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

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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-1 β 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- α (TNF- α), interleukin-1 β (IL-1 β), 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 $C_{15}H_{10}O_5$ 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 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 $C_{25}H_{22}O_{10}$ (**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

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

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 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

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.

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-1 β , 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/β 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 κ B (IKB) degradation and nuclear translocation of *nuclear factor kappa B* (NF- κ B), and reduced COX-2 activity [85–87]. Inhibition of NF- κ B activation occurs by preventing the inhibitory κ B (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- κ B transcriptional activation [94]. Apigenin suppresses LPS -induced NF- κ B 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-1 β , IL-8, and TNF- α by suppressing NF- κ B 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-1 β , and TNF- α , leukocyte count, and percentage of neutrophils in bronchoalveolar lavage fluid by suppressing COX-2 and NF- κ B 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-1 β , 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- κ B 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- κ B 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-1 β , 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- κ B 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- κ B 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- κ B pathway in indomethacin-induced gastric ulcer [131]. In another study was determined that Morin attenuates the expression of inflammatory cytokine with down-regulation of MAPK and NF- κ B 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- κ B/TLR4 signaling pathway in LPS/D-galactosamine-induced acute liver injury [127]. Also, Morin prevents inflammation

by inhibiting PI3K/AKT/NF- κ B signaling pathway the cigarette smoke-induced lung inflammation in mice. Morin significantly inhibits the levels of proinflammatory cytokines as TNF- α , and IL-1 β and reduces the inflammatory cells, including neutrophils and macrophages [133]. NF- κ B-signaling pathway is a crucial regulator of proinflammatory cytokines such as TNF- α , IL-6, IL-1 β , 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-1 β 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-1 β 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 silybin, 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- κ B signaling [138]. Silymarin regulates inflammatory mediators such as interleukins, TNF- α , and inhibits NF- κ B activation [139–142]. Silymarin inhibits the inflammatory cytokines (IFN- γ , IFN- α , and IL-1 β) [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- κ B. 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-1 β , MCP-1, TGF- β 1, 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- κ B, TNF- α , IL-6, and IL-1 β 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.

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.

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 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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References

- [1] Huang Q, Wu X, Zheng X, Luo S, Xu S, Weng J. Targeting inflammation and cytokine storm in COVID-19. *Pharmacol Res* 2020;159:105051. <https://doi.org/10.1016/j.phrs.2020.105051>.
- [2] Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev* 2020;54:62-75. <https://doi.org/10.1016/j.cytogfr.2020.06.001>.
- [3] Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol* 2020;39:2085-94. <https://doi.org/10.1007/s10067-020-05190-5>.
- [4] Gelen V, Şengül E, Yıldırım S, Çelebi F, Çınar A. Ratlarda Cyclophosphamide ile İndüklenen Hemorajik Sistitte Mesane Kontraktilitesi ve Histopatolojisi Üzerine Rutin'in Etkileri. *Atatürk Üniversitesi Vet Bilim Derg* 2018;13:337-46. <https://doi.org/10.17094/ataunivbd.370609>.
- [5] Gelen V, Şengül E. Antioxidant, anti-inflammatory and antiapoptotic effects of naringin on cardiac damage induced by cisplatin. *Indian J Tradit Knowl* 2020;19:459-65.
- [6] Gelen V, Şengül E, Yıldırım S, Atila G. The protective effects of naringin against 5-fluorouracil-induced hepatotoxicity and nephrotoxicity in rats. *Iran J Basic Med Sci* 2018;21:404-10. <https://doi.org/10.22038/ijbms.2018.27510.6714>.
- [7] Gelen V, Şengül E. Hematoprotective Effect of Naringin on 5-FU Toxicity in Rats. *Chem Reseach* 2018;3:127-30.
- [8] Kükürt A, Gelen V, Başer ÖF, Deveci HA, Karapehlivan M. Thiols: Role in Oxidative Stress-Related Disorders. *Lipid Peroxidation [Working Title]*, IntechOpen; 2021. <https://doi.org/10.5772/intechopen.96682>.
- [9] Kara A, Gedikli S, Sengul E, Gelen V, Ozkanlar S. Oxidative Stress and Autophagy. *Free Radicals Dis., InTech*; 2016. <https://doi.org/10.5772/64569>.
- [10] Volkan Gelen, Emin Şengül, Dursun Ali Çınar. The effects of rutin and quercetin on ECG parameters in 5-FU-induced cardiotoxicity rat model. *World J Adv Res Rev* 2021;9:253-7. <https://doi.org/10.30574/wjarr.2021.9.3.0104>.
- [11] Sengul E, Gelen V. Protective effects of naringin in indomethacin-induced gastric ulcer in rats. *GSC Biol Pharm Sci* 2019;8:006-14. <https://doi.org/10.30574/gscbps.2019.8.2.0132>.
- [12] Kaya İ, Deveci HA, Karapehlivan M, Kükürt A. Investigation of oxidative stress index in pyridine and ellagic acid treated mice. *Eurasian J Vet Sci* 2015;31:148-148. <https://doi.org/10.15312/EurasianJVetSci.2015310971>.
- [13] Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020;20:355-62. <https://doi.org/10.1038/s41577-020-0331-4>.
- [14] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033-4. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).
- [15] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and

immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130. <https://doi.org/10.1172/JCI137244>.

[16] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clin Immunol* 2020;214:108393. <https://doi.org/10.1016/j.clim.2020.108393>.

