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REVIEW

Hesperetin as an anti-SARS-CoV-2 agent can inhibit COVID-19-associated cancer progression by suppressing intracellular signaling pathways

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Abstract

Hesperetin, an aglycone metabolite of hesperidin with high bioavailability, recently gained attention due to its anti-COVID-19 and anti-cancer properties. Multiple studies revealed that cancer patients are prone to experience a severe form of COVID-19 and higher mortality risk. In addition, studies suggested that COVID-19 can potentially lead to cancer progression through multiple mechanisms. This study proposes that hesperetin not only can be used as an anti-COVID-19 agent but also can reduce the risk of multiple cancer progression by suppressing several intracellular signaling pathways in cancer patients with COVID-19. Therefore, in this review, we attempted to provide evidence demonstrating anti-COVID-19/cancer properties of hesperetin with several mechanisms.

Keywords COVID-19 · Cancer · Signaling pathways · Hesperetin · SARS-CoV-2

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS2	Transmembrane serine protease 2
PI3K	Phosphoinositide 3-kinases
TNF-α	Tumor necrosis factor-alpha
VEGF	Vascular endothelial growth factor
HIF-1α	Hypoxia-inducible factor-1alpha
mTOR	Mammalian target of rapamycin
STAT3	Signal transducer and activator of transcription
ERK	Extracellular signal-regulated kinase

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Introduction

Hesperetin is a flavanone glycoside (a subclass of flavonoids), phytoestrogen, and a bioactive compound that is commonly found in various fruits and food sources, such as lemons, grapefruit, oranges, and tangerines. The compound is composed of an aglycone (Hesperetin) and a disaccharide (Rutinose), which is composed of glucose and rhamnose. The anti-oxidant, anti-inflammatory, cardioprotective, anti-atherogenic, and anti-hyperlipidemic activities of hesperidin have been studied extensively, and recently it has attracted attention for its anti-cancer and anti-COVID-19 (Coronavirus disease—2019) properties (Garg et al. 2001; Parhiz et al. 2015; Khezri et al. 2022a; Sohel et al. 2022; Sun et al. 2022; Wu et al. 2020).

Only a few studies have evaluated the antiviral effect of hesperidin before the COVID-19 occurrence and in the resulting in-depth studies, researchers reported a marked reduction of influenza A virus replication through two distinct methods. Through modulating selective MAP kinase pathways, hesperidin enhances cell-autonomous immunity by increasing the expression of p38 and cJun N(2)-terminal kinase (JNK), which are essential for defense against influenza viruses (Saha et al. 2009; Dong et al. 2014).

On the other hand, hesperetin exerts a critical role in anti-cancer mechanisms against various cancer cells such as glioblastoma, breast, lung, pancreatic, liver, prostate, colon, kidney, oral, esophageal, osteosarcoma, ovarian, thyroid, and leukemia (Sohel et al. 2022). On the other hand, multiple studies revealed that COVID-19 can lead to the progression of multiple diseases and cancers, so we addressed some cellular and molecular mechanisms in some of these studies (Zalpoor et al. 2022a, b, c, d, e, f, g). Moreover, multiple studies have confirmed the absence of adverse side effects after oral intake and the overall high safety profile of hesperidin, this flavanone might be useful as a prophylactic (Jose and Manuel 2020; Parisi et al. 2021).

However, new investigations are required to find practical therapeutic approaches to combat COVID-19-associated cancer progression, using flavonoids and bioactive compounds such as quercetin (Zalpoor et al. 2022e) and hesperetin that we addressed in this study.

Hesperetin anti-COVID-19 effects

Several studies investigated natural products with antiviral activities such as hesperetin. Newly, there has been a lot of attention to the effect of hesperetin on different aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, including viral entry, replication, and inflammatory responses through several mechanisms/pathways. In this regard, inhibition of COVID-19 entry into host cells can be affected by hesperetin through the phosphoinositide 3-kinases (PI3K)/AKT/AP2M1 pathway similar to a tyrosine kinase inhibitor, sunitinib (Fig. 1, Table 1). Sunitinib has been shown to repress angiotensin-converting enzyme 2 (ACE2)/SARS-CoV-2 entry complex into the host cells via a clathrin-mediated pathway by suppressing the phosphorylation of adapter protein complex for clathrin, AP2M1. Evidence showed that the PI3K/AKT signaling pathway plays a role in AP2M1 expression. Thus, it can be concluded that hesperetin, like sunitinib, has effects on the inhibition of COVID-19 entry to host cells by the PI3K/AKT/AP2M1 pathway (Khezri et al. 2022a). Hesperetin also has important and therapeutic roles on angiotensin II (Ang II) expression level, a pro-inflammatory factor in lung fibrosis. Promotion of Ang II levels has been indicated in COVID-19 patients with the contribution of ACE2/SARS-CoV-2 endocytosis. Based on the effects of Ang II on inflammation and fibrosis induction through the PI3K/AKT pathway, hesperetin can block the AKT pathway and inhibit cardiac fibroblast proliferation and collagen expression induced by Ang II during COVID-19 infection (Khezri 2021; Khezri et al. 2022b).

