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REVIEW

An overview of possible pivotal mechanisms of Genistein as a potential phytochemical against SARS-CoV-2 infection: A hypothesis

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Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic has been caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a global problem that humanity has not yet found a definitive solution for it. In this regard, a global effort has been done to find effective or potential adjuvant therapies in order to fight this infection. Genistein is a small, biologically active phytoestrogen flavonoid that is found in high amounts in soy and plants of the Fabaceae family. This important compound is known due to its anti-cancer, anti-inflammatory, and antioxidant effects. Additionally, protective effects of genistein have been reported in different pathological conditions through modulating intracellular pathways such as PI3K, Akt, mTOR, NF-κB, PPARγ, AMPK, and Nrf2. Scientific evidence suggests that genistein could have a potential role to treat COVID-19 through its anti-inflammatory and anti-oxidant effects. Furthermore, it appears to interfere with intracellular pathways involved in viral entry into the cell. This review provides a basis for further research and development of clinical applications of genistein as a potential alternative therapy to decrease inflammation and oxidative stress in COVID-19 patients.

Practical applications

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent for the Coronavirus Disease 2019 (COVID-19), has brought unprecedented untold hardship to both developing and developed countries. The inflammation, cytokine storm, and oxidative stress have an important role in the pathogenesis of this infection. In this regard, finding plant-derived compounds with anti-inflammatory and anti-oxidative effects would be very beneficial in reducing the mortality induced by this infection. Genistein an isoflavone derived from soy-rich products possesses versatile biological activities. It has potent anti-inflammatory and anti-oxidative and

Abbreviations: ACE2, angiotensin-converting enzyme2; AKT, protein kinase B; AMPK, AMP-activated protein kinase; ARDS, acute respiratory distress syndrome; COVID-19, Coronavirus Disease 2019; COX-2, cyclooxygenase-2; ER, estrogen receptors; GLUT-4, glucose transporter-4; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MERS-CoV, Middle East respiratory syndrome coronavirus; mTOR, mechanistic target of rapamycin; NFκ B, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PGE2, Prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; PPARγ, Peroxisome proliferator-activated receptor γ; PTEN, phosphatase and tensin homolog; PTK, protein tyrosine kinase; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOD, superoxide dismutase; TLR4, toll-like receptor 4; TMPRSS2, protease Transmembrane protease serine 2; TNF-α, tum or necrosis factor- α; TXA2, Thromboxane A2.

immunomodulatory effects. Furthermore, this compound may prevent viral entry to host cells and reduce SARS-CoV2-induced lung injury. Therefore, we suggest further studies on the effects of genistein on SARS-Cov-2 infection.