[17] Gelen V, Kükürt A, Şengül E. Role of the Renin-Angiotensin-Aldosterone System in Various Disease Processes: An Overview. *Renin-Angiotensin Aldosterone Syst. [Working Title]*, IntechOpen; 2021. <https://doi.org/10.5772/intechopen.97354>.

[18] Li B, Robinson DH, Birt DF. Evaluation of Properties of Apigenin and [G-3H]Apigenin and Analytic Method Development. *J Pharm Sci* 1997;86:721-5. <https://doi.org/10.1021/js960383s>.

[19] Venigalla M, Gyengesi E, Münch G. Curcumin and Apigenin - novel and promising therapeutics against chronic neuroinflammation in Alzheimer's disease. *Neural Regen Res* 2015;10:1181. <https://doi.org/10.4103/1673-5374.162686>.

[20] Miesan KH, Mohamed S. Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. *J Agric Food Chem* 2001;49. <https://doi.org/10.1021/jf000892m>.

[21] Justesen U, Knuthsen P, Leth T. Quantitative analysis of flavonols, flavones, and flavanones in fruits, vegetables and beverages by high-performance liquid chromatography with photo-diode array and mass spectrometric detection. *J Chromatogr A* 1998;799:101-10. [https://doi.org/10.1016/S0021-9673\(97\)01061-3](https://doi.org/10.1016/S0021-9673(97)01061-3).

[22] Kaldas MI, Walle UK, Walle T. Resveratrol transport and metabolism by human intestinal Caco-2 cells. *J Pharm Pharmacol* 2010;55:307-12. <https://doi.org/10.1211/002235702612>.

[23] Bradamante S, Barengi L, Villa A. Cardiovascular protective effects of resveratrol. *Cardiovasc Drug Rev* 2004;22. <https://doi.org/10.1111/j.1527-3466.2004.tb00139.x>.

[24] Khokhar TS, Memon S, Memon AA, Bhatti AA, Bhatti AA. Improved Solubility of Morin Using p-sulphonatocalix[4]arene as Encapsulating Agent: HPLC Analysis and their Molecular Modelling. *Polycycl Aromat Compd* 2020;40:609-21. <https://doi.org/10.1080/10406638.2018.1464037>.

[25] Jacob V, Hagai T, Soliman K. Structure-Activity Relationships of Flavonoids. *Curr Org Chem* 2011;15:2641-57. <https://doi.org/10.2174/138527211796367309>.

[26] Fraschini F, Demartini G, Esposti D. Pharmacology of silymarin. *Clin Drug Investig* 2002;22. <https://doi.org/10.2165/00044011-200222010-00007>.

[27] Kren V, Walterova D. Silybin and silymarin - new effects and applications. *Biomed Pap* 2005;149:29-41. <https://doi.org/10.5507/bp.2005.002>.

[28] Levy E, Delvin E, Marcil V, Spahis S. Can phytotherapy with polyphenols serve as a powerful approach for the prevention and therapy tool of novel coronavirus disease 2019 (COVID-19)? *Am J Physiol Metab* 2020;319:E689-708. <https://doi.org/10.1152/ajpendo.00298.2020>.

[29] Karamese M, Guvendi B, Karamese SA, Cinar I, Can S, Erol HS, et al. The protective effects of epigallocatechin gallate on lipopolysaccharide-induced hepatotoxicity: An in

vitro study on Hep3B cells. Iran J Basic Med Sci 2016;19:483-9. <https://doi.org/10.22038/ijbms.2016.6932>.

[30] Şengül E, Gelen V, Gedikli S, Özkanlar S, Gür C, Çelebi F, et al. The protective effect of quercetin on cyclophosphamide-Induced lung toxicity in rats. Biomed Pharmacother 2017;92:303-7. <https://doi.org/10.1016/j.biopha.2017.05.047>.

[31] Gelen V, Şengül E, Gedikli S, Atila G, Uslu H, Makav M. The protective effect of rutin and quercetin on 5-FU-induced hepatotoxicity in rats. Asian Pac J Trop Biomed 2017;7:647-53. <https://doi.org/10.1016/j.apjtb.2017.06.013>.

[32] Gelen V, Şengül E, Gedikli S, Gür C, Özkanlar S. Therapeutic effect of quercetin on renal function and tissue damage in the obesity induced rats. Biomed Pharmacother 2017;89:524-8. <https://doi.org/10.1016/j.biopha.2017.02.057>.

[33] Sengul E, Gelen V, Gedikli S. Cardioprotective Activities of Quercetin and Rutin in Sprague Dawley Rats Treated with 5-Fluorouracil. J Anim Plant Sci 2020;31:423-31. <https://doi.org/10.36899/JAPS.2021.2.0231>.

[34] Ogun M, Ozcan A, Karaman M, Merhan O, Ozen H, Kukurt A, et al. Oleuropein ameliorates arsenic induced oxidative stress in mice. J Trace Elem Med Biol 2016;36:1-6. <https://doi.org/10.1016/j.jtemb.2016.03.006>.

[35] Kaya İ, Kaya MM, Kükürt A, Özcan A, Karaman M, Deveci HA, et al. Effect of Ellagic Acid on Some Oxidative Stress Parameters and Cyclooxygenase-2 Reactivity in Mice with Experimental Gastric Injury. Japanese J Gastroenterol Hepatol 2019;2:1-9.

[36] Deveci HA, Nur G, Kırpık MA, Kükürt A, Karapehlivan M. Akut

klorprifos-etil toksikasyonunda kafeik asit fenetil esterinin total sialik asit, nitrik oksit ve aminotransferaz düzeylerine etkisi. Kafkas Üniversitesi Fen Bilim Enstitüsü Derg 2016;9:39-45.

