nuclear factor erythroid 2-related factor 2 (Nrf2) is known to inhibit the activation of proinflammatory cytokines, viz., IL-6, IL-1β, TNF-α, and promote the upregulation of anti-inflammatory gene responses (S. M. U. Ahmed et al., 2017). In this context, it is noteworthy to mention that inflammatory storm, which engenders during SARS-CoV-2 infection, can be effectively managed by the flavonoids through targeting JAK-STAT, MAPK, NF-κB, and Nrf2 inflammatory signaling pathways (J. S. Kim et al., 2021; Serafini et al., 2010; Tisoncik et al., 2012; Zeinali, Rezaee, & Hosseinzadeh, 2017). On the other hand, NF-κB, a transcription factor, is activated by inflammatory stimuli and stimulates IκB kinase in the cytosol (Brasier, 2010). Consequently, signaling pathways lead to migration of NF-κB toward the nucleus via canonical or noncanonical, which initiate the target-specific gene. Upon stimulation, NF-κB pathway acts very quickly and subsequently elevated the proinflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α), ultimately results in apoptosis. Again, signaling of TNF-α receptor plays a significant role in the canonical pathway of NF-κB in cellular apoptosis. Following the discussion in the previous section, IL-6 is one of the main activators of JAK/STAT signaling pathway and associated with acute inflammation and cytokine storm (Luo et al., 2020; Mehta et al., 2020; Qin et al., 2020; Tisoncik et al., 2012). It had been demonstrated that activation of membrane-bound IL-6 receptor stimulates the downstream activation of JAK/STAT signaling, which further triggers the production of IL-6 (Zhang, Wu, Li, Zhao, & Wang, 2020). These pathways had been reported to be activated aberrantly in COVID-19 patients, thereby aggravating the inflammatory response within host (Catanzaro et al., 2020). Several repurposed drugs have been identified based on the target, including viral protease, regulating immunity, reducing the inflammatory CRS, declining viral loads, and improving pulmonary function. Currently, the treatment of COVID-19 disease is primarily focused on symptomatic treatment of inflammation, CRS, and compromised respiratory function targeting the inflammatory signaling pathways (Nile et al., 2020). A specific anti-cytokine approach had been proven to be more effective in treating cytokine storm syndromes targeting IL-1 and IL-6 (Nasonov & Samsonov, 2020; Q. Ye et al., 2020). However, rapid research on the pathophysiology of SARS-CoV-2 helps to reveal some novel targets for potential treatment. Several drugs that have been experimented based on different

TABLE 1 Potential drugs/therapeutic agents with its target on immune system for the treatment of SARS-CoV-2 infection

Drugs/Therapeutic agents	Targets/Mechanism of action	References
Chloroquine	Suppression of IL-6 and TNF-α	(Gao, Tian, & Yang, 2020)
Hydroxychloroquine	Reduce viral load by inhibiting the IL-6 and TNF-α	(Gautret et al., 2020)
Azithromycin	Blockage of IL-6 and TNF-α	(Chen et al., 2020; Gautret et al., 2020)
Anakinra	Inhibits the secretion of IL-6	(Monteagudo, Boothby, & Gertner, 2020)
Dexamethasone	Reduce the level of inflammatory cytokines, chemokines, and adhesion molecules	(Horby et al., 2020)
Tocilizumab	IL-6 receptor antagonists and block IL-6 signaling to revert the cytokine storm production	(Zhang, Wu, et al., 2020)
Adalimumab	Specific blockade of TNF-α	(Rizk et al., 2020)
Certolizumab	Anti-TNF-α antibody	(Zhang et al., 2020)
Eculizumab	Inhibitor of the terminal complement system	(Scavone et al., 2020)
Baricitinib	Targets JAK-STAT and inhibits viral entry and inflammation	(Cantini et al., 2020; Zhang, Zhang, Qiao, Zhang, & Qi, 2020)
Ruxolitinib	JAK-STAT inhibitor	(Luo et al., 2020)
Fedratinib	JAK-STAT inhibitor	(Stebbing et al., 2020)
Tofacitinib	JAK-STAT and TYK2 inhibitor	(Luo et al., 2020)
Sarilumab	Inhibits anti-human IL-6R	(Benucci et al., 2020)
Myo-inositol	Reduction in IL-6 levels, and prevent the cascade inflammation response	(Bizzarri, Laganà, Aragona, & Unfer, 2020)
Chymotrypsin and papain-like protease	Inhibits the host innate immune responses	(L. Chen et al., 2005)
Mesenchymal stem cell	Down-regulation of IL-1, IL-12, TNF-α, and IFN-γ	(Leng et al., 2020)
Convalescent plasma therapy	Inhibits viremia and regulate overactive immune system (cytokine storm)	(Chen, Xiong, Bao, & Shi, 2020b)

immuno targets to manage SARS-CoV-2 infection are represented in Table 1, and their clinical trials are ongoing at an exceptional pace to validate their efficacy and safety to combat the severity of the disease. In recent times, synthetic drugs like hydroxychloroquine, azithromycin, adalimumab, tocilizumab, and baricitinib have been explored under purview of management inflammatory conditions in SARS-CoV-2 infection, however, these agents are associated with several adverse effects including QT prolongation, hepatotoxicity, dyspepsia, abdominal cramps, erythema, eosinophilia, and so on (Bakadia et al., 2020; Falcão et al., 2020; Funck-Brentano et al., 2020; Million et al., 2020; Sernicola et al., 2020; Srinivasa, Tosounidou, & Gordon, 2017; Tsilimbaris et al., 2009; Zhang, Zhang, et al., 2020). Alternatively, the convalescent serum has become one of the best options in the treatment of SARS-CoV-2 infection; however, transfusion of plasma has several side effects, including allergic and anaphylactic reactions, hemolysis, and transfusion-related acute lung injury (MacLennan & Barbara, 2006). A higher level of inflammation induced by viral load aggravates these adverse effects, especially the hyperactivity of bronchial lining followed by apnea, hypoxia, and multi-organ failure, even leading to death (Fajgenbaum & June, 2020; Gibson, Qin, & Puah, 2020; Huang, Wang, et al., 2020; Wang, Hu, et al., 2020). Therefore, there is a high demand for suitable alternatives from natural sources where plant-based natural products can safely fulfill the purpose.

4 | POTENTIAL OF FLAVONOIDS TO BE PHYTOTHERAPEUTICS FOR SARS-COV-2 INFECTION

According to the WHO report, approximately 80% of the world's population relies on natural products to satisfy their health necessities. Moreover, there are a large number of marketed drugs, which are directly or indirectly obtained from plant-based natural origin (Gurnani et al., 2014; Thomford et al., 2018). Additionally, recent experimental results of different supplement therapies provide a level of hope in the current scenario of SARS-CoV-2 infection toward symptomatic management (Infusino et al., 2020). Jayawardena, Sooriyaarachchi, Chourdakis, Jeewandara, & Ranasinghe (2020) demonstrated that vitamins (A and D), trace elements (selenium, zinc), nutraceuticals, and probiotics benefit in patients infected with COVID-19 to reduce inflammation-related syndromes. These supplementations have shown a positive impact on enhancing immunity during viral infections. Molecular docking, in vitro, and in vivo studies have suggested that plant-based natural products have the potential to interfere with viral entry, inhibition of protease enzymes, viral assembly, reverse transcriptase, and inflammation associated with SARS-CoV-2 (Colunga Biancatelli, Berrill, Catravas, & Marik, 2020; Elfiky, 2020; M. Russo, Moccia, Spagnuolo, Tedesco, & Russo, 2020; Upadhyay et al., 2020; Yang, Zhang, et al., 2020). Under these circumstances,