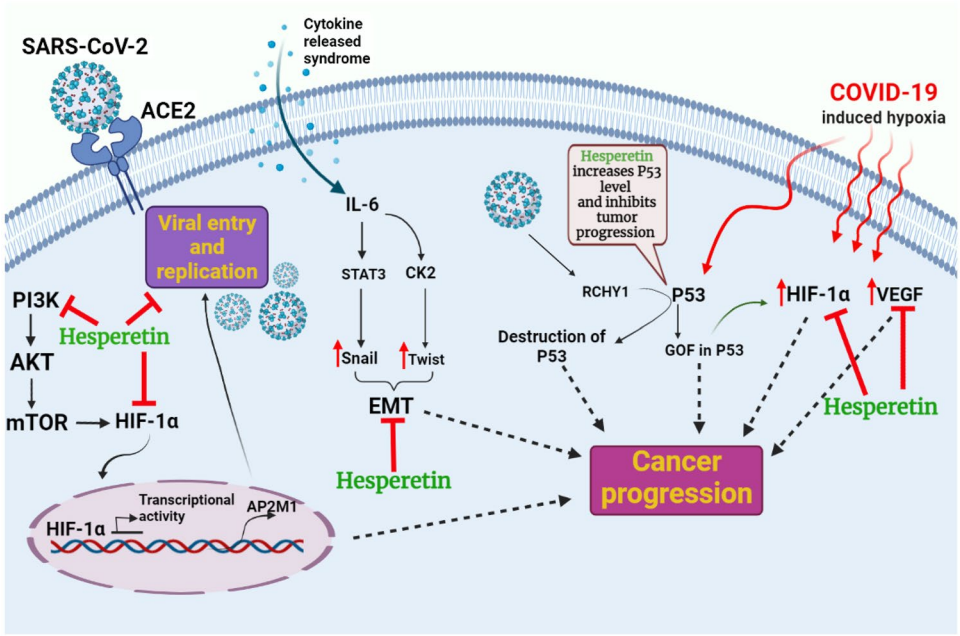

Fig. 1 Hesperetin effects as an anti-SARS-CoV-2 and anti-COVID-19-associated cancer progression agent by targeting intracellular signaling pathways

Table 1 Anti-COVID-19 effects of hesperetin

Anti-COVID-19 activity	Factor/pathway	Description	Refs
Virus entry	Inhibition of PI3K/AKT signaling pathway	Similar sunitinib suppresses the phosphorylation of AP2M1 as an adapter protein complex for clathrin Inhibits the AKT pathway and Cardiac fibroblast proliferation and collagen expression induced by Ang II during COVID-19 infection	(Agrawal et al. 2021; Cheng et al. 2021; Khezri et al. 2022a; Ngwa et al. 2020)
	High interaction with ACE2 receptor and transmembrane serine protease 2 (TMPRSS2)	Disrupting the interaction of ACE2 with receptor-binding domain (RBD) of the spike glycoprotein even more than the chloroquine	
Virus replication	Inhibiting of SARS-CoV-2 3CL protease and NSP15 endoribonuclease	Two viral enzymes needed for the virus replication	(Lin et al. 2005; Al-Mazaideh et al. 2021)
Host cell inflammatory response	Interferon regulatory factor 7 (IRF-7)	Triggering the IRF-7 expression to fight back against the virus Modulating the pro-inflammatory cytokines expression such as IL-1β, IL-6, and TNF-α to prevent ARDS	(Agrawal et al. 2021)

