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REVIEW

Potential effects of icariin, the *Epimedium*-derived bioactive compound in the treatment of COVID-19: a hypothesis

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected the world's health systems for more than two years. This disease causes a high mortality rate followed by cytokine storm–induced oxidative stress and acute respiratory distress syndrome (ARDS). Therefore, many drugs have been considered with emphasis on their anti-inflammatory and antioxidant effects in controlling the consequences of SARS-CoV-2 infection. Icariin is a major bioactive pharmaceutical compound derived from *Epimedium* plants, which is known due to its anti-inflammatory and antioxidant effects. Additionally, the protective effects of icariin have been studied in different pathologies through modulating intracellular pathways. In addition to the potential effect of this compound on inflammation and oxidative stress caused by SARS-CoV-2 infection, it appears to interfere with intracellular pathways involved in viral entry into the cell. Therefore, this paper aims to review the molecular mechanisms of anti-inflammatory and antioxidant properties of icariin, and hypothesizes its potential to inhibit SARS-CoV-2 entry into host cells through modulating the intracellular pathways.

Keywords Icariin · Cytokine storm · Oxidative stress · SARS-CoV-2 · COVID-19

Background

The coronavirus disease 2019 (COVID-19) epidemic originated in Wuhan, China, and it has now spread worldwide. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new member of the coronavirus family. Despite the development of vaccines, there is no definitive cure for reducing the mortality rate caused by it. Icariin (C33H40O15) is the most abundant and the main phytochemical (secondary metabolite) of the ancient Chinese medicinal plant, *Epimedium prenylflavonoids* (EP), used for its potent anti-inflammatory and antioxidant properties for centuries (Li et al. 2022). It exhibits wide positive effects on bone, cardiovascular, neurologic, lung, and liver against different pathologies (Zeng et al. 2022). Table 1 summarizes the anti-inflammatory and anti-oxidative effects of icariin in experimental studies. Although no study has been conducted to investigate the effect of this compound on COVID-19, its molecular mechanisms indicate its possible effect on various aspects of the pathophysiology of this disease. Therefore, the aim of this review is to hypothesize the therapeutic potential of icariin on molecular factors involved in SARS-CoV-2 infection.

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Anti-inflammatory properties of icariin

Cytokine storm is known as one of the main causes of mortality followed by SARS-CoV-2 infection (Ghasemnejad-Berenji 2021; Jiang et al. 2022). Elevated levels of different pro-inflammatory cytokines such as IL (interleukin)-1, IL-6, and tumor necrosis factor α (TNF-α) have been detected in COVID-19 patients associated with acute respiratory

Table 1 Anti-inflammatory and antioxidant properties of icariin

	Model	Number of animals	Effect	Result	Reference
Icariin	H9c2 cells	-	Reduce protein expression levels of Bax and cleaved-caspase 3	Protective effects against Ang II-induced apoptosis	Zhou et al. 2014
	Human brain vascular smooth muscle cells	-	Inhibit NADPH oxidase activity and reduce ROS production	Ameliorate Ang II-induced cerebrovascular remodeling	Dong et al. 2019
	BALB/c mice exposed to cigarette smoke	40	Decrease inflammatory cells and production of TNF-α, IL-8 via suppression of NF-κB	Ameliorate cigarette smoke–induced inflammatory responses	Zhou et al. 2014
	Lipopolysaccharide (LPS) stimulated RAW264.7 macrophages	-	Inhibit TNF-α production, inducible nitric oxide synthase, and cyclooxygenase-2 mRNA expression	Suppress inflammatory responses	Chen et al. 2010
	Ischemic stroke induced by cerebral ischemia–reperfusion (I/R) injury in rats	40	Reduce TNF-α expression through NF-κB suppression and PPARγ upregulation	Suppress inflammatory responses	Xiong et al. 2016
	Mice model of colitis and naive T cells	-	Inhibit the production of pro-inflammatory cytokines and expression of p-STAT1 and p-STAT3	Suppress Th1/Th17 responses	Tao et al. 2013
	Mice model of rheumatoid arthritis	-	Inhibit cathepsin K and STAT3, suppress IL-17 expression	Decrease Th17 cells and suppress inflammatory responses	Chi et al. 2014
	Ovalbumin-induced murine asthma model	120	Reduce the expression of IL-6, IL-17, and TGF-β level	Regulate Th17/Treg responses and suppress inflammatory responses	Wei et al. 2015
	Lipopolysaccharide-induced inflammation in rats lung	40	Suppress NF-κB and cycloxygenase-2	Suppress inflammatory responses	Xu et al. 2010
	Human umbilical venous endothelial cells	-	Inhibit NADPH oxidase and ROS generation, suppress NF-κB and IL-6 expression	Inhibit oxidative stress and inflammation induced by high glucose	Sun et al. 2019
	Bleomycin-induced lung fibrosis in rats	30	Suppress NF-κB	Protect against fibrosis induced by bleomycin	Du et al. 2021
	Rabbits fed a high-cholesterol diet	40	Improve the imbalance between plasminogen activator inhibitor-1 and tissue-type plasminogen activator activities	Suppress platelet activation and inhibit blood coagulation	Zhang et al. 2013
	A549 human lung epithelial cells	-	Induce Nrf2 activation, suppress ROS generation	Inhibit cigarette smoke–mediated oxidative stress	Wu et al. 2014
	Hypoxia/reoxygenation-induced ferroptosis of cardiomyocytes	-	Induce the expression of Nrf2 and HO-1	Attenuates H/R-induced ferroptosis of cardiomyocytes	Liu et al. 2021