[37] Deveci HA, Karapehlivan M, Kaya İ, Kükürt A, Alpay M. Protective role of caffeic acid phenethyl ester against to chlorpyrifos-ethyl acute poisoning. Ankara Üniversitesi Vet Fakültesi Derg 2015;62:255-60. https://doi.org/10.1501/Vetfak_00000002689.

[38] Ginwala R, Bhavsar R, Chigbu DI, Jain P, Khan ZK. Potential Role of Flavonoids in Treating Chronic Inflammatory Diseases with a Special Focus on the Anti-Inflammatory Activity of Apigenin. Antioxidants 2019;8:35. <https://doi.org/10.3390/antiox8020035>.

[39] Kapikian AZ, James HD, Kelly SJ, Dees JH, Turner HC, McIntosh K, et al. Isolation from Man of 'Avian Infectious Bronchitis Virus-like' Viruses (Coronaviruses) similar to 229E Virus, with Some Epidemiological Observations. J Infect Dis 1969;119:282-90. <https://doi.org/10.1093/infdis/119.3.282>.

[40] Zhong N, Zheng B, Li Y, Poon L, Xie Z, Chan K, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 2003;362:1353-8. [https://doi.org/10.1016/S0140-6736\(03\)14630-2](https://doi.org/10.1016/S0140-6736(03)14630-2).

[41] Fung TS, Liu DX. Human Coronavirus: Host-Pathogen Interaction. Annu Rev Microbiol 2019;73:529-57. <https://doi.org/10.1146/annurev-micro-020518-115759>.

[42] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation

and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565-74. [https://doi.org/10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8).

[43] Başer ÖF, Kükürt A, Karapehlivan M. Oksidatif stresin azaltılmasında anjiyotensin dönüştürücü enzimin rolü. In: Evereklioglu C, editor. Sağlık Bilim. Teor. ve Araştırmalar II, Gece Kitaplığı; 2020, p. 243-53.

[44] Pillay TS. Gene of the month: the 2019-nCoV/SARS-CoV-2 novel coronavirus spike protein. *J Clin Pathol* 2020;73:366-9. <https://doi.org/10.1136/jclinpath-2020-206658>.

[45] Hoffmann M, Kleine-Weber H, Pöhlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. *Mol Cell* 2020;78:779-784.e5. <https://doi.org/10.1016/j.molcel.2020.04.022>.

[46] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020;181:271-280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>.

[47] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).

[48] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46:846-8. <https://doi.org/10.1007/s00134-020-05991-x>.

[49] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmun Rev* 2020;19:102537. <https://doi.org/10.1016/j.autrev.2020.102537>.

[50] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect* 2020;80:607-13. <https://doi.org/10.1016/j.jinf.2020.03.037>.

[51] Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Möller R, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell* 2020;181:1036-1045.e9. <https://doi.org/10.1016/j.cell.2020.04.026>.

[52] Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* (80-) 2020;369:718-24. <https://doi.org/10.1126/science.abc6027>.

[53] Jenkins MR, Rudd-Schmidt JA, Lopez JA, Ramsbottom KM, Mannering SI, Andrews DM, et al. Failed CTL/NK cell killing and cytokine hypersecretion are directly linked through prolonged synapse time. *J Exp Med* 2015;212:307-17. <https://doi.org/10.1084/jem.20140964>.

[54] Vastert SJ, van Wijk R, D'Urbano LE, de Vooght KMK, de Jager W, Ravelli A, et al. Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis. *Rheumatology* 2010;49:441-9. <https://doi.org/10.1093/rheumatology/kep418>.

[55] Wulffraat NM. Reduced perforin expression in systemic juvenile idiopathic arthritis is restored by autologous

stem-cell transplantation. Rheumatology 2003;42:375-9. <https://doi.org/10.1093/rheumatology/keg074>.

[56] Trouillet-Assant S, Viel S, Gaymard A, Pons S, Richard J-C, Perret M, et al. Type I IFN immunoprofiling in COVID-19 patients. J Allergy Clin Immunol 2020;146:206-208.e2. <https://doi.org/10.1016/j.jaci.2020.04.029>.

[57] The COVID-19 Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. Eur J Hum Genet 2020;28:715-8. <https://doi.org/10.1038/s41431-020-0636-6>.

[58] Volkan Gelen, Emin Şengül. Protective effects of resveratrol on kidney function tests and renal histopathology in carbon tetrachloride-induced renal toxicity in rats. World J Adv Res Rev 2021;10:156-61. <https://doi.org/10.30574/wjarr.2021.10.1.0155>.

[59] Sengul E, Gelen V, Yildirim S, Tekin S, Dag Y. The Effects of Selenium in Acrylamide-Induced Nephrotoxicity in Rats: Roles of Oxidative Stress, Inflammation, Apoptosis, and DNA Damage. Biol Trace Elem Res 2021;199:173-84. <https://doi.org/10.1007/s12011-020-02111-0>.

[60] Gedikli S, Gelen V, Sengul E, Ozkanlar S, Gur C, Agirbas O, et al. Therapeutic Effects of Melatonin On Liver And Kidney Damages In Intensive Exercise Model of Rats. Endocrine, Metab Immune Disord Targets 2015;15:308-14. <https://doi.org/10.2174/1871530315666150827103043>.