KEYWORDS
anti-inflammatory, anti-oxidant, COVID-19, flavonoid, genistein, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA-enveloped virus. A large number of glycosylated S proteins cover the surface of SARS-CoV-2 and bind to the host cell receptor angiotensin-converting enzyme 2 (ACE2), mediating viral cell entry. When the S protein binds to the receptor, TM protease serine 2 (TMPRSS2), a type 2 TM serine protease located on the host cell membrane, promotes virus entry into the cell by activating the S protein. Once the virus enters the cell, the viral RNA is released, polyproteins are translated from the RNA genome, and replication and transcription of the viral RNA genome occur via protein cleavage and assembly of the replicase–transcriptase complex. Viral RNA is replicated, and structural proteins are synthesized, assembled, and packaged in the host cell, after which viral particles are released. So, attacks the host using angiotensin-converting enzyme2 ACE2 receptors have a crucial role in the pathogenesis of SARS-CoV-2 (Bian & Li, 2021; Khezri, Yousefi, & Ghasemnejad-Berenji, 2021). Since these receptors have been broadly distributed on immune cells and various tissues, SARS-CoV-2 infection, motivates the immune responses by stimulating the monocytes and macrophages as well as, adaptive T and B cell immune responses and cytokines production, in the lung tissue (Jafarzadeh et al., 2020). Subsequently, the replication of SARS-CoV-2 induced programmed cell death (pyroptosis) in the airway epithelial cells. Finally, this process induces vascular leakage and triggers severe destructive inflammatory responses (Wang, Yang, & Xu, 2021). For instance, interleukin (IL-)1β, which is one of the major inflammatory cytokines released during SARS-CoV-2 infection, is involved in viral-induced pyroptosis (Ferreira et al., 2021; Li et al., 2020). In this regard, a wide range of clinical symptoms from mild forms such as myalgia, cough, and fever to moderate forms such as localized inflammation and pneumonia which require hospitalization could happen(Lechien et al., 2020). It should be mentioned that the cytokine storm which is a main pathological sign of COVID-19 is an unregulated production of inflammatory cytokines inducing destructive inflammation and causing organ failure such as severe cardiovascular, pulmonary, and kidney injuries in SARS-CoV-2 infection (Catanzaro et al., 2020; Ghasemnejad-Berenji et al., 2021; Robba et al., 2020). In addition, oxidative stress, mitochondrial dysfunction, and apoptosis pathways are involved in this multiple organ failure (de Las Heras et al., 2020). Since in this viral infection various signaling pathways are affected at the molecular level, in the lack of a specific treatment for this novel infection, finding a safe and effective compound that could inhibit the effects of this virus on infected cells could be a valuable achievement in controlling this pandemic (Zhang & Liu, 2020). Genistein is a multifunctional natural isoflavonoid class of flavonoids. Similar to other plant constituents, such as lignans, which possess an estrogenic effect, genistein is a typical example of a phytoestrogen compound (Sharma et al., 2017). The best-known sources of genistein are soy-based foods, such as soy cheese or soy drinks (i.e., soy milk and soy-based beverages). The content of genistein in mature soybeans has been shown to range from 5.6 to 276 mg/100 g, and an average content of 81 mg/100 g is often described for comparative purposes (Spagnuolo et al., 2015). Facile routes for the chemical synthesis of genistein are available, and the production of genistein can be engineered in transgenic plants (Dixon & Ferreira, 2002). To extract the genistein from plants, solvents such as methanol, ethanol, and acetonitrile are normally used (Zhao et al., 2019). Genistein possesses many therapeutic potentials and pharmacologic properties, such as anti-carcinogenic (Tuli et al., 2019), anti-microbial (Wang et al., 1956), anti-viral (LeCher et al., 2019), antioxidant (Borrás et al., 2006), and anti-inflammatory activity (Ginwala et al., 2019). In vivo and in vitro analyses indicated that genistein can modulate numerous signaling cascades in inflammatory diseases. Furthermore, it has been shown that genistein could inhibit the infectivity of various viruses affecting humans and animals, including adenovirus, herpes simplex virus, HIV, respiratory syndrome virus, and rotavirus (Andres et al., 2009). In this regard, we hypothesized that genistein could exert beneficial effects against SARS-CoV-2 infection. So, this review will highlight the promising targets of genistein in pathological manifestations of SARS-CoV-2 infection, which can be exploited in preclinical and clinical investigations. To the best of review literature to date, there is no laboratory or clinical investigation which confirms the potential of genistein against SARS-CoV-2. However, the vast pharmacological properties of genistein promise the potential of genistein against SARS-CoV-2-induced oxidative stress and inflammation.

2 | GENISTEIN STRUCTURE

Genistein [4′,5,7-trihydroxyisoflavone or 5,7-dihydroxy-3-(4-hydroxyphenyl) chromen-4-one] ($C_{15}H_{10}O_5$) belongs to a multifunctional natural isoflavonoid class of flavonoids with a 15-carbon skeleton. (Węgrzyn et al., 2010). It has been isolated from Genista tinctoria L. for the first time and its name originated from this plant (Spagnuolo et al., 2015). The isoflavones are structurally characterized by their 3-phenylchromen-4-one backbone, which consists of two benzene

rings linked by a heterocyclic pyran ring. In addition to this heterocyclic core, genistein and its related isoflavone family members are polyphenols, in that they contain several hydroxyl groups attached to core phenyl rings. These phenols lend significant antioxidant activity to this class of compounds, with genistein and other related flavonoids, such as epigallocatechin 3-gallate possessing significant activity against free radicals in tissue (Andersen & Markham, 2005). Importantly, genistein is a recognized protein-tyrosine kinase inhibitor (Akiyama et al., 1987). This activity is presumed to stem from genistein's C4′ phenolic group, which structurally resembles the phosphoacceptor moiety of tyrosine (Pavese et al., 2010). As shown in Figure 1, there is a similarity between the chemical structure of genistein and estradiol (Figure 1), leading to its binding ability to estrogen receptors (ERs) (Vaya & Tamir, 2004). Genistein shares structural features with the potent estrogen estradiol-17β (4), particularly the phenolic ring and the distance (11.5 A) between its 4′- and 7- hydroxyl groups (Figure 1). These features confer the ability to bind estrogen receptors and sex-hormone binding proteins, and genistein can thus exert both estrogenic and anti-estrogenic activity, the latter by competing for receptor binding by estradiol (Dixon & Ferreira, 2002). Many epidemiological studies have indicated the beneficial effects of plant-based foods rich in isoflavones on human health including cancers, cardiovascular diseases, osteoporosis, diabetes, and postmenopausal symptoms (Goldwyn et al., 2000; Pabich & Materska, 2019; Setchell & Cassidy, 1999; Sirtori, 2001). Thus, many studies have been conducted to clarify the effects of these compounds, especially genistein, in human pathological and physiological states (Behloul & Wu, 2013).