flavonoids, the polyphenolic secondary metabolites of plants, play a crucial role in protecting patients with several diseases. Normally, people consume these agents as dietary supplements/health booster as well as to mitigate ailments. Flavonoids represent the group of natural compounds with phenolic structures and are present in fruit, vegetables, grains, flowers, stems, bark, roots, tea, and wine (Del Rıo et al., 2004; Harnly et al., 2006; Lairon & Amiot, 1999; Nielsen, Freese, Kleemola, & Mutanen, 2002; Zakaryan, Arabyan, Oo, & Zandi, 2017). Flavonoids are characterized into different classes based on their chemical structures (Brodowska, 2017; Kumar & Pandey, 2013), which are useful as antioxidant, antiviral, antimicrobial, anti-inflammatory, immunomodulatory, anticancer, and antithrombotic activities (X. Feng & Hao, 2021; Friedman, 2014; García-Lafuente et al., 2009; Juan, PÉrez-VizcaÍno, JimÉnez, Tamargo, & Zarzuelo, 2001; Kaul, Middleton Jr, & Ogra, 1985; H. P. Kim, Son, Chang, & Kang, 2004; S.-S. Zhang, Tan, & Guan, 2021). These flavonoids have the potential to control lung inflammation in various disorders, including lung emphysema, asthma, ARDS, and COPD (Geraets et al., 2009; Jantan, Ahmad, & Bukhari, 2015; Kojima et al., 2019; Lago et al., 2014; Tanaka & Takahashi, 2013; Zeinali et al., 2017; R. Zhang et al., 2017). It has been illustrated earlier in this section that inflammatory cytokines could be the therapeutic targets for the treatment of inflammatory diseases (Siebert, Tsoukas, Robertson, & McInnes, 2015). Therefore, the impact of flavonoids on inflammatory mediators, mainly via modulating cytokines, is significant for the development of alternative treatments for inflammation-related diseases like COVID-19. During inflammation, these flavonoids are known to inhibit the inflammatory mediators, viz., reactive oxygen species (ROS) and nitric oxide (NO); regulate the activity of inflammatory enzymes and inducible NO synthase; decrease the expression of cytokines production by modulating the transcription factors, including activating protein-1 (AP-1), NF-κB, MAPK, and JAK-STAT pathway (A. Ahmad, Kaleem, Ahmed, & Shafiq, 2015; S. M. U. Ahmed et al., 2017; Hämäläinen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007; Hougee et al., 2005; H. P. Kim et al., 2004; Kumar & Pandey, 2013). During an unregulated immune-inflammatory response, there is an augmentation in the level of inflammatory mediators, which might lead to several chronic diseases (Leyva-López, Gutierrez-Grijalva, Ambriz-Perez, & Heredia, 2016). In this direction, the use of flavonoids as IL-6, IL-1β, and TNF-α inhibitors can be an effective alternative to neutralize the emergence in CRS. Moreover, these compounds also have the potential to interfere with virus attachment to the host cell, main protease, reverse transcriptase, viral assembly, and polymerase enzyme of SARS-CoV-2 (Colunga Biancatelli et al., 2020; Elfiky, 2020; M. Russo et al., 2020). They also showed synergistic potential against COVID-19 with conventional drugs and decline systemic toxicity. It has been demonstrated that flavonoids reduce the expression and production of cytokines without exerting any adverse effects during chronic consumption (Leyva-López et al., 2016). Hence, flavonoids are considered to be pleiotropic compounds because of their promising role to interact with diverse cellular targets and block multiple pathways (G. L. Russo, Tedesco, Spagnuolo, & Russo, 2017; M. Russo et al., 2020; Spagnuolo, Moccia, & Russo, 2018). These features constitute flavonoids as potential candidates to combat the progression of severe illness and the pathophysiological process associated with COVID-19 disease. The mechanism of actions to obtain the physiological role depends on several pathways that can be targeted to combat the production of a cytokine storm in COVID-19. The targets with different pathways for action are depicted in Figure 2. Alternatively, the effect of flavonoids on major cytokines and pathways of action using cell-based in vitro assay models are summarized in Table 2. The anti-inflammatory action of flavonoids on inhibition of serum cytokines, including IL-6, IL-1β, and TNF-α, along with their pathways of action in the preclinical model of in vivo inflammation like lung injury model is presented in Table 3, whereas the clinical data of flavonoids toward the cytokine inhibition are summarized in Table 4. Their antiviral effects can be an added advantage in developing as phytotherapeutics. Their potential can have great importance to reduce the mortality in severe and critically ill COVID-19 patients. We have summarized a few of the important flavonoids in the connecting sections, which are possessing prominent roles toward combating COVID-19.

4.1 | Epicatechin

Epicatechin is a flavonoid that belongs to the class of flavan-3-ol. It is widely present in tea (Chan et al., 1999). Epicatechin exhibited significant inhibition of IL-6 andIL-8 in human whole blood culture stimulated with phytohemagglutinin (PHA) and lipopolysaccharide (LPS) (Al-Hanbali et al., 2009). It also has ability to impede significantly the IL-1β action (Mitjans et al., 2004). Epicatechin at a dose of 15 mg/kg in a preclinical mice model of acute lung injury had depicted noticeable inhibition of IL-6 and TNF-α secretion by interfering with p38 MAPK signaling pathways (Xing et al., 2019). Epicatechin exhibited the role of a potent reverse transcriptase inhibitor activity in HIV (Chang, Hsu, & Lin, 1994; Chu, Hsieh, & Lin, 1992). Tea catechins, which contain both epicatechin and epigallocatechin gallate (EGCG), are permitted for use in adults at 500–1000 mg/day (or *Camellia sinensis* extract at 1000–2000 mg/day) as nutraceuticals (FSSAI, 2016). A recent in silico report by Ghosh and team revealed that three polyphenols of green tea extract, specifically EGCG, and gallocatechin-3-gallate, possess drug likeliness with less conformational fluctuations. Furthermore, the authors suggested its efficacy against the main protease of SARS-CoV-2 to prevent the key component of a viral replication (Ghosh, Chakraborty, Biswas, & Chowdhuri, 2020). Similarly, Storozhuk also reported that catechin constituents in green tea are favorable to decrease the associated risks of COVID-19 disease (Storozhuk, 2020).

4.2 | EGCG

EGCG is another compound from the class of flavan-3-ol and is also widely present in tea (Chan et al., 1999). It had been reported that EGCG inhibits IL-6, TNF-α, and IL-8 levels in phorbol 12-myristate

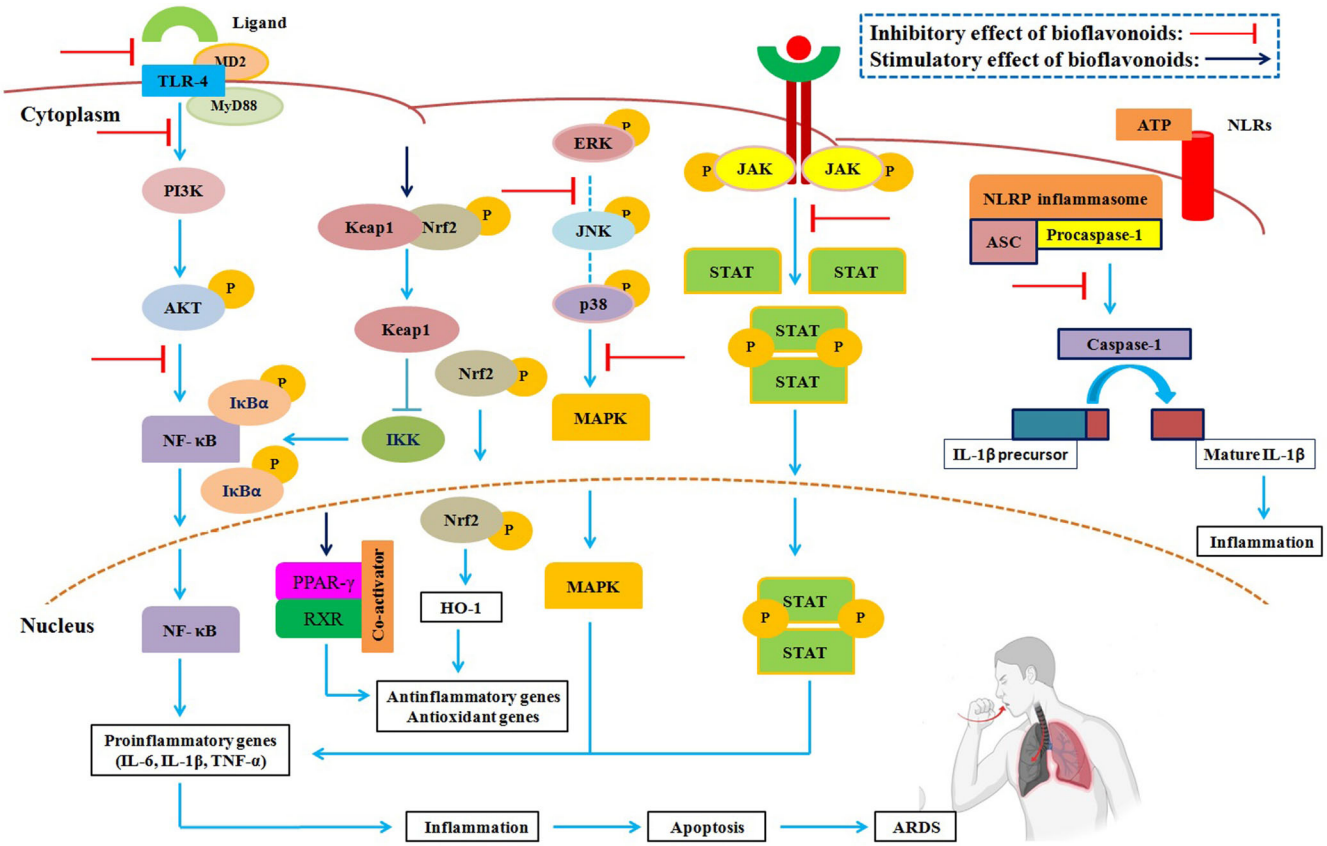

FIGURE 2 A schematic overview of flavonoids for its action on possible immuno targets to counteract cytokine storm associated with SARS-CoV-2 infection [Colour figure can be viewed at wileyonlinelibrary.com]