[61] Karamese M, Aydin H, Gelen V, Sengul E, Karamese SA. The anti-inflammatory, anti-oxidant and

protective effects of a probiotic mixture on organ toxicity in a rat model. Future Microbiol 2020;15:401-12. <https://doi.org/10.2217/fmb-2020-0005>.

[62] Gelen V, Gelen SU, Celebi F, Cinar A, Yildirim S, Eser G. The protective effect of *Lactobacillus rhamnosus*, *Lactobacillus fermentum* and *Lactobacillus brevis* against cisplatin-induced hepatic damage in rats. Fresenius Environ Bull 2019;28.

[63] Karamese M, Aydin H, Sengul E, Gelen V, Sevim C, Ustek D, et al. The Immunostimulatory Effect of Lactic Acid Bacteria in a Rat Model. Iran J Immunol 2016;13:220-8. <https://doi.org/10.1007/s13337-016-0037-7>.

[64] Gedikli S, Ozkanlar S, Gur C, Sengul E, Gelen V. Preventive effects of quercetin on liver damages in high-fat diet-induced obesity. J Histol Histopathol 2017;4:7. <https://doi.org/10.7243/2055-091X-4-7>.

[65] Sengul E, Gelen S, Yildirim S, Çelebi F, Çınar A. Probiotic bacteria attenuates cisplatin-induced nephrotoxicity through modulation of oxidative stress, inflammation and apoptosis in rats. Asian Pac J Trop Biomed 2019;9:116. <https://doi.org/10.4103/2221-1691.254605>.

[66] Liskova A, Koklesova L, Samec M, Smejkal K, Samuel SM, Varghese E, et al. Flavonoids in Cancer Metastasis. Cancers (Basel) 2020;12:1498. <https://doi.org/10.3390/cancers12061498>.

[67] Abotaleb M, Samuel S, Varghese E, Varghese S, Kubatka P, Liskova A, et al. Flavonoids in Cancer and Apoptosis. Cancers (Basel) 2018;11:28. <https://doi.org/10.3390/cancers11010028>.

[68] Senthilvel P, Lavanya P, Kumar KM, Swetha R, Anitha P, Bag S, et al. Flavonoid from *Carica papaya* inhibits NS2B-NS3 protease and prevents Dengue

2 viral assembly. Bioinformation 2013;9:889-95. <https://doi.org/10.6026/97320630009889>.

[69] Andreu L, Nuncio-Jáuregui N, Carbonell-Barrachina ÁA, Legua P, Hernández F. Antioxidant properties and chemical characterization of Spanish *Opuntia ficus-indica* Mill. cladodes and fruits. J Sci Food Agric 2018;98. <https://doi.org/10.1002/jsfa.8628>.

[70] Meng XH, Liu C, Fan R, Zhu LF, Yang SX, Zhu HT, et al. Antioxidative Flavan-3-ol Dimers from the Leaves of *Camellia fangchengensis*. J Agric Food Chem 2018;66. <https://doi.org/10.1021/acs.jafc.7b04572>.

[71] Gelen V, Şengül E, Yıldırım S, Senturk E, Tekin S, Kükürt A. The protective effects of hesperidin and curcumin on 5-fluorouracil-induced nephrotoxicity in mice. Environ Sci Pollut Res 2021. <https://doi.org/10.1007/s11356-021-13969-5>.

[72] Kang SY, Kang J-Y, Oh M-J. Antiviral activities of flavonoids isolated from the bark of *Rhus verniciflua* Stokes against fish pathogenic viruses In Vitro. J Microbiol 2012;50:293-300. <https://doi.org/10.1007/s12275-012-2068-7>.

[73] Fukuchi K, Okudaira N, Adachi K, Odai-Ide R, Watanabe S, Ohno H, et al. Antiviral and Antitumor Activity of Licorice Root Extracts. In Vivo (Brooklyn) 2016;30:777-86. <https://doi.org/10.21873/in vivo.10994>.

[74] Roschek B, Fink RC, McMichael MD, Li D, Alberte RS. Elderberry flavonoids bind to and prevent H1N1 infection in vitro. Phytochemistry 2009;70:1255-61. <https://doi.org/10.1016/j.phytochem.2009.06.003>.

[75] Ngwa W, Kumar R, Thompson D, Lyster W, Moore R, Reid T-E, et al.

Potential of Flavonoid-Inspired Phytomedicines against COVID-19. Molecules 2020;25:2707. <https://doi.org/10.3390/molecules25112707>.

[76] Song J-W, Long J-Y, Xie L, Zhang L-L, Xie Q-X, Chen H-J, et al. Applications, phytochemistry, pharmacological effects, pharmacokinetics, toxicity of *Scutellaria baicalensis* Georgi. and its probably potential therapeutic effects on COVID-19: a review. Chin Med 2020;15:102. <https://doi.org/10.1186/s13020-020-00384-0>.

[77] Li T, Li X, Dai T, Hu P, Niu X, Liu C, et al. Binding mechanism and antioxidant capacity of selected phenolic acid - β -casein complexes. Food Res Int 2020;129. <https://doi.org/10.1016/j.foodres.2019.108802>.

[78] Korkmaz H. Could Sumac Be Effective on COVID-19 Treatment? J Med Food 2020;jmf.2020.0104. <https://doi.org/10.1089/jmf.2020.0104>.

[79] Hamza M, Ali A, Khan S, Ahmed S, Attique Z, Ur Rehman S, et al. nCoV-19 peptides mass fingerprinting identification, binding, and blocking of inhibitors flavonoids and anthraquinone of *Moringa oleifera* and hydroxychloroquine. J Biomol Struct Dyn 2020;1-11. <https://doi.org/10.1080/07391102.2020.1778534>.