3 | PHARMACOLOGICAL EFFECTS OF GENISTEIN AS A PROBABLE BENEFICIAL COMPOUND FOR SARS-COV-2 INFECTION

3.1 | Antiviral effects of genistein

The antiviral effects of genistein against viruses including cytomegalovirus, bovine herpesvirus-1, HSV-1 human immunodeficiency virus, African swine fever virus, human papillomavirus, and respiratory syndrome virus have been reported previously (LeCher et al., 2019). It has been shown that genistein could inhibit viral replication with various mechanisms (Arabyan et al., 2018). Furthermore, the inhibitory effect of genistein on human cytomegalovirus via blocking viral immediate-early protein function has been reported previously (Akula et al., 2002; Arabyan et al., 2018; LeCher et al., 2019; Sauter et al., 2014).

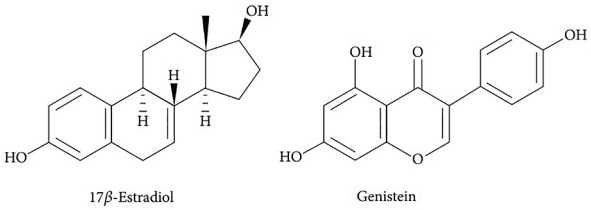

FIGURE 1 Structural similarity between genistein and 17β-Estradiol.

3.2 | Genistein effect on estrogen receptors (ERs)

Estrogen has anti-inflammatory properties by decreasing gene and protein expressions of inflammatory elements (Pelekanou et al., 2016; Suuronen et al., 2005). Studies have indicated that low doses of estrogen could subside persistent inflammation (Samantaray et al., 2016). Genistein has structural similarity to estrogen and it binds to ERs, suggesting that it may show estrogenic function (Ishimi et al., 2000). Protective effects of ERs mediators were also reported in murine models of pulmonary inflammation induced by influenza virus infection (Robinson et al., 2014; Vermillion et al., 2018). Consistently, ER modulators and estrogen hormones such as estradiol have been presently reviewed as beneficial agents for reducing the severity of SARS-CoV-2 infection (Ghasemnejad-Berenji et al., 2020; Suba, 2020; Zhang & Liu, 2020). It has been reported that ERs activation disrupts NF-κB transactivation and inhibits the transcription factors NF-IL6 and subsequently suppresses the expression of IL-6 gene (Liu et al., 2005). Furthermore, Th17 cell differentiation is affected by estradiol (Fuseini et al., 2019). Previous studies have shown that ER-α activation in immune cells could reduce Th1 and Th17 responses and skew cytokine production (Calderone et al., 2020; Vegeto et al., 2010). Genistein has shown the ability to modulate the estrogen receptors (Sutrisno et al., 2018) and therefore, could subside the inflammatory cascades with these properties (Du et al., 2018). In addition, modulation of ER has been suggested in a murine experimental model of pulmonary inflammation as a beneficial therapeutic strategy. In particular, ER-α is expressed in infiltrated or resident inflammatory cells of the respiratory system and activation of these receptors by estradiol markedly decreases the biochemical and histological markers of hyper-inflammation (Calderone et al., 2020; Murphy, 2010). In this regard, it has been reported that estrogen receptor mediators could exert protective effects in murine models of pulmonary inflammation induced by influenza virus infection (Vermillion et al., 2018). As genistein has estrogenic activity in tissues (Kavoosi et al., 2016), considering the role of ERs activation in the prevention of SARS-CoV-2 induced hyper-inflammation, it could be hypothesized that activation of estrogen receptors by genistein inhibits the development of inflammation in COVID-19.

3.3 | Genistein and inhibition of tyrosine kinase

Genistein inhibits protein tyrosine kinase (PTK) at pharmacological dosage (Russo et al., 2016). Observations signify that the tyrosine kinase signaling cascade can be an important target for pharmacologic intervention in order to prevent airway inflammation (Duan et al., 2003). PTK plays a fundamental role in maintaining cellular

homeostasis and accommodation to the external environment stress through diverse cellular processes, such as inflammation, proliferation, migration, differentiation, and preservation of cellular barrier integrity (Aschner & Downey, 2018). According to these regulatory effects, PTK dysregulation might play a critical role in the pathogenesis of many inflammatory pulmonary dysfunctions, with an overlap in various disease states, proposing their wide-range function as potential pharmacologic targets (Assaad & Assaad-Khalil, 2020). Also, over-activation of tyrosine kinase has been detected as a potential cascade contributing to the induction of inflammatory cells such as eosinophils, mast cells, neutrophils, and macrophages (Berkow et al., 1989; Dong et al., 1993; Elmarakby et al., 2011). It has been reported that enhanced tyrosine phosphorylation is involved in many destructive diseases such as inflammation-induced respiratory complications (Aschner & Downey, 2018; Page et al., 2009). Furthermore, PTK has a key role in cytokine production(Hsu et al., 2001). Many cytokines, including IL-10 and IL-6 and tumor necrosis factor- α (TNF-α), uses tyrosine kinases in their signaling pathways (Dahle et al., 2004; Page et al., 2009). It has been shown that inhibition of tyrosine kinase by genistein reduces monocyte chemoattractant protein (MCP-1) excretion via inhibition of TNF-α-induced NFκ B activation (Čoma et al., 2021; Kim, 2021). In this regard, genistein-induced inhibition of tyrosine kinase exerts anti-inflammatory effects which could be a potential mechanism for preventing SARS-CoV-2-induced lung injury.

