Chapter

Can Polyphenols be Used as Anti-Inflammatory Agents against Covid-19 (SARS-CoV-2)-Induced Inflammation?

Volkan Gelen, Abdulsamed Kükürt, Emin Şengül, Ömer Faruk Başer and Mahmut Karapehlivan

Abstract

Covid-19 is the causative agent of a beta coronavirus that causes severe inflammatory pneumonia, so excessive inflammation is considered a risk factor for the disease. In Covid-19 disease, an inflammatory response develops in the body. It has been reported as a result of various studies that this response causes damage to various organs and tissues, especially the lungs. According to reports, cytokine storms are largely responsible for death in such patients. Some of the consequences of severe inflammation and cytokine storms include acute respiratory distress syndrome, acute lung injury, and multiple organ dysfunction syndromes. Many studies are showing that there may be various agents to prevent or treat these effects of Covid-19 disease. Some of these agents are phenolic compounds. Phenolic compounds are the most abundant substances in vegetables and fruits. Inflammasomes, their function. It has been stated that phenolic compounds inhibit inflammation by inhibiting cytosolic multiprotein complexes that assemble in response to cytosolic pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) to form active forms of IL-1β and IL-18. It suggested that Apigenin, Resveratrol, Morin, and Silymarin an anti-inflammatory, antioxidant, anti-viral, and anti-microbial compound could be a potential therapeutic agent for severe inflammation from Covid-19.

Keywords: anti-inflammatory, apigenin, covid-19, resveratrol, morin, silymarin

1. Introduction

Treatment of Covid-19 (SARS-CoV-2) disease which is characterized by acute respiratory syndrome and continues widely in the world and causes a serious number of deaths, is among the discussed topics [1]. The clinical symptoms of this disease, such as fatigue, headache, diarrhea, cough, fever, and dyspnea, occur after an incubation period (about 5–7 days) [2]. In some patients, respiratory failure, acute respiratory distress syndrome (ARDS), or multiple organ failure may take shape. In most patients, it can be asymptomatic or mild [1–3]. However, some conditions such as old age cardiovascular diseases, chronic kidney disease,

diabetes, hypertension, and chronic obstructive pulmonary disease (COPD) predispose to severe Covid-19 disease. The covid-19 disease can cause several complications such as COPD, coagulation dysfunction, septic shock, metabolic acidosis, cardiac arrhythmia, heart failure, liver dysfunction, kidney damage, or secondary infections [2]. Many studies have noted that inflammation is a natural defense mechanism against various pathogens and its association with oxidative stress in various pathological conditions [4–12]. There is a great deal of evidence that systemic hyper-inflammation plays a role in the occurrence of lung and multi-organ failure in Covid-19 patients [1]. High levels of ferritin, fibrinogen, D-dimer, interleukin-6 (IL-6), C-reactive protein, and procalcitonin were found in the sera of Covid-19 patients. It has been determined that these laboratory and clinical signs are associated with macrophage activation syndrome and hyper inflammation [3]. Macrophages and monocytes play an important role in the inflammatory reactions that accompany severe Covid-19 infection [13]. These immune cells secrete large amounts of proinflammatory cytokines (Tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8)) typical for critically ill patients with Covid-19 [14–17]. Cytokine excessive release in Covid-19 disease causes acute heart damage, acute respiratory failure, or the development of multi-organ failure and worsening of the situation [2]. For this reason, the use of anti-inflammatory agents in the treatment of Covid-19 disease plays a very important role in preventing the severity of the disease. Identifying new agents in addition to existing agents will contribute to developing new strategies to overcome the pandemic [1].