[80] Solnier J, Fladerer J-P. Flavonoids: A complementary approach to conventional therapy of COVID-19? Phytochem Rev 2020. <https://doi.org/10.1007/s11101-020-09720-6>.

[81] Muchtaridi M, Fauzi M, Khairul Ikram NK, Mohd Gazzali A, Wahab HA. Natural Flavonoids as Potential Angiotensin-Converting Enzyme 2 Inhibitors for Anti-SARS-CoV-2. Molecules 2020;25:3980. <https://doi.org/10.3390/molecules25173980>.

- [82] Sung B, Chung HY, Kim ND. Role of Apigenin in Cancer Prevention via the Induction of Apoptosis and Autophagy. *J Cancer Prev* 2016;21:216-26. <https://doi.org/10.15430/JCP.2016.21.4.216>.
- [83] Hostetler GL, Ralston RA, Schwartz SJ. Flavones: Food Sources, Bioavailability, Metabolism, and Bioactivity. *Adv Nutr An Int Rev J* 2017;8:423-35. <https://doi.org/10.3945/an.116.012948>.
- [84] Liang Y-C, Huang Y-T, Tsai S-H, Lin-Shiau S-Y, Chen C-F, Lin J-K. Suppression of inducible cyclooxygenase and inducible nitric oxide synthase by apigenin and related flavonoids in mouse macrophages. *Carcinogenesis* 1999;20:1945-52. <https://doi.org/10.1093/carcin/20.10.1945>.
- [85] Lee J-H, Zhou HY, Cho SY, Kim YS, Lee YS, Jeong CS. Anti-inflammatory mechanisms of apigenin: inhibition of cyclooxygenase-2 expression, adhesion of monocytes to human umbilical vein endothelial cells, and expression of cellular adhesion molecules. *Arch Pharm Res* 2007;30:1318-27. <https://doi.org/10.1007/BF02980273>.
- [86] Huang C-H, Kuo P-L, Hsu Y-L, Chang T-T, Tseng H-I, Chu Y-T, et al. The Natural Flavonoid Apigenin Suppresses Th1- and Th2-Related Chemokine Production by Human Monocyte THP-1 Cells Through Mitogen-Activated Protein Kinase Pathways. *J Med Food* 2010;13:391-8. <https://doi.org/10.1089/jmf.2009.1229>.
- [87] Lapchak PA, Boitano PD. Effect of the Pleiotropic Drug CNB-001 on Tissue Plasminogen Activator (tPA) Protease Activity in vitro: Support for Combination Therapy to Treat Acute Ischemic Stroke. *J Neurol Neurophysiol* 2014;5:214.
- [88] Madunić J, Madunić IV, Gajski G, Popić J, Garaj-Vrhovac V. Apigenin: A dietary flavonoid with diverse anticancer properties. *Cancer Lett* 2018;413:11-22. <https://doi.org/10.1016/j.canlet.2017.10.041>.
- [89] Kükürt A. Doğal bir antioksidan olarak propolis tedavisinin koruyucu etkileri. In: Evereklioğlu C, editor. *Sağlık Bilim. Teor. ve Araştırmalar II*, Gece Kitaplığı; 2020, p. 501-15.
- [90] Kükürt A, Kuru M, Karapehlivan M. Nitrik oksit, nitrik oksit sentaz ve dişi üreme sistemindeki rolleri. In: Evereklioğlu C, editor. *Sağlık Bilim. Alanında Akad. Çalışmalar - II*, Gece Kitaplığı; 2020, p. 113-23.
- [91] Ha SK, Lee P, Park JA, Oh HR, Lee SY, Park J-H, et al. Apigenin inhibits the production of NO and PGE2 in microglia and inhibits neuronal cell death in a middle cerebral artery occlusion-induced focal ischemia mice model. *Neurochem Int* 2008;52:878-86. <https://doi.org/10.1016/j.neuint.2007.10.005>.
- [92] Patel D, Shukla S, Gupta S. Apigenin and cancer chemoprevention: Progress, potential and promise (Review). *Int J Oncol* 2007;30. <https://doi.org/10.3892/ijo.30.1.233>.
- [93] Shukla S, Gupta S. Apigenin: A Promising Molecule for Cancer Prevention. *Pharm Res* 2010;27:962-78. <https://doi.org/10.1007/s11095-010-0089-7>.
- [94] Funakoshi-Tago M, Nakamura K, Tago K, Mashino T, Kasahara T. Anti-inflammatory activity of structurally related flavonoids, Apigenin, Luteolin and Fisetin. *Int Immunopharmacol* 2011;11:1150-9. <https://doi.org/10.1016/j.intimp.2011.03.012>.
- [95] Cardenas H, Arango D, Nicholas C, Duarte S, Nuovo G, He W, et al. Dietary Apigenin Exerts Immune-Regulatory Activity in Vivo by Reducing NF-κB