3.4 | Genistein and PI3K/Akt/mTOR pathway

Protein kinase B (Akt) is a potential pharmacological target for the advanced-stage SARS-CoV-2 infection; its inhibition will effectively suppress the pathological fibroproliferation, cytokine storm, platelet activation, and inflammation associated with COVID-19 (Basile et al., 2021). Furthermore, this inhibition could prevent scarring and lung injuries (Wang, Lin, et al., 2021). In addition, since inhibition of Akt by pharmacologic inhibitors has also been reported to reduce ACE2 expression, a crucial receptor for the viral entry into the respiratory system cells, targeting Akt for COVID-19 seems to be a feasible option (Somanath, 2020). The phosphoinositide 3 (PI3)-kinase/Akt pathway induces hyper-inflammation in various pathologic states (Khezri, Moloodsouri, et al., 2022; Zhang et al., 2021) and, Akt inhibition could suppress inflammation (Zhang, Ma, et al., 2020). It has been reported that inhibition of Akt could suppress inflammation and alleviate lung tissue injury in acute respiratory distress syndrome (ARDS) (Liu et al., 2020). Furthermore, in ARDS lung wound resolution, vascular regeneration, and limiting scar formation have been observed by this inhibition(Qi et al., 2016). In this regard, the potential therapeutic benefits of Akt inhibitors such as genistein in treating ARDS in advanced-stage COVID19 patients have been suggested recently (Li & Sarkar, 2002; Somanath, 2020). Interestingly, some of the inhibitors of the PI3K/Akt/mTOR pathway, especially rapamycin, which targets the mechanistic target of rapamycin (mTOR) function, were indicated to suppress the replication of viruses such as the Middle East respiratory syndrome coronavirus (MERS-CoV) (Kindrachuk et al., 2015) and the influenza virus (Murray et al., 2012). This suggests the potential beneficial effects of genistein in inhibiting the replication of SARS-CoV-2. In addition when patients progress to uncontrolled immune responses, targeting this pathway could be a potential therapeutic strategy to inhibit neutrophil recruitment, suppress the cytokine storm, and enhance the suppressor regulatory T cells (Ghasemnejad-Berenji, 2021b). Furthermore, due to the involvement of this signaling pathway in clot formation (Abu-Eid & Ward, 2021; Meng et al., 2021), inhibiting this pathway could exert a preventive effect on thrombosis associated with severe COVID-19 cases. It has been reported that genistein inhibits the PI3K/Akt/mTOR pathway either directly or indirectly (Lee et al., 2016; Malloy et al., 2018; Sahin et al., 2012; Tan et al., 2014). So, the potential beneficial role of genistein in COVID-19 by inhibiting the PI3K/Akt/mTOR pathway could be explained in three steps. In the early stages of infection, inhibiting this pathway by genistein could prevent the entry and replication of the SARS-CoV-2 and decrease the viral load and subsequently ameliorate patient outcomes. It should be mentioned that, during the initial stages of the immune responses, inhibiting PI3K and Akt by genistein could eradicate the virus before the induction of severe immune dysregulation. In addition, the uncontrolled immune responses in the progressive stage of COVID-19 targeting this pathway by genistein could be a potential pharmacologic strategy to enhance the suppressor regulatory T cells, inhibit neutrophil recruitment, and suppress the cytokine storm. The other probable beneficial effect of genistein that could be related to PI3K/AKT inhibition is the impact of PI3K/AKT on glucose transporter-4 (GLUT-4) (Figure 2). GLUT-4 is the major glucose transporter in cardiac and skeletal muscles and adipose tissue (Langfort et al., 2003). It has been reported that Akt activation, induces rapid translocation of intracellular vesicles which includes GLUT4 to the cell surface, resulting in an enhancement of the cellular glucose transport activity. So, inhibition of glucose uptake by GLUT4 could inhibit glucose transport and viral replication (Yu et al., 2011). In this regard, it has been hypothesized that activation of the PI3K/AKT signaling pathway by SARS-CoV-2 contributes to inducing glucose uptake through GLUT-4 leading to increase glycolysis and viral replication in host cells (Malgotra & Sharma, 2021). Since it has been reported that genistein is a potent and direct inhibitor of GLUT-4 (Lewicki et al., 2018), the direct inhibition of GLUT-4 by genistein from one side and inhibition of the PI3K/AKT pathway from another side could disrupt the viral replication (Figure 2). Furthermore, due to the involvement of the PI3K/AKT pathway in clot formation, targeting this pathway by genistein could prevent thrombosis in COVID-19 patients.