Apigenin is a yellow-colored flavone with a closed formula of C15H10O5 and a molecular weight of 270.24 g/mol. It is chemically known as 4′,5,7-trihydroxyflavone or 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyren-4-one (**Figure 1A**). Apigenin is mostly found in the flowers of *Matricaria chamomilla* (German chamomile) from the Asteraceae family, but it is also abundant in *Apium graveolens* (celery) leaves, *Allium sativum L.* (garlic) and *Petroselinum crispum L.* (parsley) species [18–20]. It was determined that it was found at a higher rate in the leaf part of the plants [21]. Resveratrol is in the structure of 3,4′,5 trihydroxystilbene and has two isomers as trans and cis isomers (**Figure 1B**). Trans isomers have higher biological activities than cis isomers. The chemical structure of resveratrol is similar to the synthetic estrogen, diethylstilbestrol. It is also the main component of a molecular family that includes glucosides and polymers, and has

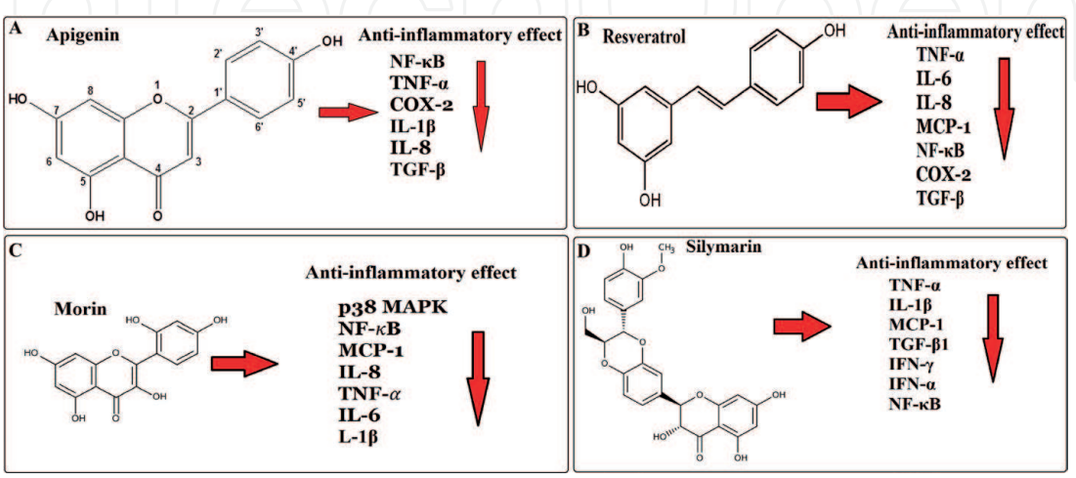

Figure 1.
Chemical structures and anti-inflammatory effects of related phenolic compounds. A (Apigenin), B (Resveratrol), C (Morin), and D (Silymarin).

been shown to be found in grapevines, peanuts, and mulberries [22, 23]. Morine has been named a natural polyphenol (3, 5, 7, 20, 40-pentahydroxyflavone). The hydroxyl groups at the 3 and 4′ positions in morin can be electrochemically oxidized to form the corresponding quinones (**Figure 1C**) [24, 25]. The chemical formula of Silymarin is C25H22O10 (**Figure 1D**). The main ingredient of silymarin is silybin. Flavolignans constitute 70–80% of silymarin. 20–30% consists of polyphenolic components. Silydiadin, silychristin and isosilybin make up the remaining 40% of the compound [26, 27].

Polyphenols are plant-derived phenolic compounds. Polyphenols have been characterized by extensive biological activities in a variety of mammalian systems. These compounds act as free radical scavengers and exhibiting anti-mutagenic, anti-inflammatory, antioxidants, and antiviral effects [28]. In various studies conducted recently, the use of phenolic compounds as anti-inflammatory and antioxidant has become widespread [29–37]. Some factors such as the cheapness of flavonoids and the absence of side effects also increase their usability [38]. As such, the use of flavonoids as an anti-inflammatory will be effective in suppressing hyper-inflammation caused by Covid-19 disease, which is quite common and quite deadly worldwide and thus decreases the mortality rates by reducing the severity of the disease. Therefore, in this study, it will be emphasized that Apigenin, Resveratrol, Morin, and Silymarin, which are natural flavonoids, can be potential agents that can suppress hyper-inflammation in Covid-19 patients.