- Activity, Halting Leukocyte Infiltration and Restoring Normal Metabolic Function. *Int J Mol Sci* 2016;17:323. <https://doi.org/10.3390/ijms17030323>.
- [96] Nicholas C, Batra S, Vargo MA, Voss OH, Gavrilin MA, Wewers MD, et al. Apigenin Blocks Lipopolysaccharide-Induced Lethality In Vivo and Proinflammatory Cytokines Expression by Inactivating NF- κ B through the Suppression of p65 Phosphorylation. *J Immunol* 2007;179:7121-7. <https://doi.org/10.4049/jimmunol.179.10.7121>.
- [97] Yano S, Umeda D, Yamashita T, Ninomiya Y, Sumida M, Fujimura Y, et al. Dietary flavones suppresses IgE and Th2 cytokines in OVA-immunized BALB/c mice. *Eur J Nutr* 2007;46:257-63. <https://doi.org/10.1007/s00394-007-0658-7>.
- [98] Wang J, Liu Y-T, Xiao L, Zhu L, Wang Q, Yan T. Anti-Inflammatory Effects of Apigenin in Lipopolysaccharide-Induced Inflammation in Acute Lung Injury by Suppressing COX-2 and NF- κ B Pathway. *Inflammation* 2014;37:2085-90. <https://doi.org/10.1007/s10753-014-9942-x>.
- [99] He X, Li C, Wei Z, Wang J, Kou J, Liu W, et al. Protective role of apigenin in cisplatin-induced renal injury. *Eur J Pharmacol* 2016;789:215-21. <https://doi.org/10.1016/j.ejphar.2016.07.003>.
- [100] Rezai-Zadeh K, Ehrhart J, Bai Y, Sanberg PR, Bickford P, Tan J, et al. Apigenin and luteolin modulate microglial activation via inhibition of STAT1-induced CD40 expression. *J Neuroinflammation* 2008;5:41. <https://doi.org/10.1186/1742-2094-5-41>.
- [101] Choi AY, Choi JH, Lee JY, Yoon K-S, Choe W, Ha J, et al. Apigenin protects HT22 murine hippocampal neuronal cells against endoplasmic reticulum stress-induced apoptosis. *Neurochem Int* 2010;57:143-52. <https://doi.org/10.1016/j.neuint.2010.05.006>.
- [102] Ergin K, Yaylalı A. Resveratrol ve Etkileri Üzerine Bir Gözden Geçirme. *SDÜ Tıp Fak Derg* 2013;20:115-20. <https://doi.org/10.17343/sdutfd.94607>.
- [103] Signorelli P, Ghidoni R. Resveratrol as an anticancer nutrient: molecular basis, open questions and promises. *J Nutr Biochem* 2005;16:449-66. <https://doi.org/10.1016/j.jnutbio.2005.01.017>.
- [104] Barreiro-Hurlé J, Colombo S, Cantos-Villar E. Is there a market for functional wines? Consumer preferences and willingness to pay for resveratrol-enriched red wine. *Food Qual Prefer* 2008;19:360-71. <https://doi.org/10.1016/j.foodqual.2007.11.004>.
- [105] Fernández-Mar MI, Mateos R, García-Parrilla MC, Puertas B, Cantos-Villar E. Bioactive compounds in wine: Resveratrol, hydroxytyrosol and melatonin: A review. *Food Chem* 2012;130:797-813. <https://doi.org/10.1016/j.foodchem.2011.08.023>.
- [106] Çetin A, Sağdıç O. A concise review: Antioxidant effects and bioactive constituents of grape. *Erciyes Tıp Derg* 2009;31:369-75.
- [107] Cenesiz S, Ciftci G, Gulbahar MY, Yarım GF, Nisbet HO, Kabak Y, et al. Investigation of the Effects of N-Acetyl Cysteine and Resveratrol to Acute Phase Response in Rats with Experimentally Induced Arthritis. *Kafkas Univ Vet Fak Derg* 2012;18:991-6. <https://doi.org/10.9775/kvfd.2012.6900>.
- [108] Cenesiz S, Yarım GF, Karabulut AB, Ara C. Changing of antioxidant enzyme activity on the biliary obstructed rats treated with resveratrol. *Dtsch Tierarztl Wochenschr* 2007;114:345-8. <https://doi.org/10.2377/0341-6593-114-345>.