3.5 | immunomodulatory and anti-inflammatory effects of genistein

It has been approved that inflammation plays an essential role in the development of COVID-19-induced lung injury (Khezri, Zolbanin, et al., 2021). Thus, suppressing the immune

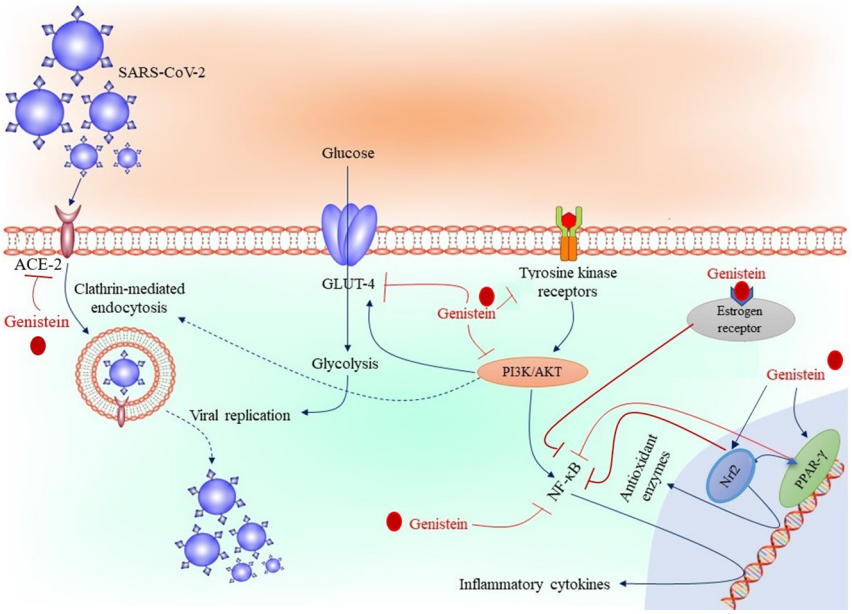

FIGURE 2 Possible molecular mechanisms of genistein against COVID-19. ACE-2: angiotensin-converting enzyme 2, Nrf2: nuclear factor erythroid 2-related factor 2, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, PI3K: phosphoinositide 3 kinase, GLUT-4: glucose transporters-4, PPAR-γ: Peroxisome proliferator-activated receptor gamma, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

responses with immunomodulatory drugs may be as crucial as addressing SARS_CoV-2 replication to inhibit the progression of multiorgan injuries (Rizk et al., 2020). Immunologically, viral immunopathogenesis involved in SARS-CoV2 infection is specified by increased amounts of proinflammatory cytokines, as well as upregulated frequency and over-function of Th1 and Th17 cells (Alshammary & Al-Sulaiman, 2021; Tahmasebi et al., 2021). In this regard pharmacological inhibition of IL-1, IL-6, and TNF-α, is a good practical example for the application of inflammatory cytokine suppression strategy (Buonaguro et al., 2020). It has been reported previously that genistein is a highly pleiotropic molecule with the ability to interact with different cellular targets involved in hyper-inflammation states (Ji et al., 2011; Verdrengh et al., 2003; Zhao et al., 2016). It has been reported that genistein exerts its anti-inflammatory properties via several mechanisms, for example, it has been shown that genistein could downregulate the NF-κB, leading to a reduction in the expression of IL-6, IL-1, and TNF-α (Calveley et al., 2010; Mohammad-Shahi et al., 2011; Sutrisno et al., 2015). In addition, the inhibitory effect of mitogen-activated protein kinase (MAPK) pathways by this molecule which are the pathways activated by most inflammatory stimuli in humans have been reported in several studies (Li et al., 2008; Linford et al., 2001). Since genistein has been indicated to downregulate cytokine-induced signal transduction pathways in the immune system cells, we hypnotized that it may also, exert anti-inflammatory effects on COVID-19. These immunoregulatory effects of genistein could be attributed to the inhibitory effect of this compound on the production of cytokines and chemokines like IL-6, TNF-α, and Macrophage inflammatory protein-1 alpha (MIP-1a) (Kim et al., 2004; Verdrengh et al., 2003). TNF induces leukocyte adhesion and MIP-1a acts as a chemoattractant for T cells, macrophages, and neutrophils, thus recruiting inflammatory immune cells into the inflamed focus (Bhavsar et al., 2015). Furthermore, very high levels of IL-6 in serum of patients with COVID-19 have been reported (Ulhaq & Soraya, 2020) which indicates the important role of that in the development of SARS-Cov-2 induced ARDS (Magro, 2020). Previously it has been reported that genistein could downregulate the TNF and IL-6 production by immune cells in *in vitro* models of lipopolysaccharide (LPS) induced inflammation (Choi et al., 2016; Du et al., 2018; Ji et al., 2012). The other molecular effect of genistein is the ability of this compound to inhibit the secretion of granule enzymes by activated neutrophils and macrophages which leads to the downregulation of the inflammatory responses (Kang et al., 2001; Kim et al., 2001). Furthermore, it has been reported that genistein could inhibit NF-kB DNA binding by blocking the phosphorylation of the inhibitory protein IkBa, which will inhibit the nuclear translocation of the NF-kB (Davis et al., 1999; Romier et al., 2008; Shukla et al., 2015). Genistein significantly inhibited NF-kB activation by the DNA-damaging agents TNF-α and H_2O_2 (Mazumder & Hongsprabhas, 2016). The migration of inflammatory cells is also blocked by genistein by inhibiting the adherence of leukocytes to endothelial cells (McGregor et al., 1994). For instance, the ability of genistein as an anti-inflammatory agent has been reported in preclinical models of Alzheimer's disease. Furthermore, by induced expression levels of Peroxisome proliferator-activated receptor γ (PPARγ) in cultured astrocytes, the ability of genistein in preventing inflammation has been reported previously (Devi