2. Virus morphology and way of attachment to the cell

When you look at the morphological structure of the Coronavirus, the Virus is a member of a single-stranded (+) RNA enveloped virus family. This virus was identified by scientists in the United States and the United Kingdom in the sixties as a causative agent of the common cold in humans [39]. Coronaviruses are pleomorphic or spherical and are 80–120 nm in diameter. As a result of research conducted in 1968, electron microscope images determined that this family has virus crown-like structures resembling “solar corona”, whose name is derived from the Latin word “coronavirus” [40]. It has been determined that there are four main structural proteins in the structure of the coronavirus. These proteins: The first is the trimeric Spike glycoprotein, localized on the surface of the virus envelope and required for virus entry into cells, and this

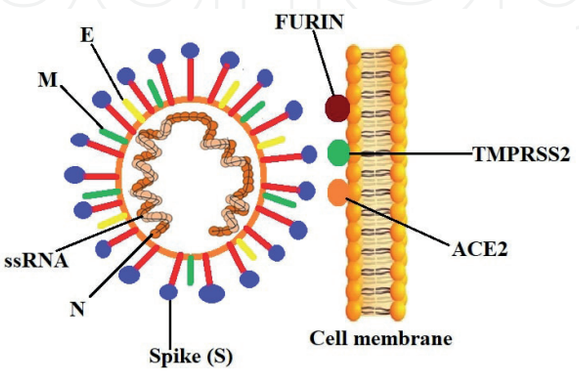

Figure 2.
The structure of the coronavirus and its entryway into the cell. ssRNA: Single-stranded RNA, N: Nucleocapsid proteins. S: The trimeric spike glycoprotein. It recognizes the ACE2 receptor on the cell membrane after cleavage and activation by two serine proteases: FURIN and TMPRSS2. M: Membrane or matrix protein, E: Small envelope protein.

protein is named S. The second is called matrix or membrane protein, and is named M. The third is the small envelope protein required for the collection and release of virions and is named E. The fourth is called the nucleocapsid protein and is named N, which helically binds to the RNA genome forming the symmetrical nucleocapsid (**Figure 2**.) [41]. However, homology modeling revealed that the new virus has a similar receptor binding domain structure (RBD) to that of SARS-CoV, despite amino acid variation at several key residues. It was hypothesized that the virus entered cells using the Angiotensin Receptor Enzyme-2 (ACE2) protein, which is widely expressed in the kidney, heart, lung, testis, and gastrointestinal tract [42]. ACE2 is a membrane-bound protein responsible for the reduction of Ang II to Ang 1–7 [43]. Several steps are required to initiate and complete the Covid-19 infection cycle: These steps 1. Recognize and bind to the cellular receptor (s). The second is that changes occur in the structure and proteolysis of the S protein. The third is fusion to the cellular membrane. The fourth is the entry of the virus into host cells by endocytosis [44]. In host cells, the virus uses an endogenous cellular mechanism to replicate viral RNA. It is well known that the spiky glycoprotein S located on the surface of the viral phospholipidic membrane is very important for coronavirus pathogenesis and infection. The life cycle of SARS-CoV-2 begins with the RBD of the S protein in contact with the ACE2 receptor in cells [45, 46]. It was determined that two host serine proteases, TMPRSS2 and the endo-protease Furin, were involved in this event (**Figure 2**).

3. Cytokine storm and inflammatory pathways associated with Covid-19

In Covid-19, clinical deterioration and a high risk of death may be associated with the cytokine storm that develops as a result of the inflammatory response stimulated [14]. Blood levels of various cytokines such as monocyte chemoattractant protein 1 (MCP1), and interferon-alpha (IFN-α), IL-1ß, interferon-gamma (IFN-γ), induced protein 10 (IP10) increased in Covid-19 patients. Also, it has been determined that IL-10, IL-7, IL-2, macrophage inflammatory protein 1-α, IP10, granulocyte colony-stimulating factor (G-CSF), MCP1, and TNF-α levels are quite high in severe Covid-19 patients [47]. It was determined that those who had the severe Covid-19 disease and died had very high IL-6 levels [48]. This shows the importance of cytokines in the severe course of Covid-19. In a study, cytokine storm was divided into two stages [49]. The first stage is an immunodeficiency state. The secondary stage is an overactive immune state that appears to be a clinical manifestation of a cytokine storm [50]. Experimental studies have determined that the effect of coronavirus on cytokines stimulates the delayed secretion of type I and III IFNs including IFN-α/ß in the early stage and the excessive secretion of pro-inflammatory cytokines from mononuclear macrophages in the next stage [51]. It has been shown that impaired type 1 IFN responses and hyperinflammatory responses involving IL-6 and TNF-α occur with the low level of IFN activity and down-regulation of IFN-induced genes [52]. Based on this information, it is understood why COPD accompanies severe Covid-19. Failure of the immune response in the initial period of infection causes general hyper-inflammation of the lung leading to acute lung injury and COPD. In some studies, it has been determined that there is a genetic predisposition that makes some patients more sensitive to cytokine storms in Covid-19 disease [53–57].