Replication of a variety of viruses can also be inhibited by hesperetin in in-vitro conditions such as; SARS-CoV, influenza A, herpes simplex virus type-1, respiratory syncytial virus, poliovirus type-1, and parainfluenza virus type-3. Specifically, docking simulations showed that hesperetin, hesperidin, and naringin, are highly binding to the ACE2 receptor (Agrawal et al. 2021). In-silico investigations by Rameshwar S. Cheke et al. evidenced the inhibition of SARS-CoV-2 spike glycoprotein-human ACE2 complex by natural candidates such as hesperetin (Cheke et al. 2021) highlighting hesperitin's capability to disrupt the interaction of ACE2 with the receptor-binding domain (RBD) of the virus spike glycoprotein. Furthermore, Ngwa and colleagues compared the in silico effects of hesperetin with chloroquine based on the in silico docking of hesperetin to the ACE2 receptor (PDB ID: 1R4L). Hesperetin binds more strongly to the ACE2 receptor than chloroquine, suggesting it is potentially effective against COVID-19 (Ngwa et al. 2020).

In a molecular docking study by Ghassab M. Al-Mazaideh et al. it was revealed that naringenin and hesperetin may be as potent natural drugs to suppress SARS-CoV-2 viral replication by altering the activity of two pivotal proteins, 3CL protease and NSP15 endoribonuclease (Fig. 1) (Al-Mazaideh et al. 2021). As evidenced in a study on the effects of the Chinese medicinal plant *Isatis tinctoria* root on SARS-CoV-2, hesperetin (IC50 = 8.3 lM) is also an impressive inhibitor of SARS-CoV 3CLpro (Lin et al. 2005). Further in silico studies demonstrated that hesperetin and Hesperidin strongly bind to two proteins that are critical for the cellular entry of SARS-CoV-2: transmembrane serine protease 2 (TMPRSS2) and ACE2 (Cheng et al. 2021). According to a study by Rohmad Yudi Utomo et al. hesperidin indicated a great binding affinity toward TMPRSS, 3CL-pro, subunit 2 of spike receptor-binding domain (S2-RBD), and PD domain of ACE2 (PD-ACE2) to inhibit the SARS-CoV-2 infection (Utomo et al. 2020). Computational studies have shown that hesperidin could exert significant antiviral activity on SARS-CoV-2 through its affinity for binding to spike protein, ACE2, and major protease (Bellavite and Donzelli 2020; Meneguzzo et al. 2020).

Moreover, it has been reported that upregulation of interferon regulatory factor 7 (IRF-7) transcription factor may be triggered by citrus flavonoids including hesperetin and hesperidin and in this way, they display antiviral activities. The major cause of acute respiratory distress syndrome (ARDS) in COVID-19 infection is cytokine storm which is defined by a lot of production of immune-active molecules such as interleukins (e.g. IL-1β, IL-2, IL-6), interferons (e.g. IFN-γ), tumor necrosis factor-alpha (TNF-α), and chemokines. Research demonstrated that modulation of inflammatory cytokines expressions such as IL-1β, IL-6, and TNF-α have been affected by hesperetin/hesperidin in the lungs, heart, and central nervous system of several animal models (Agrawal et al. 2021; Gour et al. 2021). According to Ding et al. (2018), hesperidin attenuated lung injury in male rats induced by influenza A virus (H1N1) by inhibiting pro-inflammatory cytokine production, including IFN-α, TNF-α, and IL-6, through suppressing MAPK signaling pathways (Ding, Sun, & Zhu, 2018). In lipopolysaccharide (LPS)-induced acute lung injury model in Wistar rats hesperidin

can act as the potential natural drug to inhibit the expression of TNF-α, IL-12, and IL-1β as well as increasing the production of IL-10 and IL-4 via down-regulation of NF-κB and AP-1 signaling (Yeh et al. 2007).

In vitro (Choi and Lee 2010; Ren et al. 2016) and in vivo investigations (Ye et al. 2019) have indicated that hesperetin has potential to inhibit IL-1β, IL-6, and TNF-α expression significantly via forbidding multiple signaling pathways such as MAPK, JNK, and NF-κB. In addition, based on a randomized, double-blind, placebo-controlled clinical trial by Zahra Yari et al. hesperidin could decrease systolic blood pressure, triglyceride, fasting glucose level and TNF-α in metabolic syndrome (MetS) patients. Furthermore, hesperidin significantly reduced insulin, low density lipoprotein cholesterol and total cholesterol in MetS patients' group, however, in control group only insulin and glucose significantly reduced (Yari et al. 2020).Therefore, hesperetin can inhibit the secretion of pro-inflammatory cytokines with its high anti-inflammatory activities and also it has anti-adipogenic, anti-oxidant, and anti-hypercholesterolemic effects. Overall, hesperetin can be a potential treatment for inhibition of SARS-CoV-2 entry into host cells and by its pharmacological properties suppressing viral particles replication and pro-inflammatory overreaction. Nowadays, it is considered safe to administer hesperidin as a nutraceutical (Gour et al. 2021) and recently, this has been studied in clinical trials to treat COVID-19 (NCT04452799; NCT04715932) (https://clinicaltrials.gov/ct2/show/NCT04715932).