13-acetate and calcium ionophore A23187 (PMACI)-stimulated human mast cells (HMC-1) (Shin et al., 2007). On the other hand, EGCG suppresses the secretion of IL-6, IL-1β, and TNF-α in fluoride (Shanmugam et al., 2016) and sea aspiration (Liu, Dong, et al., 2014)-induced lung injury in rat model via regulation of Nrf2/Keap1 and JAK/STAT pathways, respectively. Vázquez-Calvo et al. reported in vitro antiviral property of EGCG against west Nile virus, Zika virus, dengue virus, and influenza virus by targeting the replication (J.-M. Song, Lee, & Seong, 2005; Vázquez-Calvo, Jiménez de Oya, Martín-Acebes, Garcia-Moruno, & Saiz, 2017). EGCG possessed a remarkable inhibition of reverse transcriptase enzymatic activity in murine leukemia virus (Chang et al., 1994; Chu et al., 1992). Carneiro et al. reported significant ability of EGCG in inhibiting the entry of Zika virus within host cells in Vera cultured cells and representing a virucidal activity at a concentration less than 5 μM (Carneiro, Batista, Braga, Nogueira, & Rahal, 2016). It also exhibited considerable inhibition of SARS-CoV 3CLpro with an IC_{50} value of 47–73 μM. It also demonstrated significant inhibitory activity against the main protease of SARS-CoV-2 in a dose-dependent manner with IC_{50} of 7.5 μg/ml in cultured cells (Jang et al., 2020). Furthermore, EGCG is considered safe and already included in the list of nutraceuticals as per FSSAI guidelines (FSSAI, 2016). Molecular docking studies exhibited that EGCG has a greater affinity to bind with the S-protein of SARS-CoV-2 (Dzobo et al., 2021; Khan, Khan, Khan, Ahamad, & Ansari, 2020). It has also been reported that EGCG could be used for the COVID-19 treatment as it interferes with the transition that exists between the closed and open state of the viral spike (Maiti & Banerjee, 2020). It inhibits viral activity by binding to the $3CL^{pro}$ active site and the 3-OH galloyl group (Chojnacka, Witek-Krowiak, Skrzypczak, Mikula, & Młynarz, 2020). Additionally, Ohgitani and co-researchers reported significant efficacy of EGCG and other derivatives of catechins, theasinensin A (TSA), and galloylated theaflavins toward the inactivation of the SARS-CoV-2 (Adhikari et al., 2020; Ohgitani et al., 2020). Overall, it could be summarized that EGCG could be a potential candidate to combat SARS-Cov-2.

4.3 | Hesperidin

Hesperidin is the most common citrus flavonoid from the class of flavanones and is widely found in lemons, sweet oranges, and in a few other fruits and vegetables (Zanwar, Badole, Shende, Hegde, & Bodhankar, 2014). Its inhibitory role in the production of IL-6, IL-1β, TNF-α, and IL-8 in THP-1 cells had been reported (C.-C. Yeh et al., 2007). Hesperidin has the potential to inhibit the expression of TNF-α, IL-1β, and IL-12 as well as enhancing the production of IL-4 and IL-10 in LPS-induced acute lung injury model in Wistar rats via downregulation of NF-κB and AP-1 signaling (C.-C. Yeh et al., 2007).

TABLE 2 In vitro effect of flavonoids on cytokines

Flavonoid's name	Action on cytokines (Test concentration)				Assay cell lines	Pathway of action	References
	IL-6	IL-1β	TNF-α	Other cytokines			
Catechin	⊥[6.25–25 μM]	–	⊥[6.25–25 μM]	↑IL-4	Mouse microglial cell line BV-2	Inhibition of NF-κB signaling pathway	(Syed Hussein, Kamarudin, & Abdul Kadir, 2015)
	–	–	⊥[25μg/ml]	–	macrophages	–	(Guruvayoorappan & Kuttan, 2008)
Epicatechin	⊥[1–100 μg/ml]	–	–	⊥IL-8 and ↑IL-10	Whole blood culture	Inhibition of NF-κB activation	(Al-Hanbali et al., 2009)
	–	⊥[20–120 μM]	–	–	Human blood culture	–	(Mitjans et al., 2004)
EGCG	⊥[57.3% at 100 μM]	–	⊥[39.4% at 100 μM]	⊥IL-8	HMC-1 cells	Inhibition of NF-κB signaling pathway	(Shin et al., 2007)
Theaflavin	⊥[50 μg/ml]	–	–	–	Bone marrow cells	Down-regulation of NF-κB and MAPK pathways	(S. Kim & Joo, 2011)
	⊥[6.25–50 μM in U937 cells] and ⊥[6.25–50 μM in RAW cells]	⊥[12.5–50 μM in U937 cells] and ⊥[6.25–50 μM in RAW cells]	⊥[6.25–50 μM in U937 cells] and ⊥[6.25–50 μM in RAW cells]	–	U937 human leukemia and RAW 264.7 cells	Down-regulation of NF-κB and MAPK pathways	(Y. Wu et al., 2017)
	⊥[25 and 50 μM]	⊥[25 and 50 μM]	⊥[50 μM]	↑IL-10	RAW 264.7 cells	Downregulation of NF-κB	(Ko, Lo, Wang, Chiou, & Lin, 2014)
Hesperidin	⊥[50 μM]	⊥[50 μM]	⊥[50 μM]	⊥IL-8	THP-1 cells	Downregulation NF-κB and AP-1 signaling pathways	(C.-C. Yeh et al., 2007)
Hesperitin	⊥[1 and 10 μM]	–	–	–	SW982 synovial cells	Inhibition of JNK signaling	(Choi & Lee, 2010)
	⊥[10–40 μM]	⊥[10–40 μM]	⊥[10–40 μM]	–	RAW 264.7 cells	Inhibition of NF-κB and activation of Nrf2 pathways	(Ren et al., 2016)
Liquiritigenin	⊥[10 and 30 μM]	⊥[10 and 30 μM]	⊥[10 and 30 μM]	–	RAW 264.7 cells	Downregulation of NF-κB	(Y. Kim et al., 2008)
	⊥[50 and 100 μM]	⊥[50 and 100 μM]	⊥[50 and 100 μM]	–	Mouse microglial cell line BV-2	–	(Yu et al., 2015)
Eriodictyol	⊥[2.5–10 μM]	⊥[10 μM]	⊥[10 μM]	–	RAW 264.7 cells	Inhibition of NF-κB activation, MAPK, ERK, and JNK pathways	(J. K. Lee, 2011)
Taxifolin	⊥[100 and 200 μM]	⊥[100 and 200 μM]	–	–	RAW 264.7 cells	Downregulation of NF-κB signaling	(Rhee et al., 2008)
Naringenin	⊥[25 and 50 μM]	⊥[10–50 μM]	⊥[25 and 50 μM]	⊥IL-8	U937 cells	Regulation of phosphorylation of ERK and MAPK	(Bodet, La, Epifano, & Grenier, 2008)
Pinocembrin	⊥[100–300 μg/ml]	⊥[200–300 μg/ml]	⊥[100–300 μg/ml]	↑IL-10	RAW 264.7 cells	Inhibition of phosphorylation of IκBα, ERK, JNK, and p38/MAPK pathways	(Soromou et al., 2012)

TABLE 2 (Continued)