4. Flavonoids and phenolic compounds in COVID-19

Various studies have shown that the use of some natural substances with anti-inflammatory properties can prevent inflammation-induced tissue damage [58–65]. Flavonoids are one of these natural ingredients. Flavonoids and phenolic compounds have significant anti-oxidant, anti-bacterial, anti-cancer, immunomodulatory, and anti-inflammatory abilities [66–71]. Additionally, flavonoids and phenolic compounds exhibit a strong anti-viral capability in multiple pathologies [72–75]. More importantly, flavonoids and phenolic compounds have been determined to exhibit immunomodulatory and anti-viral activities against coronaviruses [76, 77]. Therefore, the anti-viral abilities of flavonoids and phenolic compounds may also apply in the current Covid-19 pandemic. The potentially beneficial role of polyphenols in the Covid-19 pandemic is currently a widely debated topic [78–80]. One of the recommended targets of SARS-CoV-2 treatments is the ACE-2 receptor [81]. Moreover, the biological activity of flavonoids and phenolic compounds predetermines their efficacy in the modulation of the immune and inflammatory pathways of the pathology associated with SARS-CoV-2.

4.1 Anti-inflammatory effects of Apigenin

Among the flavonoids, Apigenin is one of the most widely found and most studied phenolics in the plant kingdom. Apigenin is commonly found in many fruits, vegetables, and plants, mainly in parsley, celery, artichoke, onion, spinach, chamomile, thyme, basil, wheat sprouts, and oranges [82, 83]. Apigenin has been found to have an anti-inflammatory effect by suppressing lipopolysaccharide (LPS)-induced *Cyclooxygenase-2* (COX-2) and nitric oxide synthetase-2 activities and expressions in mouse macrophages [84]. It has been reported that Apigenin regulates different anti-inflammatory pathways including PI3K/Akt and p38/Mitogen-activated protein kinase (MAPK), also prevents inhibitory kB (IKB) degradation and nuclear translocation of *nuclear factor kappa B* (NF-κB), and reduced COX-2 activity [85–87]. Inhibition of NF-κB activation occurs by preventing the inhibitory kB (IkB) degradation [88]. Nitric oxide (NO) is an important intra and intercellular signal molecule that plays a role in the regulation of physiological and pathophysiological mechanisms. It relaxes vascular smooth muscles, inhibits platelet aggregation, stimulates angiogenesis, lowers blood pressure, transmits neuronal signals, activates macrophages, and can act as a cytotoxic agent in inflammation [89, 90]. The anti-inflammatory properties of apigenin are formed by the dose-dependent suppression of the inflammatory mediator's prostaglandin and NO by inhibition of *inducible nitric oxide synthase* (iNOS), and COX-2 in BV-2 murine microglial cells [91]. It has been reported that Apigenin exerts most of its effects in both human and murine cell culture models through interactions with signaling molecules in the 3 major MAPK pathways (p38, JNK, and ERK) [92, 93]. Apigenin suppresses TNF-α-induced NF-κB transcriptional activation [94]. Apigenin suppresses LPS -induced NF-κB activity in lung tissue, reduces the infiltration of inflammatory cells, and reduces the accumulation of chemotactic factors [95]. Apigenin inhibits the production of proinflammatory cytokines IL-1β, IL-8, and TNF-α by suppressing NF-κB activity in mouse macrophages stimulated by LPS, and that apigenin suppresses inflammation and modulates immune responses [96]. It has been determined that dietary apigenin administration to ovalbumin-sensitized BALB/c mice inhibits the release of interleukin-4 (IL-4) from Th2 cells [97].