Hesperetin anti-cancer effects by suppressing intracellular signaling pathways

SARS-CoV-2 virus infection clearly causes regional hypoxia in the infected areas. This hypoxia may benefit the stabilization of hypoxia-inducible factor-1alpha (HIF-1α) and the overexpression of vascular endothelial growth factor (VEGF) in the endothelial and cancer cells (Fig. 1) (Serebrovska et al. 2020). So, SARS-CoV-2 virus infection causes hypoxia and promotes angiogenesis. Likewise, to prevent angiogenesis, an experiment on C6 glioma rat cells found that hesperetin blocks the HIF-1α/VEGF/VEGFR2 signaling pathway in glioma endothelial cells (Stanisic et al. 2018).

According to a review article by Zhang et al. hypoxia is one of the causes of mutation of gain of function (GOF) in p53 (loss of ability to prevent cancer). This type of mutation also stabilizes HIF-1α in the cell and gives the cell more potential to initiate multiple signaling pathways for angiogenesis (Zhang et al. 2021). On the other hand, replication of the virus inside the host cell can cause the p53 molecule to be destroyed. Thus, when the mammalian target of rapamycin (mTOR) is overactive in the cell, viral translocation accelerates. But to prevent this event, host cells use p53-dependent microRNAs (miRNAs), which attach to the 3' end of mTOR and prevent its activity. According to a hypothesis by M. J. Ramalah et al., the non-structural proteins of the SARS-CoV-2 virus interact with E3 ubiquitin (E3U) ligase ring-finger and CHY zinc-finger domain-containing 1 (RCHY1) and stabilize it, which eventually leads to the destruction of p53 (Ramaiah 2020). Although COVID-19 inhibits p53 function and causes cancer progression, studies by Hermawan et al. have found that hesperetin has positive effects on the intracellular level of p53 in breast cancer stem cells (BCSC). Accordingly, p53, which was impaired in many cancer stem cells, reached significant levels in BCSC cells with hesperetin treatment (Hermawan et al. 2021).

In addition to increasing the expression of wild-type (wt) p53 in cancerous cells, hesperidine also increases the expression of p53 in vivo in colon carcinoma. Further, the corresponding aglycone hesperetin induced a wt p53 increase in an in vivo breast cancer model and a siHa cervical adenocarcinoma cell line. In a number of cancer cell lines, the use of hesperetin and hesperidin elevated p21 expression, which resulted in a G1 arrest in the cell cycle. Inhibiting cell cycle progression by forming complexes with Cdk2, -4, and -6 is one of the functions of p21 (Alshatwi et al. 2013; Xia et al. 2018).

Cancer cell lines were found to be inhibited during the G1/S transition by hesperidin and hesperetin. The effects of hesperidin exposure on A549 lung adenocarcinoma are both increased p21 and decreased cyclin D1, both of which result in G1-phase arrest. Hesperetin also showed similar effects in Eca-109 esophageal carcinoma cells (Wu et al. 2018).

Furthermore, decreased cyclin E and Cdk2 levels were detected in HeLa cervical cancer cells as well as in MCF-7 breast cancer cells, suggesting an extended time between replication and DNA replication (Wang et al. 2016).

Endothelial cells undergo a phenomenon called epithelial-mesenchymal transition (EMT) which gains invasion ability and contributes to the progression of cancer. According to studies, many inflammatory cytokines are among the factors that accelerate this phenomenon. Signal transducer and activator of transcription 3 (STAT3), extracellular signal-regulated kinase 1/2 (ERK1/2) and AKT signaling pathways are involved in controlling the growth of some tumors, resulting in some interleukin-6 (IL-6) production (Shirzad et al. 2017).

The IL-6 through the STAT3 signaling pathway increases Snail levels in head and neck squamous cell carcinomas (HNSCC) cells or phosphorylates Twist via casein kinase 2 (CK2) to make it more stable (Smith et al. 2013). Thus, infection with the SARS-CoV-2 virus, which produces inflammatory cytokines, can help EMT.