Flavonoid's name	Action on cytokines (Test concentration)				Assay cell lines	Pathway of action	References
	IL-6	IL-1β	TNF-α	Other cytokines			
	⊥[3 and 10 μM]	⊥[3 and 10 μM]	⊥[10 μM]	–	Mouse microglial cell line BV-2	Down-regulation of NF-κB activation, and TLR4 expression	(Lan et al., 2017)
	⊥[10 and 30 μM]	⊥[3–30 μM]	⊥[3–30 μM]	–	hBMECs	Inhibition of NF-κB activation and MAPK pathways	(Liu, Li, et al., 2014)
Myricetin	⊥[30 μM]	-	⊥[30 μM]	–	HMC-1 cells	Downregulation of NF-κB signaling	(Park et al., 2008)
	–	⊥[30 μM]	–	–	RAW 264.7 cells	–	(Blonska, Czuba, & Krol, 2003)
Quercetin	⊥[30 μM]	⊥[30 μM]	⊥[30 μM]	⊥IL-8	HMC-1 cells	Downregulation of NF-κB	(Park et al., 2008)
	⊥[5 μM]	⊥[5 μM]	⊥[5 μM]	–	A549 cells	Down-regulation of TLR4/NF-κB signaling	(T.-C. Wu et al., 2018)
	–	⊥[30 μM]	–	–	RAW 264.7 cells	–	(Blonska et al., 2003)
Rutin	⊥[30 μM]	⊥[30 μM]	⊥[30 μM]	⊥IL-8	HMC-1 cells	Downregulation of NF-κB signaling	(Park et al., 2008)
	–	–	⊥[25-100 μM]	–	HUVECs	Downregulation of NF-κB signaling	(W. Lee, Ku, & Bae, 2012)
Casticin	⊥[1–10 μM]	⊥[3 and 10 μM]	⊥[1–10 μM]	–	RAW 264.7 cells	Inhibition of NF-κB activation and ERK pathways	(Liou et al., 2014)
	⊥[5 and 10 μg/ml]	–	–	⊥IL-8	16-HBE cells	Inhibition of Nrf2/Keap1 and NF-κB pathways	(J. Wang, 2018)
	⊥[10 and 20 μg/ml]	⊥[5–20 μg/ml]	⊥[10 and 20 μg/ml]	⊥IL-8 and MCP-1	A549 and H460 cells	Inhibition of NF-κB, PI3K-Akt, and MAPK signaling	(Liou & Huang, 2017)
Galangin	⊥[25 and 50 μM]	–	⊥[50 μM]	–	RAW 264.7 cells	Inhibition of NF-κB activation and ERK pathways	(Jung et al., 2014)
	–	⊥[30 μM]	–	–	RAW 264.7 cells	–	(Blonska et al., 2003)
Kaempferol	–	⊥[30 μM]	–	–	RAW 264.7 cells	–	(Blonska et al., 2003)
Fisetin	⊥[30 μM]	⊥[30 μM]	⊥[30 μM]	⊥IL-8	HMC-1 cells	Regulation of NF-κB signaling	(Park et al., 2008)
	⊥[10 μM]	-	⊥[10 μM]	⊥IL-1α, IL-12, and IL-17	Bone marrow derived dendritic cells	Suppression of NF-κB activation	(S.-H. Liu et al., 2010)
	⊥[10 and 30 μM]	–	⊥[10 and 30 μM]	⊥IL-8 and MCP-1	A549 cells	Suppression of NF-κB and ERK pathways	(Peng, Huang, Cheng, & Liou, 2018)
Luteolin	⊥[10 μM]	–	⊥[10 μM]	–	RAW 264.7 cells	Decreased NF-κB stimulated promoter activity	(Xagorari et al., 2001)
	–	⊥[IC_{50}–5.1 μM]	⊥[IC_{50}–7.9 μM]	–	PBMCs	–	(Hougee et al., 2005)
	⊥[5 μM]	⊥[5 μM]	⊥[5 μM]	⊥IL-10	A549 cells	Downregulation of TLR4/NF-κB signaling	(T.-C. Wu et al., 2018)

(Continues)

TABLE 2 (Continued)

Flavonoid's name	Action on cytokines (Test concentration)				Assay cell lines	Pathway of action	References
	IL-6	IL-1β	TNF-α	Other cytokines			
	⊥[20 μM]	–	⊥[20 μM]	–	RAW 264.7 cells	Inhibition of NF-κB activation and MAPK pathways	(Xie et al., 2012)
Apigenin	⊥[IC_{50}-4.8 μM]	⊥[IC_{50}-5.3 μM]	⊥[IC_{50}-8.9 μM]	–	PBMCs	–	(Hougee et al., 2005)
	⊥[5 μM]	⊥[5 μM]	⊥[5 μM]	–	A549 cells	Downregulation of TLR4/NF-κB signaling	(T.-C. Wu et al., 2018)
	⊥[20 μM]	–	⊥[20 μM]	–	RAW 264.7 cells	Inhibition of NF-κB activation and MAPK pathways	(Xie et al., 2012)
Chrysin	⊥[IC_{50}-10.8 μM]	⊥[IC_{50}-10.7 μM]	⊥[IC_{50}-17.8 μM]	–	PBMCs	–	(Hougee et al., 2005)
	⊥[5 μM]	⊥[5 μM]	⊥[5 μM]	–	A549 cells	Downregulation of TLR4/NF-κB signaling	(T.-C. Wu et al., 2018)
Baicalein	⊥[5 and 10 μM]	–	⊥[5 and 10 μM]	–	HUVECs	Downregulation of NF-κB signaling	(W. Lee, Ku, & Bae, 2015)
	–	⊥[30 μM]	–	–	RAW 264.7 cells	–	(Blonska et al., 2003)
	⊥[10–40 μM]	–	↓ [10–40 μM]	⊥IL-8	A549 cells	Reduction of virus-induced activation of AKT, ERK, and NF-kB signaling	(Sithisarn, Michaelis, Schubert-Zsilavecz, & Cinatl Jr, 2013)
Baicalin	⊥[10 and 20 μM]	–	⊥[10 and 20 μM]	⊥IL-8	Type II pneumocytes	Inhibition of NF-kB activation	(Lixuan et al., 2010)
Wogonin	⊥[5 and 10 μM]	–	⊥[5 and 10 μM]	–	HUVECs	Downregulation of NF-κB signaling	(W. Lee et al., 2015)
Velutin	⊥[20 μM]	–	⊥[5–20 μM]	–	RAW 264.7 cells	Inhibition of NF-κB activation and MAPK pathways	(Xie et al., 2012)
Genistein	⊥[50 μM]	–	⊥[50 μM]	–	RAW 264.7 cells	Decreased NF-kB stimulated promoter activity	(Xagorari et al., 2001)
	⊥[10^{-5}–10^{-9} μM]	–	⊥[10^{-5}-10^{-9} μM]	–	Jurkat E6.1 T cells	–	(Karieb & Fox, 2013)
	⊥[50 μM]	⊥[50 μM]	–	–	HMC-1 cells	Inhibition of the ERK pathway	(D. H. Kim et al., 2014)
Biochanin-A	⊥[10–50 μM]	⊥[10–50 μM]	⊥[10–50 μM]	–	RAW 264.7 cells	Downregulation of NF-κB signaling	(Kole, Giri, Manna, Pal, & Ghosh, 2011)
	⊥[10–40 μM]	–	↓[10–40 μM]	–	A549 cells	Reduction of virus-induced activation of Akt, ERK, and NF-kB signaling	(Sithisarn et al., 2013)
Formononetin	⊥[0.1–10 μM]	⊥[0.1–10 μM]	⊥[0.1–10 μM]	–	RBL-2H3 cells	Downregulation of NF-κB	(N. Xu & An, 2017)
Silibinin	⊥[10 and 50 μM]	⊥[10 and 50 μM]	⊥[10 and 50 μM]	⊥IL-8 and ↑IL-10	PBMCs	–	(Gugliandolo et al., 2020)
	–	⊥[50 and 100 μM]	⊥[50 and 100 μM]	–	RAW 264.7 cells	Inhibition of NF-κB and NLRP3 activation	(B. Zhang, Wang, Cao, Wang, & Wu, 2017)

Note: ⊥, Significant inhibition; ↓, In-significant inhibition; ↑, Activation.

TABLE 3 In vivo effect of flavonoids on cytokines in the preclinical model

Flavonoid's name	Action on cytokines‡[Biological tissue/fluid analyzed]				Study design [Animal species; Dose; Test article administration route; Disease model; Inducing agent]	Pathway of action	References
	IL-6	IL-1β	TNF-α	Other cytokines			
Epicatechin	⊥[Lung tissue and BALF]	—	⊥[Lung tissue]	—	C57BL6/N mice; 15 mg/kg; nasogastric; acute lung injury; *LPS*	Inhibition of the p38 MAPK signaling pathway	(Xing et al., 2019)
EGCG	⊥[Lung tissue]	⊥[Lung tissue]	⊥[Lung tissue]	—	Wistar rats; 40 mg/kg; oral; lung injury; fluoride	Activation of the Nrf2/Keap1 pathway	(Shanmugam, Selvaraj, & Poomalai, 2016)
	—	—	⊥[Lung tissue]	⊥IL-1, ↑IL-10	Sprague-Dawley rats; 10 mg/kg; intraperitoneal; acute lung injury; seawater aspiration	Inhibition of JAK/STAT pathways	(Liu, Dong, et al., 2014)
Theaflavin	⊥[Serum]	↓ [Serum]	⊥[Serum at 40 mg/kg]	—	C57BL6/N mice; 20 and 40 mg/kg; intraperitoneal; acute lung injury; *LPS*	—	(Y. Wu et al., 2017)
Hesperidin	—	⊥[BALF]	⊥[BALF]	⊥IL-12; ↑IL-4 and IL-10	Balb/c mice; 200 mg/kg; oral; acute lung injury; *LPS*	Down-regulation NF-κB and AP-1 signaling	(C.-C. Yeh et al., 2007)
Hesperitin	⊥[Serum]	⊥[Lung tissue]	⊥[Lung tissue]	↑IL-10	Wistar rats; 100 mg/kg; oral; acute lung injury; *LPS*	Down-regulation of NF-κB signaling	(Kaya, 2020)
	⊥[Serum, BALF and lung tissue]	⊥[Serum, BALF and lung tissue]	⊥[Serum, BALF and lung tissue]	—	C57BL/6 mice; 25 and 50 mg/kg; oral; acute lung injury; *LPS*	Inhibition of MAPK pathway activation via targeting TLR4/MD2 protein	(J. Ye et al., 2019)
Eriodictyol	⊥[Serum and BALF]	⊥[Serum and BALF]	⊥[Serum and BALF]	⊥MIP-2	C57BL/6 mice; 30 mg/kg; oral; acute lung injury; *LPS*	Regulation of Nrf2 pathway	(G. F. Zhu, Guo, Huang, Wu, & Zhang, 2015)
Naringenin	⊥[Serum and BALF]	⊥[Serum and BALF]	⊥[Serum and BALF]	⊥MIP-2	C57BL/6 mice; 100 mg/kg; oral; acute lung injury; *LPS*	Inhibition of the PI3K/Akt pathway	(Minghong Zhao et al., 2017)
	⊥[Lung tissue at 100 mg/kg]	—	⊥[Lung tissue]	—	Sprague–Dawley rats; 50 and 100 mg/kg; oral; acute lung injury; *LPS*	Down-regulation of NF-κB signaling	(Fouad, Albuali, & Jresat, 2016)
Naringin	⊥[Lung tissue]	⊥[Lung tissue]	⊥[Lung tissue]	—	C57BL/6 mice; 80 mg/kg, intraperitoneal; acute lung injury; acrolein	Regulation of MAPK, p53, and NF-κB signaling pathways	(J. K. Kim et al., 2018)
	⊥ [Pleural exudates]	—	⊥ [Pleural	⊥IL-17 and IL-2; ↑IL-4 and IL-10	Balb/c mice; 40 and 80 mg/kg; oral; acute lung inflammation; carrageenan	Inhibition of NF-κB and STAT3 signaling	(S. F. Ahmad et al., 2015)
Pinocembrin	⊥[BALF]	⊥[BALF]	⊥[BALF]	↑IL-10	Balb/c mice; 20 and 50 mg/kg; intraperitoneal; acute lung inflammation; *LPS*	Inhibition of MAPK and NF-κB activation	(Soromou et al., 2012)