Apigenin has been reported to have anti-inflammatory potential by suppressing T helper cell-1 and -2 (Th1-Th2) related chemokine production by human monocyte cells by modulating mitogen-activated protein kinase pathways [86]. Prophylactic administration of apigenin in mice with intratracheal acute lung injury caused increased levels of IL-6, IL-1β, and TNF-α, leukocyte count, and percentage of neutrophils in bronchoalveolar lavage fluid by suppressing COX-2 and NF-κB pathways. It has an anti-inflammatory effect by reducing it [98]. In a study investigating the effects and molecular mechanisms of apigenin on cisplatin-induced kidney damage in mice; It has been shown that apigenin improves the pathological changes induced by cisplatin in a dose-dependent manner and decreases the increases in TNF-α, IL-1β, and transforming growth factor-beta (TGF-β) mRNA expressions in a dose-dependent manner [99]. Apigenin also strongly suppressed CD40, TFN-α, and IL-6 production levels in murine microglia through inhibition of IFN- γ induced phosphorylation of signal transducer and activator of transcription 1 (STAT1) [100]. Apigenin has demonstrated neuroprotective properties against apoptosis induced by endoplasmic reticulum stress in HT22 murine hippocampal neuronal cells through reduction of ROS, mitochondrial damage, and endoplasmic reticulum-stress-related proteins [101].

4.2 Anti-inflammatory effects of Resveratrol

Resveratrol is a polyphenolic compound found in peanuts, carob molasses, blueberries, grapes, and red wine [102, 103]. It has been reported in various studies that it stimulates nitric oxide synthesis while suppressing oxidative stress [104–109]. Besides, studies have reported that resveratrol plays a protective role in major respiratory diseases such as ARDS, COPD, and allergic inflammation [110]. These diseases increase the susceptibility to Covid-19 disease and the probability of death increases [22]. In vitro studies have reported that resveratrol has anti-inflammatory and antioxidant properties in COPD patients. It has been reported that resveratrol reduces glutathione (GSH) consumption by activating the nuclear factor (erythroid derivative 2) derivative (Nrf2) pathway, which is a redox-sensitive transcription factor [111]. In other studies, resveratrol has also been reported to inhibit COPD-associated inflammatory mediators such as TNF-α, IL-6, IL-8, MCP-1, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and reduced nuclear NF-κB expression [112–114]. In another study conducted using cigarette smoke, resveratrol reduced the histological damage of the lung, lowered pro-inflammatory protein levels TNF-α, IL-17, IL-6, and transforming growth factor TGF-beta, and prevented airway remodeling, and It has been reported to reduce excessive mucus secretion [115]. Resveratrol SIRT1 and PGC-1 have also been reported to reduce inflammation and restructuring of small airways in lung tissue by increasing α expression [116]. Consistent with in vitro data, resveratrol treatment has been reported to increase superoxide dismutase (SOD) and catalase (CAT) activities and glutathione (GSH) levels, and in addition to preventing NF-κB translocation and binding activity to the nucleus [111]. In-vivo studies conducted over the past few years have shown that resveratrol can effectively control asthma in mouse models [110]. Resveratrol exerts its anti-inflammatory effect by suppressing the passage of inflammatory cells, especially eosinophils, to bronchoalveolar lavage fluid (BALF) and lung tissue by suppressing AHR [101]. Total immunoglobulin E (IgE) and ovalbumin (OVA) specific IgE levels were reported to be decreased

in the OVA-induced asthma model and decreased levels of TNF-*α*, IL-4 and IL-5 cytokines [110]. In another study, it was reported that TGF and TGF-B1/phosphorylated Smad 2/3 receptor expression levels decreased significantly as a result of treatment with resveratrol [117, 118]. Currently, there is still no effective treatment for COPD, but resveratrol has been added to existing treatment protocols for its beneficial effect against lung damage and its beneficial effect in reducing inflammation through several possible molecular mechanisms. Resveratrol reduces myeloperoxidase protein expression and activity in the treatment of structural changes in the lung, reducing pulmonary edema, improving lung functions, decreasing neutrophil infiltration. Regarding cytokines, resveratrol IL-1ß, IL-18, IL-6; It has been reported that COX-2 and macrophage inflammatory protein-1 (MIP-1) significantly modulate BALF and systemic TNF-α. Considering the findings obtained in these studies, it is thought that resveratrol can prevent inflammation caused by Covid-19 as in other respiratory system diseases.