Furthermore, mounting evidence indicates that both inflammation and oxidative stress directly contribute to

cellular cancers by inactivating tumor suppressor genes, activating oncogenes, and disrupting cell signal transduction pathways via SARS-CoV-2 (Colotta et al. 2009).

Furthermore, Hesperetin has been found to have strong anti-oxidative properties against inflammation, oxidative stress, free radical damage, carcinogenesis, proliferation, apoptosis, hyperglycemia, and lipid disorders (hyperlipidemia, hypertension, and hyperglycemia) according to a wide number of studies (Li et al. 2019; Lorzadeh et al. 2019).

Researchers have shown that hesperetin has anti-inflammatory mechanisms by reducing the levels of inflammation-inducing factors such as VCAM-1, COX-2, MMP-2, MMP-9, PGE2 (prostaglandin E2), IL-4, IL-6, iNOS, and NO2 (Parhiz et al. 2015).

Hesperetin significantly inhibited nitric oxide production and induced inducible nitric oxide synthase in LPS-stimulated BV-2 microglial cells as part of its anti-inflammatory effects, which were also demonstrated in LPS-stimulated microglial cells. As well as IL-1β and IL-6, hesperetin significantly reduced inflammatory cytokine secretion. The anti-inflammatory effects of hesperetin were also found in its down-regulation of extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase. So, by suppressing the expression of inflammatory cytokines and MAPKs, Hesperetin is able to inhibit neuroinflammation on microglia (Jo et al. 2019).

Interestingly, according to Dabin Choi et al. studies, hesperetin can be effective in EMT prevention. In this study, which was performed on podocyte cells, the cells were first treated with TGF-β, which showed a significant increase in mesenchymal markers such as fibronectin and vimentin and a significant decrease in epithelial markers such as nephrin and zonula occludens-1 (ZO-1). These effects of TGF-β were surprisingly inhibited after hesperetin treatment (Choi et al. 2020). Furthermore, it was confirmed in another study that TGF-β1 treatment increases MDA-MB-231 tumor progression including aberrant wound healing and invasion ability, which is suppressed by co-treatment with hesperetin. In addition, hesperetin decreased the development of actin stress fibers mediated by TGF-β1 (Lu et al. 2022).

Also, using single-molecule force measurements and single-molecule fluorescence imaging show, generally, it was shown that hesperetin is able to inhibit the transforming growth factor-b (TGF-b) signaling pathway. In this line, hesperetin interferes with ligand–receptor interactions. Moreover, Western blot analysis demonstrated that hesperetin inhibits the phosphorylation of Smad3, a downstream target of the TGF-β pathway, hindering the migration and invasion of cancer cells induced by TGF-β1 (Yang et al. 2012).

The SARS-CoV-2 virus, in addition to progressing cancer by secondary conditions such as the production of inflammatory cytokines or hypoxia, can also accelerate the cell cycle of cancer cells. For example, virus replication within host cells phosphorylates AKT and activates the AKT/TSC1/2/Rheb/mTOR signaling pathway, or directly activates mTOR, thereby accelerating the cell cycle (Mashayekhi-Sardoo and Hosseinjani 2022). According to studies, hesperetin has the ability to inhibit the oncogenic activity of mTOR and AKT in cancer cells (Ahmadi et al. 2015).

Conclusion

In this article, we discussed the anti-COVID-19 and anti-cancer effects of hesperetin. We hypothesized that hesperetin could be beneficial for multiple cancer patients with COVID-19 by suppressing the intracellular signaling pathway to reduce the severity of the infection and inhibiting COVID-19-associated cancer progression. This study can shed light on new investigations during and after the COVID-19 pandemic. However, future clinical and in-vitro studies are required to understand the effectiveness of natural compounds like hesperetin and its high water solubility nano-particle for such patients by suppressing multiple intracellular signaling pathways.

Author contributions HZ: study design and concept; study supervision; writing—original draft; figure creation. MB: writing—original draft; figure creation. HS: writing—original draft and revision. PR: revision. CT: writing—original draft. MN-A: writing—original draft; study supervision. All authors read and approved the final manuscript.

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Data availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Conflict of interest There are no competing interests to declare.