- [109] Işık Bircan C, Merhan O. Kadmiyum Uygulanan Farelerde Oluşturulan Oksidatif Strese Karşı Resveratrolün Koruyucu Etkisinin Araştırılması*. Erciyes Üniversitesi Vet Fakültesi Derg 2020;215-20. <https://doi.org/10.32707/ercivet.828324>.
- [110] de Sá Coutinho D, Pacheco M, Frozza R, Bernardi A. Anti-Inflammatory Effects of Resveratrol: Mechanistic Insights. *Int J Mol Sci* 2018;19:1812. <https://doi.org/10.3390/ijms19061812>.
- [111] Liu H, Ren J, Chen H, Huang Y, Li H, Zhang Z, et al. Resveratrol Protects against Cigarette Smoke-Induced Oxidative Damage and Pulmonary Inflammation. *J Biochem Mol Toxicol* 2014;28:465-71. <https://doi.org/10.1002/jbt.21586>.
- [112] Liu X-J, Bao H-R, Zeng X-L, Wei J-M. Effects of resveratrol and genistein on nuclear factor- κ B, tumor necrosis factor- α and matrix metalloproteinase-9 in patients with chronic obstructive pulmonary disease. *Mol Med Rep* 2016;13:4266-72. <https://doi.org/10.3892/mmr.2016.5057>.
- [113] Knobloch J, Sibbing B, Jungck D, Lin Y, Urban K, Stoelben E, et al. Resveratrol Impairs the Release of Steroid-Resistant Inflammatory Cytokines from Human Airway Smooth Muscle Cells in Chronic Obstructive Pulmonary Disease. *J Pharmacol Exp Ther* 2010;335:788-98. <https://doi.org/10.1124/jpet.110.166843>.
- [114] Knobloch J, Hag H, Jungck D, Urban K, Koch A. Resveratrol Impairs the Release of Steroid-resistant Cytokines from Bacterial Endotoxin-Exposed Alveolar Macrophages in Chronic Obstructive Pulmonary Disease. *Basic Clin Pharmacol Toxicol* 2011;109:138-43. <https://doi.org/10.1111/j.1742-7843.2011.00707.x>.
- [115] Chen J, Yang X, Zhang W, Peng D, Xia Y, Lu Y, et al. Therapeutic Effects of Resveratrol in a Mouse Model of LPS and Cigarette Smoke-Induced COPD. *Inflammation* 2016;39:1949-59. <https://doi.org/10.1007/s10753-016-0430-3>.
- [116] Wang X-L, Li T, Li J-H, Miao S-Y, Xiao X-Z. The Effects of Resveratrol on Inflammation and Oxidative Stress in a Rat Model of Chronic Obstructive Pulmonary Disease. *Molecules* 2017;22:1529. <https://doi.org/10.3390/molecules22091529>.
- [117] Lee HY, Kim IK, Yoon HK, Kwon SS, Rhee CK, Lee SY. Inhibitory Effects of Resveratrol on Airway Remodeling by Transforming Growth Factor- β /Smad Signaling Pathway in Chronic Asthma Model. *Allergy Asthma Immunol Res* 2017;9:25. <https://doi.org/10.4168/aair.2017.9.1.25>.
- [118] Royce SG, Dang W, Yuan G, Tran J, El Osta A, Karagiannis TC, et al. Resveratrol has protective effects against airway remodeling and airway hyperreactivity in a murine model of allergic airways disease. *Pathobiol Aging Age-Related Dis* 2011;1:7134. <https://doi.org/10.3402/PBA.v1i0.7134>.
- [119] Caselli A, Cirri P, Santi A, Paoli P. Morin: A Promising Natural Drug. *Curr Med Chem* 2016;23:774-91. <https://doi.org/10.2174/0929867323666160106150821>.
- [120] Wu L, Wang Y, Chi G, Shen B, Tian Y, Li Z, et al. Morin reduces inflammatory responses and alleviates lipid accumulation in hepatocytes. *J Cell Physiol* 2019;234:19785-98. <https://doi.org/10.1002/jcp.28578>.
- [121] Kapoor R, Kakkar P. Protective Role of Morin, a Flavonoid, against High Glucose Induced Oxidative Stress Mediated Apoptosis in Primary Rat Hepatocytes. *PLoS One* 2012;7:e41663. <https://doi.org/10.1371/journal.pone.0041663>.
- [122] El Sayed NF, Abdallah DM, Awad AS, Ahmed KA, El-Abhar HS.

Novel peripheral role of Nurr-1/GDNF/ AKT trajectory in carvedilol and/or morin hydrate hepatoprotective effect in a model of hepatic ischemia/reperfusion. *Life Sci* 2021;273:119235. <https://doi.org/10.1016/j.lfs.2021.119235>.

[123] Jung H-J, Kim S-J, Song Y-S, Park E-H, Lim C-J. Evaluation of the Antiangiogenic, Anti-inflammatory, and Antinociceptive Activities of Morin. *Planta Med* 2010;76:273-5. <https://doi.org/10.1055/s-0029-1186079>.

[124] Lee KM, Lee Y, Chun HJ, Kim AH, Kim JY, Lee JY, et al. Neuroprotective and anti-inflammatory effects of morin in a murine model of Parkinson's disease. *J Neurosci Res* 2016;94:865-78. <https://doi.org/10.1002/jnr.23764>.

[125] Zhang Y, Li X. Lipopolysaccharide-regulated production of bone sialoprotein and interleukin-8 in human periodontal ligament fibroblasts: the role of toll-like receptors 2 and 4 and the MAPK pathway. *J Periodontal Res* 2015;50:141-51. <https://doi.org/10.1111/jre.12193>.

[126] Ma Y, Ge A, Zhu W, Liu Y-N, Ji N-F, Zha W-J, et al. Morin Attenuates Ovalbumin-Induced Airway Inflammation by Modulating Oxidative Stress-Responsive MAPK Signaling. *Oxid Med Cell Longev* 2016;2016:1-13. <https://doi.org/10.1155/2016/5843672>.

[127] Roh K-B, Jung E, Park D, Lee J. Fumaric acid attenuates the eotaxin-1 expression in TNF- α -stimulated fibroblasts by suppressing p38 MAPK-dependent NF- κ B signaling. *Food Chem Toxicol* 2013;58:423-31. <https://doi.org/10.1016/j.fct.2013.05.020>.

[128] Patel JK, Clifford RL, Deacon K, Knox AJ. Ciclesonide inhibits TNF α - and IL-1 β -induced monocyte chemotactic protein-1 (MCP-1/CCL2) secretion from human airway smooth muscle cells. *Am J*

Physiol Cell Mol Physiol 2012;302:L785-92. <https://doi.org/10.1152/ajplung.00257.2011>.

[129] Hollander C, Sitkauskienė B, Sakalauskas R, Westin U, Janciauskienė SM. Serum and bronchial lavage fluid concentrations of IL-8, SLPI, sCD14 and sICAM-1 in patients with COPD and asthma. *Respir Med* 2007;101:1947-53. <https://doi.org/10.1016/j.rmed.2007.04.010>.

