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

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).
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).

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

### 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 | (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 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) |
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) (Serebrovskia 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, hesperidin 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
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.

**Conflict of interest**

There are no competing interests to declare.

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