4.3 Anti-inflammatory effects of Morin

Morin, a natural bioflavonoid belonging to the family Moraceae, is found in the structure of many plants commonly used in alternative medicine [119, 120]. Morin has antihyperglycemic and hepatoprotective effects. Morin's anti-inflammatory effects have been reported in many studies [121–124]. MAPK signaling pathway plays an important role in the transcription of some proinflammatory cytokines as eotaxin-1, MCP-1, and IL-8, which leads to a worsened airway inflammation [125]. Morin attenuates inflammation by regulating MAPK signaling pathway in ovalbumin-induced airway inflammation [126]. Eotaxin-1 provides the delivery of eosinophils to airways and could cause tissue injury and heavy inflammation. It is known that eotaxin-1 expression is regulated by TNF-*α* via the p38 MAPK/NF-*κ*B signaling pathways [127]. MCP-1 stimulates histamine release from basophils and TNF-*α* stimulates MCP-1 secretion from airway smooth muscle cells [128]. IL-8 has proinflammatory effects on immune cells and stimulates the infiltration of neutrophils into the airways in asthma [129]. In the study has been determined that Morin significantly reduced the increases in eotaxin-1, MCP1, and IL-8 in human and Morin inhibits lung inflammation with these effects [123]. NF-κB pathway activation is considered to respond to oxidative stress [130] and leads to an increase in the expression of inflammatory cytokines and consequently, inflammation develops. It has been reported that Morin administration caused NF-κB inhibition in the Parkinson model which was experimentally created in mice [124]. It has been determined that Morin prevents inflammatory damage by regulating the NF-κB pathway in indomethacin-induced gastric ulcer [131]. In another study was determined that Morin attenuates the expression of inflammatory cytokine with downregulation of MAPK and NF-κB signaling pathways in LPS-induced primary bovine mammary epithelial cells [132]. Tian et al. has been determined that Morin has hepatoprotective effects by inhibiting to NF-κB/TLR4 signaling pathway in LPS/D-galactosamine-induced acute liver injury [127]. Also, Morin prevents inflammation by inhibiting PI3K/AKT/NF-κB signaling pathway the cigarette smoke-induced lung inflammation in mice. Morin significantly inhibits the levels of proinflammatory cytokines as TNF-α, and IL-1β and reduces the inflammatory cells, including neutrophils and macrophages [133]. NF-κB-signaling pathway is a crucial regulator of proinflammatory cytokines

such as TNF-α, IL-6, L-1β, and levels of proinflammatory cytokines increase inflammation. It was observed that Morin has protective effects by inhibiting proinflammatory cytokines in LPS-induced mastitis [134]. TNF-α, IL-6, and IL-1β promote the development of lung fibrosis and proinflammatory cytokines expression has increased in bleomycin-induced pulmonary fibrosis [135]. Morin inhibited the increase of inflammatory cells such as eosinophils, macrophages, and lymphocytes and reduces total IL-4, IL-13, and IgE levels in OVA-induced mice. Overexpression of Th2 and IgE cytokines causes eosinophil-rich inflammation, mucus hypersecretion, and increased collagen deposition in the lungs. Therefore, Morin prevents mucus hypersecretion, inflammatory cell infiltration, and collagen deposition/fibrosis. In another study reported that TNF-α, IL-6, IL-18, and IL-1β levels importantly increased in bronchoalveolar lavage fluid after LPS-induced Acute Lung Injury, and Morin treatment markedly decreased to these raises due to its anti-inflammatory effects [136].