[130] Tian Y, Li Z, Shen B, Zhang Q, Feng H. Protective effects of morin on lipopolysaccharide/ d -galactosamine-induced acute liver injury by inhibiting TLR4/NF- κ B and activating Nrf2/HO-1 signaling pathways. *Int Immunopharmacol* 2017;45:148-55. <https://doi.org/10.1016/j.intimp.2017.02.010>.

[131] Sinha K, Sadhukhan P, Saha S, Pal PB, Sil PC. Morin protects gastric mucosa from nonsteroidal anti-inflammatory drug, indomethacin induced inflammatory damage and apoptosis by modulating NF- κ B pathway. *Biochim Biophys Acta - Gen Subj* 2015;1850:769-83. <https://doi.org/10.1016/j.bbagen.2015.01.008>.

[132] Wang J, Guo C, Wei Z, He X, Kou J, Zhou E, et al. Morin suppresses inflammatory cytokine expression by downregulation of nuclear factor- κ B and mitogen-activated protein kinase (MAPK) signaling pathways in lipopolysaccharide-stimulated primary bovine mammary epithelial cells. *J Dairy Sci* 2016;99:3016-22. <https://doi.org/10.3168/jds.2015-10330>.

[133] Cai B, Gan X, He J, He W, Qiao Z, Ma B, et al. Morin attenuates cigarette smoke-induced lung inflammation through inhibition of PI3K/AKT/NF- κ B signaling pathway. *Int Immunopharmacol* 2018;63:198-203. <https://doi.org/10.1016/j.intimp.2018.07.035>.

- [134] Yu S, Liu X, Yu D, Changyong E, Yang J. Morin Protects LPS-Induced Mastitis via Inhibiting NLRP3 Inflammasome and NF- κ B Signaling Pathways. *Inflammation* 2020;43:1293-303. <https://doi.org/10.1007/s10753-020-01208-x>.
- [135] Shi J, Zhou L, Wang X, Du J, Jiang M, Song Z, et al. KLF2 attenuates bleomycin-induced pulmonary fibrosis and inflammation with regulation of AP-1. *Biochem Biophys Res Commun* 2018;495:20-6. <https://doi.org/10.1016/j.bbrc.2017.10.114>.
- [136] Tianzhu Z, Shihai Y, Juan D. The Effects of Morin on Lipopolysaccharide-Induced Acute Lung Injury by Suppressing the Lung NLRP3 Inflammasome. *Inflammation* 2014;37. <https://doi.org/10.1007/s10753-014-9930-1>.
- [137] Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. *Cancer Lett* 2008;269:352-62. <https://doi.org/10.1016/j.canlet.2008.03.053>.
- [138] Singh RP, Agarwal R. A cancer chemopreventive agent silibinin, targets mitogenic and survival signaling in prostate cancer. *Mutat Res Mol Mech Mutagen* 2004;555:21-32. <https://doi.org/10.1016/j.mrfmmm.2004.05.017>.
- [139] Flaig TW, Gustafson DL, Su L-J, Zirrollo JA, Crighton F, Harrison GS, et al. A phase I and pharmacokinetic study of silybin-phytosome in prostate cancer patients. *Invest New Drugs* 2006;25:139-46. <https://doi.org/10.1007/s10637-006-9019-2>.
- [140] Au AY, Hasenwinkel JM, Frondoza CG. Silybin inhibits interleukin-1 β -induced production of pro-inflammatory mediators in canine hepatocyte cultures. *J Vet Pharmacol Ther* 2011;34:120-9. <https://doi.org/10.1111/j.1365-2885.2010.01200.x>.
- [141] de Souza CO, Peraçoli MTS, Weel IC, Bannwart CF, Romão M, Nakaira-Takahagi É, et al. Hepatoprotective and anti-inflammatory effects of silibinin on experimental preeclampsia induced by l-NAME in rats. *Life Sci* 2012;91:159-65. <https://doi.org/10.1016/j.lfs.2012.06.036>.
- [142] Tyagi A, Agarwal C, Dwyer-Nield LD, Singh RP, Malkinson AM, Agarwal R. Silibinin modulates TNF- α and IFN- γ mediated signaling to regulate COX2 and iNOS expression in tumorigenic mouse lung epithelial LM2 cells. *Mol Carcinog* 2012;51:832-42. <https://doi.org/10.1002/mc.20851>.
- [143] Wu J-W, Lin L-C, Tsai T-H. Drug-drug interactions of silymarin on the perspective of pharmacokinetics. *J Ethnopharmacol* 2009;121:185-93. <https://doi.org/10.1016/j.jep.2008.10.036>.
- [144] Karapehlivan M, Kükürt A, Özen H, Kaya İ, Kasacı T, Deveci HA, et al. The beneficial effect of silymarin administration against nicotine-Induced oxidative stress in mice. *J Cell Neurosci Oxidative Stress* 2016;8:561.
- [145] Kang JS, Jeon YJ, Park S-K, Yang K-H, Kim HM. Protection against lipopolysaccharide-induced sepsis and inhibition of interleukin-1 β and prostaglandin E2 synthesis by silymarin. *Biochem Pharmacol* 2004;67:175-81. <https://doi.org/10.1016/j.bcp.2003.08.032>.
- [146] Sherif IO, Al-Gayyar MMH. Antioxidant, anti-inflammatory and hepatoprotective effects of silymarin on hepatic dysfunction induced by sodium nitrite. *Eur Cytokine Netw* 2013;24:114-21. <https://doi.org/10.1684/ecn.2013.0341>.