(Continues)

TABLE 3 (Continued)

Flavonoid's name	Action on cytokines‡[Biological tissue/fluid analyzed]				Study design [Animal species; Dose; Test article administration route; Disease model; Inducing agent]	Pathway of action	References
	IL-6	IL-1β	TNF-α	Other cytokines			
Myricetin	⊥[BALF]	⊥[BALF]	⊥[BALF]	—	Sprague-Dawley rats; 10-40 mg/kg; intraperitoneal; acute lung inflammation; *LPS*	Inhibition of NF-κB mediated inflammatory responses	(Mao & Huang, 2017)
	⊥[BALF]	⊥[BALF]	⊥[BALF]	—	Balb/c mice; 2.5-10 mg/kg; intraperitoneal; acute lung inflammation; *LPS*	Inhibition of both NF-κB/AKT and p38/MAPK signaling pathways	(Hou et al., 2018)
Quercetin	⊥[Serum]	⊥[Serum]	⊥[Serum]	↑IL-10	C57/BL6 mice; 60 mg/kg; oral; acute lung injury; *LPS*	Reduction of COX-2, HMGB1, iNOS expression, and NF-κB p65 phosphorylation	(L. Wang et al., 2014)
Rutin	⊥[BALF]	⊥[BALF]	⊥[BALF]	—	ICR mice, 1–100 μmol/kg; intraperitoneal; acute lung injury; *LPS*	Inhibition of oxidative stress and MAPK–NF-κB pathway	(C.-H. Yeh, Yang, Yang, Li, & Kuan, 2014)
Casticin	⊥[BALF]	⊥[BALF]	⊥[BALF]	—	Balb/c mice; 2.5–10 mg/kg; intragastric; acute lung injury; LPS	Inhibition of NF-κB and NLRP3 signaling pathways	(C. Wang, Zeng, Zhang, Liu, & Wang, 2016)
Galangin	⊥[Lung tissue]	—	⊥[Lung tissue]	—	Balb/c mice; 1.5 and 15 mg/kg; intraperitoneal; acute lung injury; *LPS*	Inhibition of NF-κB and upregulation of HO-1 signaling pathways	(Shu, Tao, Miao, Lu, & Zhu, 2014)h
Kaempferol	⊥[BALF]	⊥[BALF]	⊥[BALF]	—	Balb/c mice; 100 mg/kg; intragastric; acute lung injury; *LPS*	Suppression of MAPKs and NF-κB signaling pathways	(X. Chen et al., 2012)
Fisetin	⊥[BALF	—	⊥[BALF	—	Sprague-Dawley rats; 1–4 mg/kg; intravenous; acute lung injury; *LPS*	Suppression of TLR4-mediated NF-κB signaling pathways	(G. Feng, Jiang, Sun, Fu, & Li, 2016)
Luteolin	⊥[BALF at 70 μmol/kg]	—	⊥[BALF at 70 μmol/kg]	—	ICR mice; 18-70 μmol/kg; intraperitoneal; acute lung injury; *LPS*	Suppression of Akt/NF-κB signaling pathway	(Y.-C. Li, Yeh, Yang, & Kuan, 2012)
	⊥[Plasma and BALF]	⊥[Lung tissue]	⊥[Plasma]	—	Swiss albino mice; 0.2 mg/kg; intraperitoneal; cecal ligation and puncture	Suppression of ICAM-1, NF-κB, oxidative stress, and partially iNOS signaling pathways	(Rungsung et al., 2018)
	⊥[BALF]	—	⊥[BALF]	—	Male C57BL/6mice; 10 mg/kg; oral; bleomycin	Inhibition of TGF-β1-induced Smad3, phosphorylation	(C.-Y. Chen, Peng, Wu, Wu, & Hsu, 2010)
Apigenin	⊥[BALF]	⊥[BALF]	⊥[BALF at 20 and 40 mg/kg]	—	Balb/c mice; 10–40 mg/kg; intragastric; acute lung injury; LPS	Suppression of activation of TLR4/TRPC6 signaling pathway	(K. Li et al., 2018)
Chrysin	⊥[Pleural exudates]		⊥[Pleural exudates]	—	Sprague-Dawley rats; 20 and 40 mg/kg; oral; acute lung injury; carrageenan	Activation of SIRT1/NRF2 signaling	(Z. Yang, Guan, Li, Li, & Li, 2018)

TABLE 3 (Continued)

Flavonoid's name	Action on cytokines‡[Biological tissue/fluid analyzed]				Study design [Animal species; Dose; Test article administration route; Disease model; Inducing agent]	Pathway of action	References
	IL-6	IL-1β	TNF-α	Other cytokines			
Isovitexin	⊥[BALF]	—	⊥[BALF]	—	Balb/c mice; 50 and 100 mg/kg; intraperitoneal; acute lung injury; LPS	Inhibition of MAPK, NF-κB and activation of HO-1/Nrf2 Pathways	(Lv et al., 2016)
Morin	⊥[BALF]	⊥[BALF]	⊥[BALF]	⊥IL-18	Balb/c mice; 20 and 40 mg/kg; intragastric; acute lung injury; LPS	Suppression of lung NLRP3 inflammasome	(Tianzhu, Shihai, & Juan, 2014)
Baicalein	⊥[BALF]	⊥[BALF]	⊥[BALF]	⊥IL-18	Sprague-Dawley rats; 20 mg/kg; intraperitoneal; acute lung injury; LPS	Inhibition of NF-κB mediated inflammatory responses and upregulation of Nrf2/HO-1 signaling pathway	(Tsai, Lin, Wang, & Chou, 2014)
Baicalin	⊥[Plasma and BALF]	—	⊥[Plasma and BALF at 40 and 80 mg/kg]	↓ IL-8	Sprague-Dawley rats; 20-80 mg/kg; intragastric; acute lung injury; cigarette smoke	Inhibition of NF-kB activation	(Lixuan et al., 2010)
	⊥[Serum]	⊥[Serum]	⊥[Serum]	⊥TGF- β and IL-18	CX3CL1-knockout mice; 50-200 mg/kg; oral; acute lung injury; LPS	Inhibition of NF-kB pathway	(Ding, Pan, Wang, & Xu, 2016)
	⊥[BALF]	⊥[BALF]	⊥[BALF]	—	Specific pathogen-free male mice; 200 mg/kg; oral; acute lung injury; LPS	Regulation of Nrf2-mediated HO-1 signaling pathway	(Meng, Hu, & Li, 2019)
Wogonin	⊥[BALF and lung tissue]	⊥[BALF and lung tissue]	⊥[BALF and lung tissue]	—	C57BL/6 mice; 30 mg/kg; intravenous; acute lung injury; LPS	Inhibition of NF-kB pathway	(Yao et al., 2014)
Diosmin	⊥[Lung tissue]	-	⊥[Lung tissue]	⊥IL-17A	Balb/c mice; 50 and 100 mg/kg; oral; acute lung injury; LPS	Inhibition of TLR4-MyD88-NF-κB pathway	(Imam et al., 2015)
Diosmetin	⊥[BALF]	⊥[BALF at 25 mg/kg]	⊥[BALF]	—	Balb/c mice; 5 and 25 mg/kg; intraperitoneal; acute lung injury; LPS	Activation of Nrf2 pathway and inhibition of NLRP3 inflammasome	(Q. Liu, Ci, Wen, & Peng, 2018)
Genistein	↓ [Lung tissue]	↓[BALF]	↓ TNF-α	↓ TGF-β	Sprague-Dawley rats; 20 mg/kg; oral; lung injury; ^{60}Co γ radiation	—	(Calveley et al., 2010)
	⊥[Serum and BALF]	⊥[Serum and BALF]	⊥[Serum and BALF]	⊥TGF-β	C57BL/6J mice; 200 mg/kg; subcutaneous; pneumonitis; radiation	Downregulation of Ape1/Ref-1 expression	(Liu, Xia, et al., 2014)
Biochanin-A	⊥[BALF]	⊥[BALF]	⊥[BALF]	—	C57BL/6 mice; 12.5, 25, and 50 mg/kg; intraperitoneal; acute lung injury; LPS	Down-regulation of activation of TLR4/NF-κB signaling pathway and enhancing the expression of PPAR-γ	(Hu et al., 2020)