et al., 2017; Valles et al., 2010). For explaining this effect it should be mentioned that activated PPARγ suppresses the expression levels of NF-κB (Lim et al., 2012; Mahmoud et al., 2019). In addition, *in vitro* studies have shown that genistein could downregulate the production of IL-6 and TNF in cell lines treated with this compound (Spagnuolo et al., 2018). AMP-activated protein kinase (AMPK) is known to inhibit inflammation, by decreasing NF-kB levels and pro-inflammatory markers (Ji et al., 2012). Interestingly, genistein by down-regulating inflammation, via AMPK activation and subsequent NF-κB suppression could weaken the pro-inflammatory responses. Genistein down-regulated IL-6 and TNF, among the pro-inflammatory cytokines secreted by NF-kB signaling (Bai & Wang, 2019). Furthermore, The AMPK-dependent increase in ACE2 receptor phosphorylation by genistein could cause a conformational change which could block the ACE2 – viral spike protein binding and inhibition of viral entry into the host cells (Al-Kuraishy et al., 2021; Liu et al., 2019; Samuel et al., 2021). The other factors which have a central role in inflammation are cyclooxygenase-2 (COX-2) and Prostaglandin E2 (PGE2) (Paul et al., 2013; Schoenberger et al., 2012). It has been shown that genistein could inhibit lipopolysaccharide-induced COX-2 expression in addition to lipopolysaccharide-induced PGE2 production in over-activated macrophages (Dia et al., 2008; Hämäläinen et al., 2011; O'Leary et al., 2004). Since inflammation has an undeniable role in COVID-19-induced organ dysfunctions and according to the mentioned anti-inflammatory effects of this nutraceutical, it could be concluded that genistein could subside the inflammation-induced tissue injuries in COVID-19.

3.6 | Antioxidant effects of genistein

The pathological role of oxidative stress in Covid-19-induced tissue injury has been reported in different studies (Ghasemnejad-Berenji et al., 2021; Laforge et al., 2020). If physiological buffering capacity in cells couldn't neutralize the excessive reactive oxygen species (ROS) formation, it will induce oxidative stress. This over-production of ROS could flare the inflammation and exacerbate tissue damage in SARS-CoV-2 infection (Zorov et al., 2014). Several studies have also indicated an inverse relationship between the incidence of COVID-19-induced ARDS and using antioxidants (Soto et al., 2020). Thus, ROS has been considered a probable promising target for introducing novel therapeutic agents in controlling Covid-19-induced injuries (Beltrán-García et al., 2020). The anti-oxidative effects of Isoflavones such as genistein have been reported previously (Lee et al., 2005; Mazumder & Hongsprabhas, 2016). It has been observed that genistein protects cells against over-production of ROS by scavenging free radicals, thereby resulting in the inhibition of NF-κB activation, which has an essential role in cytokine storm and inflammation (Davis et al., 2001; Li et al., 2013; Nazari-Khanamiri & Ghasemnejad-Berenji, 2021). Park et al. have shown that genistein treatment for 24 h increases antioxidant enzyme activities through increased phosphatase and tensin homolog (PTEN) and AMPK expression (Park et al., 2010). So, the ability of genistein to activate cell signaling pathways which could inhibit ROS generation, makes it a beneficial candidate for COVID-19 treatment.