References

Agrawal PK, Agrawal C, Blunden G (2021) Pharmacological significance of hesperidin and hesperetin, two citrus flavonoids, as promising antiviral compounds for prophylaxis against and combating COVID-19. Nat Prod Commun. https://doi.org/10.1177/1934578X211042540

Ahmadi A, Shadboorestan A, Nabavi S, Setzer W, Nabavi S (2015) The role of hesperidin in cell signal transduction pathway for the prevention or treatment of cancer. Curr Med Chem 22(30):3462–3471

Al-Mazaideh G, Al-Swailmi F, Parrey M (2021). Molecular docking study reveals naringenin and hesperetin from desert truffles as promising potential inhibitors for coronavirus (COVID-19) Medicinal impact of desert truffles. Ann Clin Anal Med pp. 980–985.

Alshatwi AA, Ramesh E, Periasamy V, Subash-Babu P (2013) The apoptotic effect of hesperetin on human cervical cancer cells is mediated through cell cycle arrest, death receptor, and mitochondrial pathways. Fundam Clin Pharmacol 27(6):581–592

Bellavite P, Donzelli A (2020) Hesperidin and SARS-CoV-2: new light on the healthy function of citrus fruits. Antioxidants 9(8):742

Cheke RS, Narkhede RR, Shinde SD, Ambhore JP, Jain PG (2021) Natural product emerging as potential SARS spike glycoproteins-ACE2 inhibitors to combat COVID-19 attributed by in-silico investigations. Biointerface Res Appl Chem 11:10628–10639

Cheng F-J, Huynh T-K, Yang C-S, Hu D-W, Shen Y-C, Tu C-Y, Chen Y (2021) Hesperidin is a potential inhibitor against SARS-CoV-2 infection. Nutrients 13(8):2800

Choi EM, Lee YS (2010) Effects of hesperetin on the production of inflammatory mediators in IL-1β treated human synovial cells. Cell Immunol 264(1):1–3

Choi D, Kim C-L, Kim JE, Mo J-S, Jeong H-S (2020) Hesperetin inhibit EMT in TGF-β treated podocyte by regulation of mTOR pathway. Biochem Biophys Res Commun 528(1):154–159

Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 30(7):1073–1081

Ding Z, Sun G, Zhu Z (2018) Hesperidin attenuates influenza A virus (H1N1) induced lung injury in rats through its anti-inflammatory effect. SAGE, London, England

Dong W, Wei X, Zhang F, Hao J, Huang F, Zhang C, Liang W (2014) A dual character of flavonoids in influenza A virus replication and spread through modulating cell-autonomous immunity by MAPK signaling pathways. Sci Rep 4(1):1–12

Garg A, Garg S, Zaneveld L, Singla A (2001) Chemistry and pharmacology of the citrus bioflavonoid hesperidin. Phytother Res 15(8):655–669

Gour A, Manhas D, Bag S, Gorain B, Nandi U (2021) Flavonoids as potential phytotherapeutics to combat cytokine storm in SARS-CoV-2. Phytother Res 35(8):4258–4283

Hermawan A, Ikawati M, Khumaira A, Putri H, Jenie RI, Angraini SM, Muflikhasari HA (2021) Bioinformatics and in vitro studies reveal the importance of p53, PPARG and notch signaling pathway in inhibition of breast cancer stem cells by Hesperetin. Adv Pharm Bull 11(2):351

Jo SH, Kim ME, Cho JH, Lee Y, Lee J, Park Y-D, Lee JS (2019) Hesperetin inhibits neuroinflammation on microglia by suppressing inflammatory cytokines and MAPK pathways. Arch Pharmacal Res 42(8):695–703

Jose RJ, Manuel A (2020) COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med 8(6):e46–e47

Khezri MR (2021) PI3K/AKT signaling pathway: a possible target for adjuvant therapy in COVID-19. Hum Cell 34(2):700–701

Khezri MR, Ghasemnejad-Berenji M, Moloodsouri D (2022a) Hesperetin and the PI3K/AKT pathway: Could their interaction play a role in the entry and replication of the SARS-CoV-2? J Food Biochem. https://doi.org/10.1111/jfbc.14212

Khezri MR, Varzandeh R, Ghasemnejad-Berenji M (2022b) The probable role and therapeutic potential of the PI3K/AKT signaling pathway in SARS-CoV-2 induced coagulopathy. Cell Mol Biol Lett 27(1):1–10

Li X, Xie X, Zhang L, Meng Y, Li N, Wang M, Zhang L (2019) Hesperidin inhibits keratinocyte proliferation and imiquimod-induced psoriasis-like dermatitis via the IRS-1/ERK1/2 pathway. Life Sci 219:311–321