(Continues)

TABLE 3 (Continued)

Flavonoid's name	Action on cytokines[‡][Biological tissue/fluid analyzed]				Study design [Animal species; Dose; Test article administration route; Disease model; Inducing agent]	Pathway of action	References
	IL-6	IL-1β	TNF-α	Other cytokines			
Formononetin	⊥[BALF]	–	⊥[BALF]	–	C57BL/6 mice; 10 and 20 mg/kg; intraperitoneal; acute lung injury; LPS	Induction of PPAR-γ expression	(Ma, Ji, Fu, & Ma, 2013)
Daidzein	⊥[BALF]	–	⊥[BALF]	–	Sprague–Dawley rats; 2–8 mg/kg; intraperitoneal; acute lung injury; LPS	Inhibition of TLR4-MyD88-NF-kB activation	(G. Feng, Sun, & Li, 2015)
Silymarin	⊥[BALF]	–	⊥[BALF]	–	Wistar rats; 50–200 mg/kg; intraperitoneal; ARDS; LPS	Partly inactivation of MAPK pathway	(Z. Zhu & Sun, 2018)
Silibinin	⊥[lung tissue]	⊥[Serum, BALF, lung tissue at 100 mg/kg]	⊥[Serum, BALF, lung tissue at 100 mg/kg]	⊥ IL-17	C57/BL6 mice; 50 and 100 mg/kg; intragastric; LPS	Inhibition of NF-κB and NLRP3 activation	(B. Zhang, Wang, et al., 2017)
	–	⊥[BALF]	⊥[BALF]	⊥ IL-18	Balb/c mice; 10–40 mg/kg; intraperitoneal; acute lung injury; LPS	Inhibition of NF-κB and NLRP3 activation	(L. Tian, Li, & Wang, 2017)

Note: [‡]Dose mentioned if significant inhibition showed by flavonoid at a particular dose instead of all the experimental dose level(s); ⊥, Significant inhibition; ↓, In-significant inhibition; ↑, Activation.

Its aglycone part, namely hesperitin, is reported to inhibit TNF-α, IL-1β, and IL-6 significantly by hindering multiple pathways like JNK, NF-κB, and MAPK based on the in vitro (Choi & Lee, 2010; Ren et al., 2016) and in vivo investigations (Kaya, 2020; J. Ye et al., 2019). In a clinical study involving human adults, hesperidin exhibited a significant reduction of IL-6 level at an oral dose of 160 mg/day (Buscemi et al., 2012; Pla-Pagà et al., 2019). Computational studies demonstrated that hesperidin could perform a significant antiviral activity against SARS-CoV-2 due to its binding affinity to spike protein, ACE-2, and main protease (Bellavite & Donzelli, 2020; Meneguzzo, Ciriminna, Zabini, & Pagliaro, 2020). Furthermore, virtual screening purposed that it can interfere with the interaction of ACE-2 receptors, thus preventing the entry of the virus into lung cells (Haggag, El-Ashmawy, & Okasha, 2020). It exhibited a greater binding affinity toward 3CL-pro, S2-RBD, TMPRSS, and PD-ACE2 to inhibit the SARS-CoV-2 infection (Utomo, Putri, Salsabila, & Meiyanto, 2020). Hesperidin is considered safe to be administered as nutraceuticals (FSSAI, 2016). Recently, this is under clinical investigation for the management of COVID-19 (NCT04452799).

4.4 | Naringenin

Naringenin is an extensively used flavonoid from the class of flavanones and predominantly present in grapefruits (Pandey, Gurung, & Sohng, 2015). It had shown inhibitory effect of IL-6, IL-1β, and TNF-α levels in LPS-stimulated U937 cells and RAW 264.7 cells (Soromou et al., 2012). It had also reported inhibiting the secretion of IL-6, IL-1β, and TNF-α in LPS-stimulated acute lung injury in C57/BL6 mice by targeting the inhibition of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway (Minghong Zhao et al., 2017). It had also shown to reduce the levels of IL-6 and TNF-α in LPS-stimulated acute lung injury in rats via inhibition of the NF-κB pathway (Fouad et al., 2016). In both cases, the required effective dose was found to be 100 mg/kg through the oral route. Naringin, a glycoside of naringenin, has reported to effectively control the levels of IL-6, IL-1β, TNF-α, IL-4, and IL-17 even at a dose of 40–80 mg/kg in in vivo mice model of lung injury through regulation of NF-κB, MAPK, p53, and STAT signaling (S. F. Ahmad, Attia, et al., 2015; J. K. Kim et al., 2018). Naringenin exhibited significant antiviral activity against chikungunya and dengue virus with an IC_{50} of 6.8 μM and 52.64 μg/ml in cultured cells, respectively (Ahmadi et al., 2016; Keivan et al., 2011). Molecular docking analysis revealed that naringenin and naringin interfere with 3CLpro, and ACE-2 activity of SARS-CoV-2 (Alrasheid et al., 2021; Tutunchi, Naeini, Ostadrahimi, & Hosseinzadeh-Attar, 2020). Clementi et al. (2020) reported that naringenin could be considered to be a safe anti-SARS-CoV-2 agent endowed with SARS-CoV-2 inhibitory activity. Naringenin is also part of the FSSAI list of nutraceuticals (FSSAI, 2016).

4.5 | Quercetin

Quercetin belongs to the category of flavonols and is widely present in berries, grapes, apples, shallots, onions, and tomatoes (Baková &

TABLE 4 In vivo effect of flavonoids on cytokines in the clinical model

Flavonoid's name	Study design			Effect on cytokine	References
	Dose	Route of administration	Dose schedule		
Hesperidin	160 mg/day	Oral	1.5 weeks	Significant decrease the IL-6 level in clinical subjects with increased cardiovascular risk	(Buscemi et al., 2012; Pla-Pagà et al., 2019)
Quercetin	500–1500 mg/day in combination with azathioprine	Oral	8 weeks	Decreased the level of IL-6 in patient with active rheumatoid arthritis	(Al-Rekabi et al., 2014)
	500 mg/day	Oral	24 h	Reduced the level of IL-8 and TNF-α in sarcoidosis patients	(Boots, Drent, de Boer, Bast, & Haenen, 2011)
	120 mg/day	Oral	8 weeks	Inhibited IL-1β and TNF-α in coronary artery disease	(Chekalina et al., 2018)
	500 and 1000 mg/day in combination with vitamin C and Niacin	Oral	12 weeks	A minute reduction in IL-6 level in community-dwelling adult	(Knab et al., 2011)
Luteolin	100 mg/day	Oral	26 weeks	Reduced IL-6 and TNF-α levels in children with autism spectrum disorders	(Tsilioni, Taliou, Francis, & Theoharides, 2015)
Diosmin	1200 mg/day	Oral	12 weeks	Decreased IL-6 and TNF-α levels in patients with chronic venous disorders	(Feldo et al., 2019)
Silymarin	420 mg/day	Oral	12 weeks	Decreased serum TNF-α level and enhanced IL-4 and IFN-γ levels in β-thalassemia patients	(Gharagozloo, Karimi, & Amirghofran, 2013)
Silibinin	240 mg/day	Oral	16 weeks	Reduced IL-6, IL-8 and TNF-α levels and increased production of IL-2 and IL-10 in active rheumatoid patients	(Hussain, Mortada, Jasim, & Gorial, 2016)