3.7 | Genistein and Nrf2 signaling pathway

Nuclear factor-erythroid factor 2-related factor 2 (Nrf2) has a fundamental function in cellular antioxidant defense against oxidant injury (Chen & Kunsch, 2004). So activation of NRF2 has been reported to be involved in maintaining lung architecture in response to inflammation, and therapeutic properties of NRF2 activation have been shown in animal models of various lung disorders, including ARDS and respiratory infections (Yao et al., 2014), hence reinforcing NRF2 could be beneficial as a therapeutic target for pulmonary diseases such as COVID-19 (Cuadrado et al., 2020; Ghasemnejad-Berenji, 2021; Khan et al., 2021). NRF2 exerts anti-inflammatory and antioxidant properties via interactions that occur along various signaling pathways (Ghasemnejad-Berenji, 2021a; Khan et al., 2017). For instance, it has been reported that Nrf2-driven PPAR-γ induction has a protective function in pulmonary oxidant injury (Figure 2) (Cho et al., 2010). Furthermore, activation of Nrf2 inhibits NF-κB activation and inflammatory cytokines (Jafari et al., 2021; Park & Kim, 2020). Several studies have demonstrated that genistein can effectively induce Nrf2 expression (Guo et al., 2021; Miao et al., 2018; Yi et al., 2021; Zhai et al., 2013). Thus, the properties of genistein could consider as another reason which shows that this compound could subside the organ injuries in COVID-19 patients.

3.8 | Genistein and PPAR-γ

Peroxisome proliferator-activated receptor-gamma (PPAR-γ) is a transcription factor belonging to the nuclear hormone receptor superfamily. Various evidence indicates that PPAR-γ activation has a broad range of beneficial effects on respiratory diseases to delay the pathological changes of fibrosis (Ciavarella et al., 2020; Milam et al., 2008). In addition, PPAR-γ agonism in resident alveolar macrophages limits pulmonary inflammation following respiratory viral infections and significantly promotes host cell recovery (Chen et al., 2016; Huang et al., 2019). It has been reported that PPAR-γ agonists modulate NF-kB-dependent inflammation by upregulating IkBα, a negative regulator of NF-kB (Scirpo et al., 2015). Furthermore, PPAR-γ activation is also responsible for the control of cytokine over-production with consequent amelioration of the tissue damage (Esposito et al., 2020). Several studies have indicated that genistein increases upregulating PPAR-γ expression (Hall et al., 2019; Valles et al., 2010; Wang et al., 2014). In this regard, it may exert protective effects against SARS-CoV-2 induced-inflammation.

3.9 | The probable effect of genistein on SARS-CoV-2 cell entry

The SARS-CoV-2 has been seen to infect human cells through the S-protein (envelope spike glycoprotein), which is involved in SARS-CoV-2 cell entry and subsequent host-to-host cellular transmission (Mittal et al., 2020). During viral infection, this S-protein cleaves into S1 and S2 (Sasaki et al., 2021). The ectodomain S1 binds to the peptidase domain of the ACE-2 enzyme, while the S2 is cleaved further by the host cell serine protease Transmembrane protease serine 2 (TMPRSS2) resulting in membrane fusion (Samavati & Uhal, 2020). Both these processes are crucial for viral entry into the host cells. Since ACE2 is the entry receptor for cellular infection by SARS-CoV-2, inhibiting viral entry using ACE2-related therapy could be practical to block the spreading of infection in the whole body, especially in the respiratory system (Dalan et al., 2020). Several studies have reported that genistein could reduce the expression of ACE and TMPRSS2 in cells (Palanisamy & Venkataraman, 2013; Pihlajamaa et al., 2011; Xu et al., 2006). Consequently, it is probable that genistein could inhibit the SARS-CoV-2 entry into human cells (Figure 2). Furthermore, this broad-spectrum tyrosine kinase inhibitor could interfere with endocytosis and subsequent viral entry by inhibiting the internalization of viruses into host cells (Lecot et al., 2005; Rejman et al., 2005). Although the endocytic mechanisms used by SARS-CoV-2 have remained unclear it is probable that clathrin-dependent endocytosis may have an essential role in viral internalization (Bayati et al., 2020). It has been reported that activation of the PI3K signaling pathway leads to clathrin-dependent endocytosis (Khezri, Ghasemnejad-Berenji, & Moloodsouri, 2022; Posor et al., 2013; Shimizu et al., 2021; Xu et al., 2020). So, it is probable that inhibition of the PI3K signaling pathway by genistein inhibits the clathrin-mediated endocytosis and exerts a preventive effect on SARS-CoV-2 internalization by indirect inhibiting of clathrin-mediated endocytosis. Possible molecular mechanisms of genistein against COVID-19 have been summarized in Figure 1.