Lin C-W, Tsai F-J, Tsai C-H, Lai C-C, Wan L, Ho T-Y, Chao P-DL (2005) Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res 68(1):36–42

Lorzadeh E, Ramezani-Jolfaie N, Mohammadi M, Khoshbakht Y, Salehi-Abargouei A (2019) The effect of hesperidin supplementation on inflammatory markers in human adults: a systematic review and meta-analysis of randomized controlled clinical trials. Chem Biol Interact 307:8–15

Lu Q, Lai Y, Zhang H, Ren K, Liu W, An Y, Fan H (2022) Hesperetin inhibits TGF-β1-induced migration and invasion of triple negative breast cancer MDA-MB-231 cells via suppressing Fyn/Paxillin/RhoA pathway. Integr Cancer Ther 21:15347354221086900

Mashayekhi-Sardoo H, Hosseinjani H (2022) A new application of mTOR inhibitor drugs as potential therapeutic agents for COVID-19. J Basic Clin Physiol Pharmacol 33(1):17–25

Meneguzzo F, Ciriminna R, Zabini F, Pagliaro M (2020) Review of evidence available on hesperidin-rich products as potential tools against COVID-19 and hydrodynamic cavitation-based extraction as a method of increasing their production. Processes 8(5):549

Ngwa W, Kumar R, Thompson D, Lyerly W, Moore R, Reid T-E, Toyang N (2020) Potential of flavonoid-inspired phytomedicines against COVID-19. Molecules 25(11):2707

Parhiz H, Roohbakhsh A, Soltani F, Rezaee R, Iranshahi M (2015) Antioxidant and anti-inflammatory properties of the citrus flavonoids hesperidin and hesperetin: an updated review of their molecular mechanisms and experimental models. Phytother Res 29(3):323–331

Parisi GF, Carota G, CastruccioCastracani C, Spampinato M, Manti S, Papale M, Leonardi S (2021) Nutraceuticals in the prevention of viral infections, including COVID-19, among the pediatric population: a review of the literature. Int J Mol Sci 22(5):2465

Ramaiah MJ (2020) mTOR inhibition and p53 activation, microRNAs: the possible therapy against pandemic COVID-19. Gene Reports 20:100765

Ren H, Hao J, Liu T, Zhang D, Lv H, Song E, Zhu C (2016) Hesperetin suppresses inflammatory responses in lipopolysaccharide-induced RAW 264.7 cells via the inhibition of NF-κB and activation of Nrf2/HO-1 pathways. Inflammation 39(3):964–973

Saha RK, Takahashi T, Suzuki T (2009) Glucosyl hesperidin prevents influenza a virus replication in vitro by inhibition of viral sialidase. Biol Pharm Bull 32(7):1188–1192

Serebrovska ZO, Chong EY, Serebrovska TV, Tumanovska LV, Xi L (2020) Hypoxia, HIF-1α, and COVID-19: from pathogenic factors to potential therapeutic targets. Acta Pharmacol Sin 41(12):1539–1546

Shirzad M, Heidarian E, Beshkar P, Gholami-Arjenaki M (2017) Biological effects of hesperetin on interleukin-6/phosphorylated signal transducer and activator of transcription 3 pathway signaling in prostate cancer PC3 cells. Pharmacogn Res 9(2):188

Smith A, Teknos TN, Pan Q (2013) Epithelial to mesenchymal transition in head and neck squamous cell carcinoma. Oral Oncol 49(4):287–292

Sohel M, Sultana H, Sultana T, Al Amin M, Aktar S, Ali MC, Amin MN (2022) Chemotherapeutic potential of hesperetin for cancer treatment, with mechanistic insights: A comprehensive review. Heliyon 8(1):e08815

Stanisic D, Costa A, Fávaro W, Tasic L, Seabra A (2018) Anticancer activities of hesperidin and hesperetin in vivo and their potentiality against Bladder cancer. J Nanomed Nanptechnol. https://doi.org/10.4172/2157-7439.1000515

Sun J, Li W, Liao H, Li L, Ni H, Chen F, Li Q (2022) Adding sorbitol improves the thermostability of α-l-rhamnosidase from Aspergillus niger and increases the conversion of hesperidin. J Food Biochem 46(2):e14055