Kolesárová, 2020). In PMACI-stimulated HMC-1, quercetin notably reduced the secretion of IL-6, IL-1β, IL-8, and TNF-α (Park et al., 2008). The production of IL-6, IL-1β, and TNF-α was notably inhibited at 5 μM in A549 cells (T.-C. Wu et al., 2018). A similar result on IL-1β was also reported in RAW 264.7 cell lines (Blonska et al., 2003). The levels of IL-6, IL-1β, and TNF-α were reduced significantly in LPS-induced acute lung injury in C57/BL6 mice through reduced expression of *cyclooxygenase-2* (COX-2), *high mobility group box 1 (HMGB1)*, *inducible nitric oxide synthase* (iNOS), and NF-κB p65 phosphorylation (L. Wang et al., 2014). In clinical subjects with coronary artery disease, quercetin treatment at only 120 mg/kg through oral route significantly inhibited the secretion of IL-1β, and TNF-α (Chekalina et al., 2018). Minute reduction in IL-6 and TNF-α was observed in community-dwelling adults at 500–1000 mg/day in combination with vitamin C and niacin (Knab et al., 2011). It has been reported that administration of quercetin could lead to reduced level of IL-8 and TNF-α and IL-6 in patients with rheumatoid arthritis and sarcoidosis, respectively (Al-Rekabi et al., 2014; Boots et al., 2011). It exhibited in vitro anti-replication property by reducing the plaque formation induced by RNA and DNA viruses (De Palma, Vliegen, De Clercq, & Neyts, 2008; Pagani, 1990). In Vero cells, it showed to inhibit the dengue virus type-2 replication that can cause a 67% reduction of viral load at a concentration of 36 μg/ml (Zandi et al., 2011). Pretreatment of quercetin blocked virulence, entry, and replication of rhinovirus in BEAS-2B cells (Ganesan et al., 2012). It notably inhibited the reverse transcriptase activity in a dose-dependent manner in cultured cells infected with Maloney murine leukemia virus, Rous-associated virus-2, and Avian myeloblastosis reverse transcriptase (Spedding, Ratty, & Middleton Jr, 1989). It also demonstrated a potent inhibition activity against HIV and hepatitis C virus protease as well as ability to interfere with virus assembly by modulating the heat shock protein expression (Bachmetov et al., 2012; Gonzalez et al., 2009; H.-X. Xu, Wan, Dong, BuT, & Foo, 2000). Quercetin and its galactoside are known to interfere with the proteolytic activity by binding to SARS-CoV 3CL protease (Alrasheid et al., 2021; Colunga Biancatelli et al., 2020). In silico studies illustrated that quercetin could interfere with M^{pro} and ACE2 as well as showed potential inhibition when compared to the synthetic repurposed drug, hydroxychloroquine (Omar, Bouziane, Bouslama, & Djemel, 2020). Quercetin impedes the entry of the SARS virus by targeting ACE2 and exhibits antiviral activity (P. K. Agrawal, Agrawal, & Blunden, 2020; Chaabi, 2020; Pawar & Pal, 2020). Derosa and its team demonstrated the role of quercetin in SARS-CoV-2 due to its ability to inhibit main protease as well as its anti-inflammatory and thrombin-inhibitory activities (Bastaminejad & Bakhtiyari, 2020; Derosa, Maffioli, D'Angelo, & Di Pierro, 2020; Saeedi-Boroujeni &

Mahmoudian-Sani, 2021). A tripartite combination consisting of quercetin/vitamin D/estradiol had depicted the expression of 73% of human genes encoding SARS-CoV-2 targets (Glinsky, 2020). Aucoin and co-workers demonstrated the effect of quercetin on the prevention or treatment of COVID-19 and other respiratory tract infections in humans (Aucoin et al., 2020). It might act as a therapeutic drug to treat SARS-CoV-2 induced nephrotoxicity (Diniz, Souza, Duarte, & Sousa, 2020). Supplementation of quercetin along with multivitamin and trace elements (vitamins A, B complex, C, D and E, zinc) can be useful in prophylaxis and treatment of mild symptomatic COVID-19 patients (Petric, 2020). A novel therapy consisting of quercetin, zinc, vitamin C, and bromelain exhibited a promising result to improve clinical outcome in SARS-CoV-2 patients (A. K. Ahmed, Albalawi, Shora, Abdelseed, & Al-Kattan, 2020). Oral administration of quercetin at a dose of 30 or 40 mg/kg BID for 4 days reduced the viral load in mice inoculated with meningoencephalitis virus at a dose-dependent manner (Veckenstedt, Béládi, & Mucsi, 1978). Quercetin obtained from the extracts of citrus fruits and other vegetables is recommended as a nutraceutical, where the maximum recommended intake of quercetin is 100 mg/day (FSSAI, 2016). Quercetin in phytosomal formulation, which was developed using food grade lecithin to boost its oral absorption, was found to be effective in allergies through stabilization of the mast cell membranes to decrease the release of histamine (Colunga Biancatelli et al., 2020). Recently, this is under clinical investigation for the management of SARS-CoV-2 (NCT04377789, NCT04578158).

4.6 | Rutin

Rutin is one of the common flavonols widely distributed in citrus fruits and buckwheat (Lachman, Orsak, Pivec, & Faustusova, 2000). It is basically a glycoside form of quercetin. Treatment of rutin significantly inhibited the secretion of IL-6, IL-1β, IL-8, and TNF-α in PMACI-stimulated HMC-1 cells (Park et al., 2008). It reduced the secretion of TNF-α in LPS-stimulated human umbilical vein endothelial cells (HUVEC) (W. Lee et al., 2012). Rutin treatment decreased the secretion of IL-6, IL-1β, and TNF-α in LPS-induced acute lung injury in in vivo ICR mice by targeting the inhibition of oxidative stress and MAPK-NF-κB pathway (C.-H. Yeh et al., 2014). The simulation study revealed that rutin could be a potent inhibitor of the main protease of COVID-19 as it represents minimum binding energy of -136 (Al-Zahrani, 2020). Rutin was considered to be a potent inhibitor of SARS-CoV-2 3CL main protease and other key proteins in the life cycle of COVID-19 based on the ML prediction and molecular docking procedures (Al-Zahrani, 2020; Xu, Yang, et al., 2020). A Molecular docking study showed significant binding of rutin with RdRp, M^{pro}, PL^{pro}, and S-proteins of SARS-CoV-2 (F. Rahman et al., 2021). Rutin from fruit peels is considered as safe to use as nutraceuticals (FSSAI, 2016).

4.7 | Luteolin

Luteolin is one of the most common flavones, which are widely distributed in fruits and vegetables such as cabbages, carrots, broccoli, celery, parsley, and apple skins (López-Lázaro, 2009). In an in vitro nickel-stimulated A549 cell lines assay, luteolin considerably reduced the production of IL-6, IL-1β, IL-10, and TNF-α. It inhibited the secretion of IL-6 and TNF-α in LPS-stimulated RAW 264.7 cells (Xagorari et al., 2001). Similar downregulation activities of the important cytokines are also reported in the in vitro assay at a very low micro-molar level using PBMCs and RAW 264.7 cells (Hougee et al., 2005). In LPS induced acute lung injury, luteolin treatment significantly reduced the level of IL-6 and TNF-α in mice model via inhibition of NF-κB and transforming growth factor-beta1 (TGF-β1)-induced Smad3 pathway (C.-Y. Chen et al., 2010; Y.-C. Li et al., 2012). Rungsung et al. (2018) demonstrated significant inhibition of IL-6, IL-1β, and TNF-α in Swiss albino mice via inhibition of ICAM-1 and NF-κB pathways. In the clinical trial, the treatment of luteolin decreased the IL-6 and TNF-α in children with autism spectrum disorders (Tsilioni et al., 2015). Fan, Qian, Qian and Li (2016) reported potent antiviral activity of luteolin against replication of encephalitis virus in A549 cells with IC_{50} of 4.56 μg/ml. Luteolin inhibited the reverse transcriptase activity in breast cancer cells (L. Huang, Jin, & Lan, 2019). Luteolin was also reported to inhibit the proteolytic activity of SARS-CoV 3CLpro (Jo, Kim, Shin, & Kim, 2020). The compound possessed antiviral activity against SARS-CoV in Vero cultured cells having EC_{50} of 10.6 μM (Yi et al., 2004). Luteolin was reported to interfere with spike, main protease, and nucleocapsid protein of SARS-CoV-2 to inhibit the viral infection (Ansari, Ahamad, Khan, Khan, & Khan, 2020; Shawan, Halder, & Hasan, 2021).