3.10 | Genistein and its beneficial effects on acute lung injury models

Previous investigations have shown that genistein could inhibit the activation of NF-κB and the production of TNF-α in patients with asthma (Hozumi et al., 2001). Furthermore, previous studies have demonstrated that in patients with asthma increased consumption of genistein is related to improved lung function (Bime et al., 2012). Additionally, it has been reported that eosinophilic airway inflammation and eosinophil leukotriene C4 synthesis were reduced by dietary soy isoflavone supplementation in these patients. In this regard, Hirayama, Lee, and Hiramatsu (2010) indicated that there was a positive relationship between the intake of isoflavones including daidzein and genistein, and respiratory system function. Furthermore, a reduction in risk of COPD and breathlessness was observed with the consumption of these nutraceuticals (Hirayama, Lee, Binns, et al., 2010). Furthermore, it has been reported that consuming genistein would likely ameliorate Cystic Fibrosis (Arora et al., 2016). In addition, in experimental animal studies, it has been indicated that genistein could attenuate LPS-induced acute lung responses through inhibition of NF-κB activation and alleviating inflammatory response of cells (Kang et al., 2001). Furthermore, the protective effect of Genistein against radiation-induced lung damage has been reported previously (Liu et al., 2014).

3.11 | The probable effect of genistein on SARS-Cov-2-induced coagulopathy

Several studies have indicated that platelets are hyperactivated in COVID-19 patients (Khezri, Varzandeh, & Ghasemnejad-Berenji, 2022; Léopold et al., 2021; Rohlfing et al., 2021). These investigations have confirmed that cytokine storm may trigger hypercoagulability and hyperinflammation. Previous studies have reported that fibrinogen level is higher in patients with COVID-19 (Ranucci et al., 2020), which may exacerbate thrombotic disorder in capillaries by activating platelets (Zhang, Liu, et al., 2020). Therefore, compounds with anti-platelet activity could reduce the probability of the SARS-CoV-2 induced-coagulopathy. In this regard, several studies have shown that genistein might exert anti-platelet function through cAMP regulation (Kim et al., 2013), tyrosine kinase (Nakashima et al., 1991), and Thromboxane A2 (TxA2) pathway inhibition (Guerrero et al., 2007; McNicol, 1993). In the study by Kondo et al. on the effect of genistein on the photochemical thrombosis model, it has been reported that genistein could prolong thrombotic vessel occlusion time and suppress the in vitro platelet aggregation induced by collagen in the femoral arteries of mice. Furthermore, genistein has been shown to have an alleviating effect on lipopolysaccharide-induced disseminated intravascular coagulation by its anticoagulation effects (Chen et al., 2018). In addition, several data suggested that genistein decreases levels of TXA2 in an indirect way mainly related to inhibition of COX-1 (Faggio et al., 2017). It has been reported that SARS-CoV-2-induced platelet activation via binding of the spike to ACE2 (Chung et al., 2020). Previous studies have indicated that genistein could reduce the expression of ACE in cells (Xu et al., 2006). Therefore, these results suggest that genistein may prevent the progression of SARS-CoV-2-induced coagulopathy.

4 | LIMITATIONS OF GENISTEIN IN CLINICAL APPLICATION

The largest technological problem limiting the use of genistein in clinical application is its low water-solubility and poor oral bioavailability (Garbiec et al., 2022). The solution seems to be to carry out the procedure of encapsulating genistein in zein or zein/carboxymethyl/chitosan nanoparticles (Xiao et al., 2020). The other limitation is the effect of genistein on thyroid function. This concern is raised owing to the fact that genistein has been proved to act as an inhibitor of

thyroid peroxidase in vitro (Divi et al., 1997) and shows such inhibition in rats (Chang & Doerge, 2000). Nevertheless, as follows from studies reviewed by Messina and Redmond (2006), isoflavones do not appear to affect thyroid function in healthy adults. Possible adverse effects may be concomitant with iodine deficiency (Hüser et al., 2018).

5 | SUMMARY AND OUTLOOK

Collectively, genistein can modulate the events of SARS-CoV-2 cellular entry, and molecular cascade manifesting pathophysiological consequences of COVID-19. Although direct experimental (in vitro as well as in vivo) confirmation of the hypothesized benefits of genistein against SARS-CoV-2 are absent, previous experimental evidence indicating its efficacy in respiratory ailments, inflammatory disorders, and coagulopathy, promotes its candidature as an adjuvant drug in the treatment of COVID-19. This review of genistein and its abilities motivates its clinical investigation as an adjuvant therapeutic agent to improve COVID-19.

AUTHOR CONTRIBUTIONS

Abbas Jafari: Conceptualization. **Zeinab Esmaeilzadeh**: Investigation. **Mohhamad Rafi Khezri**: Writing - review & editing. **Hojat Ghaemnejad-Berenji**: Investigation. **Sarvin Pashapour**: Writing - original draft. **Sonia Sadeghpour**: Writing - review & editing. **Morteza Ghasemnejad-Berenji**: Conceptualization; Supervision; Writing - original draft.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

CODE AVAILABILITY

Not applicable.

DATA AVAILABILITY STATEMENT

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