4.4 Anti-inflammatory effects of Silymarin

The main content of Silybin, which is a complex compound obtained from the seeds of *Silybum marianum* is composed of slybin, and it contains isosilybin, silychristin, silydianin and taxifolin, which is a flavonoid, in its structure [137]. Milk thistle extract is noted to be anti-carcinogenic in human prostate cancer. It is stated that silibinin can be anti-carcinogenic through insulin-like growth factor receptor type I (IGF-I), epidermal growth factor receptor, and NF-κB signaling [138]. Silymarin regulates inflammatory mediators such as interleukins, TNF-α, and inhibits NF-κB activation [139–142]. Silymarin inhibits the inflammatory cytokines (IFN-γ, IFN-α, and IL-1β) [27]. It is well known that silymarin generally has antioxidative and chemo-protective properties in the liver. It is thought that the hepatoprotective activity of silymarin is due to its antioxidant and membrane stabilizing properties. Silymarin shows hepatoprotective activity by inhibiting the function of Kupfer cells and the formation of leukotriene. Silymarin shows strong antioxidant, cytoprotective, anti-inflammatory, and anti-carcinogenic activities [143, 144]. In a rat sepsis model, Silymarin has been shown to suppress transcription of the transporter gene that binds NF-κB. It was also shown in the same study that silymarin showed anti-inflammatory activity by inhibiting prostaglandin-E2 and cyclooxygenase-2 in macrophages stimulated with LPS [145]. Silymarin reduces the increase in TNF-α, IL-1β, MCP-1, TGF-β1, and CRP levels with oxidative stress caused by sodium nitrite, and also, DNA fragmentation due to decrease in cytochrome C oxidase and increase in caspase-3 activity significantly. It has been reported to improve [146]. In the Methotrexate-induced nephrotoxicity model, it was noted that the increase in NF-KB, TNF-α, IL-6, and IL - 1β levels caused by Methotrexate decreased silymarin and prevented inflammatory responses by suppressing the activation of COX-2 and iNOS. Also, silymarin has been reported to play a protective role against apoptosis and autophagy by reducing caspase-3 and light chain 3D activities.

5. Conclusion

As a result, a more effective treatment method has not yet been found against the highly contagious and deadly coronavirus epidemic. This situation encourages scientists to look for alternatives to human coronavirus infections. Looking at

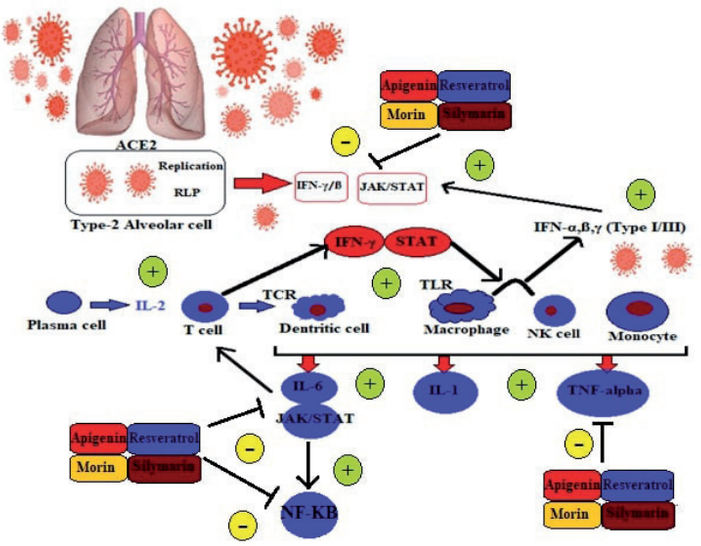

Figure 3.
Possible anti-inflammatory role of Apigenin, resveratrol, Morin, and Silymarin in the treatment of Covid-19. IFN: Interferon; IL: Interleukin; JAK/STAT; Janus kinase-signal transducer and activator of transcription; NK: Natural killer; RLR: Retinoic acid-inducible gene-1-like receptor; TCR: T cell receptor; TLR: Toll-like receptor; TNF-α: Tumor necrosis factor-alpha.

various studies, it is known that Apigenin, Resveratrol, Morin, and Silymarin play an important role in relieving inflammation in various tissues. It is seen that coronavirus causes severe inflammation in various tissues and death after tissue damage. In this context, we believe that the flavonoids and phenolic compounds mentioned can be an alternative to the agents currently used in preventing/treating these adverse effects caused by coronavirus (**Figure 3**).

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