4.8 | Baicalein

Baicalein is a flavone extracted mainly from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora (*Varsha et al., 2017*). It had shown the inhibitory effect of IL-6 and* TNF-α secretion significantly in LPS-stimulated HUVECs as well as H5N1 virus-induced stimulation of cytokines in A549 cells (Sithisarn et al., 2013). The ability to inhibit IL-8 and IL-1β was also reported using HUVECs and RAW 264.7 cells, respectively (Blonska et al., 2003). Baicalein treatment significantly decreased the level of *IL-6*, IL-1β, *and* TNF-α in LPS-induced acute lung injury in Sprague-Dawley rats through inhibition of NF-κB mediated inflammatory response and upregulation of Nrf2/*Heme oxygenase-1 (*HO-1) pathway (Tsai et al., 2014). Similar activity of hindering IL-6, TNF-α, and IL-8 was also reported for baicalin, the aglycone of baicalein in Type II pneumocytes as well as in vivo acute lung injury model (Lixuan et al., 2010; Meng et al., 2019). Moreover, this aglycone baicalin had been shown to inhibit TGF-β and IL-18 in LPS-induced CX3CL1 knockout mice model of lung injury (Ding et al., 2016). Baicalein, at a concentration of 2 μg/ml, exhibited a 70% inhibition of HIV reverse transcriptase activity (Ono, Nakane, Fukushima, Chermann, & Barré-Sinoussi, 1990). It inhibited the replication of the dengue virus in Vero cells with IC_{50} of 6.4 μg/ml (Zandi et al., 2012). Baicalein enhanced the efficacy of ribavirin against influenza virus in cultured cells as well as in the preclinical mice model (L. Chen et al., 2011). Aqueous extract of *Scutellaria bicalensis*

standardized to baicalin content not less than 50% is approved as nutraceutical at a dose level of 250–1000 mg/day (FSSAI, 2016). Baicalin had been reported to inhibit ACE activity (Yang, Islam, Wang, Li, & Chen, 2020). Baicalein and its aglycone unit possessed a significant inhibition against $3CL^{pro}$ of SARS-CoV-2 (Su et al., 2020). A recent report revealed that the application of baicalein would inhibit the replication of the SARS-CoV-2 through the interference of mitochondrial oxidative phosphorylation. The inhibitory effect of baicalein is mPTP dependent and reversible, where co-application of mPTP inhibitors with baicalein could act synergistically in the control of SARS-CoV-2 (Huang, Liu, et al., 2020).

4.9 | Diosmin

Diosmin is one of the most prevalent flavones that is consumed through diverse dietary sources like fruits, viz., grapes, citrus fruits, berries, pomegranates, and apples; vegetables, viz., onions, broccoli, and leafy greens; legumes, soy products, as well as beverages, viz., red wine and tea (Roy, Azamthulla, & Mukkerjee, 2020). Diosmin had significantly reduced the production of IL-6 and TNF-α in LPS-induced acute lung injury in Balb/c mice via targeting the TLR4-MyD88-NF-κB signaling pathway (Imam et al., 2015). Diosmin is a glycoside of diosmetin, which had also shown a significant inhibitory effect on IL-6, IL-1β, and TNF-α via activation of Nrf2 and inhibition of NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome in LPS-induced animal model of lung injury (Q. Liu et al., 2018). Diosmin decreased the production of IL-1β and TNF-α in patients with chronic venous disorders (Feldo et al., 2019). In silico studies have demonstrated that diosmin possess the ability to interfere with 3CLpro of SARS-CoV-2 by blocking its substrate-binding site, with an IC_{50} of 8.3 μM (Chen, Yiu, & Wong, 2020). Molecular docking studies revealed that diosmin is a potent candidate to inhibit the M^{pro} (Adem, Eyupoglu, Sarfraz, Rasul, & Ali, 2020). It exhibited a greater binding affinity toward 3CL-pro, S2-RBD, TMPRSS, and ACE2 to inhibit the SARS-CoV-2 infection (Utomo et al., 2020). Citrus flavonoids are safe to use at 150–600 mg/kg as mentioned in nutraceuticals guidelines (FSSAI, 2016). Recently, this agent is under clinical investigation for the management of SARS-CoV-2 (NCT04452799).

4.10 | Genistein

Genistein is an isoflavone, which is primarily found in edible legumes, red clover, and soy-based foods (Liggins et al., 2000). The level of IL-6 and TNF-α was notably inhibited by genistein in both LPS-stimulated RAW 264.7 cells and Jurkat E6.1 T cells (Karieb & Fox, 2013). D. H. Kim et al. (2014) demonstrated the inhibitory effect of genistein on IL-6 and IL-1β production in PMA-stimulated HMC-1 cells. In the preclinical mice model of LPS-induced acute lung inflammation, it was reported to inhibit the secretion of IL-6, IL-1β, TNF-α, and TGF-β via downregulation of expression of Ape1/Ref-1 (Liu, Xia, et al., 2014). The above compound inhibited the production of virus and prevented plaque generation with an IC_{50} of 46 μM and 33μM for macaque and human fibroblasts, respectively. Genistein reduced the viral load by 99% and 93% in combination with ganciclovir and acyclovir, respectively, using the same concentration of IC_{50} (LeCher, Diep, Krug, & Hilliard, 2019). It inhibited in vitro viral replication and its associated proteins in Vero cells infected with the swine flu virus (Arabyan et al., 2018). Molecular docking studies reported that genistein interferes with M^{pro} and RdRp to inhibit the activity of SARS-CoV-2 (Khan et al., 2020). Genistein or its sources like soya protein isolate/edible legume seed protein isolate are safe to use as a nutraceutical (FSSAI, 2016).

4.11 | Biochanin A

Biochanin A is an isoflavone that is widely present in zigzag clover, red clover, crimson clover, and also in other plants such as soy, peanuts, alfalfa, and chickpea (Sundaresan, Radhiga, & Deivasigamani, 2018). It had been reported to inhibit IL-6, IL-1β, and TNF-α production in LPS-stimulated RAW 264.7 cells via regulating the NF-κB pathway (Kole et al., 2011). Moreover, treatment of Biochanin A significantly reduced the secretion of IL-6 in H5N1 virus-induced stimulation of cytokines in A549 cells via reducing the activation of multiple pathways like Akt, extracellular signal-regulated kinases (ERK), and NF-κB (Sithisarn et al., 2013). In an in vivo model of LPS-induced acute lung injury in C57/BL6 mice, biochanin A notably reduced the level of IL-6, IL-1β, and TNF-α through downregulation of TLR4/NF-κB signaling pathway and upregulation in the expression of *peroxisome proliferator-activated receptor-gamma* (PPAR-γ) (Hu et al., 2020). The replication of the avian influenza H5N1 virus strain was reduced to 55-fold by biochanin A at a concentration of 40 μM in A549 cells (Sithisarn et al., 2013). Molecular docking analysis revealed that biochanin A significantly binds to the active sites of RBD-Sand ACE2 to inhibit the viral infection (Gorla, Rao, Kulandaivelu, Alavala, & Panda, 2020).

4.12 | Silymarin

Silymarin is one of the common flavonolignans and is widely present in milk thistle (Vaknin, Hadas, Schafferman, Murkhovsky, & Bashan, 2008). Treatment of silymarin had decreased the level of IL-6 and TNF-α significantly in LPS-induced acute lung injury in Wistar rats via downregulation of the NF-κB signaling pathway (Z. Zhu & Sun, 2018). In β-thalassemia patients, oral treatment of silymarin at a dose of 420 mg/day demonstrated a reduced level of TNF-α but enhanced the production of IL-4 and IFN-γ (Gharagozloo et al., 2013). The compound exhibited threefold inhibition at a concentration of 25 μg/ml against the chikungunya virus in cultured cells (Lani et al., 2015). It possessed a significant inhibition of Zika virus with an IC_{50} of 34 μg/ml (da Silva et al., 2020). Silymarin at a concentration of 100 μg/ml demonstrated anti-influenza viral activity of 98% in cultured cells (J. Song & Choi, 2011). Molecular docking analysis revealed that silymarin considerably interferes with RBD-Sand ACE2 to inhibit the SARS-CoV-2 infection (Gorla et al., 2020). Standardized *Silybum*

marianum extract containing silymarin can be taken as a nutraceutical at a dose level of 250–1000 mg/day (FSSAI, 2016). Recently, this natural compound is under clinical investigation for the management of SARS-CoV-2 (NCT04394208).

4.13 | Other flavonoids

The potential role of flavonoids is not limited to the above examples in the management of SARS-CoV-2 conditions. There are several other flavonoids of different subclass at different stages of research, which have shown activities in in vitro and in vivo models, such as flavan-3-ols like catechin and theaflavin; flavanones like liquiritigenin, eriodictyol, taxifolin, and pinocembrin; flavonols like myricetin, casticin, galangin, and kaempferol; flavones like fisetin, apigenin, chrysin, wogonin, and velutin; isoflavones like formononetin. Their actions on major inflammatory cytokines are highlighted in Tables 2 and 3.

5 | CONCLUSION

In spite of rapid advances in the modern system of medicines, there is no effective and safe therapy available to date for the management of COVID-19. Therefore, exploration of dietary supplementation was evaluated for their beneficial role in the management of the critical situation, where these were found to be an effective option to boost up the immunity for the prevention and recovery from SARS-CoV-2 infection. Based on the inhibitory effect of important cytokines, e.g., IL-6, IL-1β & TNF-α, with their pathways of action in in vitro and in vivo studies on preclinical and clinical models, molecular docking studies information on interference with SARS-CoV-2 infection, antiviral activity, and intake level as a safe nutraceutical, a number of flavonoids have been found to possess excellent potential to combat against SARS-CoV-2 infection. Clinical exploration is warranted to establish suitable phytotherapeutics and their regimens for the effective and safe management of the cytokine storm in COVID-19 condition to manage ARDS.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated (Review article).

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