Utomo RY, Putri DDP, Salsabila IA, Meiyanto E (2020) The chemopreventive potential of diosmin and hesperidin for COVID-19 and its comorbid diseases. Indones J Cancer Chemoprevention 11(3):154–167

Wang H, Chen G, Guo X, Abbasi AM, Liu RH (2016) Influence of the stage of ripeness on the phytochemical profiles, antioxidant and antiproliferative activities in different parts of *Citrus reticulata* Blanco cv Chachiensis. LWT-Food Sci Technol 69:67–75

Wu D, Li J, Hu X, Ma J, Dong W (2018) Hesperetin inhibits Eca-109 cell proliferation and invasion by suppressing the PI3K/AKT signaling pathway and synergistically enhances the anti-tumor effect of 5-fluorouracil on esophageal cancer in vitro and in vivo. RSC Adv 8(43):24434–24443

Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Li X (2020) Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sinica B 10(5):766–788

Xia R, Sheng X, Xu X, Yu C, Lu H (2018) Hesperidin induces apoptosis and G0/G1 arrest in human non-small cell lung cancer A549 cells. Int J Mol Med 41(1):464–472

Yang Y, Wolfram J, Shen H, Fang X, Ferrari M (2012) Hesperetin: an inhibitor of the transforming growth factor-β (TGF-β) signaling pathway. Eur J Med Chem 58:390–395

Yari Z, Movahedian M, Imani H, Alavian SM, Hedayati M, Hekmatdoost A (2020) The effect of hesperidin supplementation on metabolic profiles in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled clinical trial. Eur J Nutr 59(6):2569–2577

Ye J, Guan M, Lu Y, Zhang D, Li C, Li Y, Zhou C (2019) Protective effects of hesperetin on lipopolysaccharide-induced acute lung injury by targeting MD2. Eur J Pharmacol 852:151–158

Yeh C-C, Kao S-J, Lin C-C, Wang S-D, Liu C-J, Kao S-T (2007) The immunomodulation of endotoxin-induced acute lung injury by hesperidin in vivo and in vitro. Life Sci 80(20):1821–1831

Zalpoor H, Akbari A, Nabi-Afjadi M (2022a) Ephrin (Eph) receptor and downstream signaling pathways: a promising potential targeted therapy for COVID-19 and associated cancers and diseases. Hum Cell 35(2):952–954

Zalpoor H, Akbari A, Nabi-Afjadi M, Forghaniesfidvajani R, Tavakol C, Barzegar Z, Farrokhi MR (2022b) Hypoxia-inducible factor 1 alpha (HIF-1α) stimulated and P2X7 receptor activated by COVID-19, as a potential therapeutic target and risk factor for epilepsy. Hum Cell. https://doi.org/10.1007/s13577-022-00747-9

Zalpoor H, Akbari A, NayerainJazi N, Liaghat M, Bakhtiyari M (2022c) Possible role of autophagy induced by COVID-19 in cancer progression, chemo-resistance, and tumor recurrence. Infect Agents Cancer 17(1):1–4

Zalpoor H, Akbari A, Samei A, Forghaniesfidvajani R, Kamali M, Afzalnia A, Khoshmirsafa M (2022d) The roles of Eph receptors, neuropilin-1, P2X7, and CD147 in COVID-19-associated neurodegenerative diseases: inflammasome and JaK inhibitors as potential promising therapies. Cell Mol Biol Lett 27(1):1–21

Zalpoor H, Bakhtiyari M, Liaghat M, Nabi-Afjadi M, Ganjalikhani-Hakemi M (2022e) Quercetin potential effects against SARS-CoV-2 infection and COVID-19-associated cancer progression by inhibiting mTOR and hypoxia-inducible factor-1α (HIF-1α). Phytother Res 36(7):2679–2682

Zalpoor H, Rezaei M, Yahyazadeh S, Ganjalikhani-Hakemi M (2022f) Flt3-ITD mutated acute myeloid leukemia patients and COVID-19: potential roles of autophagy and HIF-1α in leukemia progression and mortality. Hum Cell 35(4):1304–1305

Zalpoor H, Shapourian H, Akbari A, Shahveh S, Haghshenas L (2022g) Increased neuropilin-1 expression by COVID-19: a possible cause of long-term neurological complications and progression of primary brain tumors. Hum Cell 35(4):1301–1303

Zhang C, Liu J, Wang J, Zhang T, Xu D, Hu W, Feng Z (2021) The interplay between tumor suppressor p53 and hypoxia signaling pathways in cancer. Front Cell Dev Biol 9:273