distress syndrome (ARDS) (Jiang et al. 2022). Accordingly, anti-inflammatory agents are an important part of treatment strategies against SARS-CoV-2 infection. One of the most well-known features of icariin is its anti-inflammatory effects, which have been studied in different models. Here, the mechanism of anti-inflammatory effects of this compound is investigated.

Angiotensin II (Ang II) is the main effector molecule of the renin-angiotensin system which is thought to be involved in inducing inflammatory responses in COVID-19 patients. Decreased ACE2 levels on the cell surface followed by its endocytosis contribute to increasing Ang II, as shown in COVID-19 patients (Khezri 2021). Elevated Ang II level has been associated with different inflammatory pathologies. One of the main targets of Ang II is angiotensin type 1 receptor (AT1R), which its activation leads to induces inflammatory responses (Phillips and Kagiyama 2002). The main downstream effector of AT1R followed by Ang II binding is the PI3K/AKT signaling pathway which activates inflammatory factors such as NF-κB (El-Shoura et al. 2018). Regardless of the PI3K/AKT/NF-κB pathway activation by Ang II, it has been shown that ORF7a protein of SARS-CoV-2 activates NF-κB leading to induce the expression of pro-inflammatory cytokines such as IL-1β, IL-1α, IL-6, IL-10, IL-8, and TNF-α (Su et al. 2021). In this case, there are numerous studies indicating the effect of icariin on the activity of mentioned factors. For instance, it has been reported that icariin suppresses the destructive effects of Ang II on human umbilical vein endothelial cells (Wang et al. 2008), cardiomyocytes (Zhou et al. 2014), and cerebrovascular remodeling (Dong et al. 2019). On the other hand, it has been reported that icariin suppresses cigarette smoke–induced TNF-α expression through NF-κB inhibition (Li et al. 2014). Also, it has been indicated that icariin has protective effects against lipopolysaccharide-stimulated macrophages through NF-κB suppression leading to inhibit TNF-α expression (Chen et al. 2010). Additionally, protective effects of icariin in a rat model of cerebral ischemia–reperfusion injury have been shown to be mediated by peroxisome proliferator–activated receptors-γ (c-γ) activation and NF-κB suppression (Xiong et al. 2016).

The other main intracellular factor involved in inflammatory responses is the signal transducer and activator of transcription (STAT), which its over-activity has been detected in the kidney of COVID-19 patients (Salem et al. 2021). Also, it has been proposed that elevated level of leptin in COVID-19 patients is associated with STAT3 and AKT over-activity and pro-inflammatory cytokine expression (Wang et al. 2021). On the other hand, STAT over-activity may be involved in Th17 response in COVID-19 patients (Martonik et al. 2021). However, the inhibitory effect of icariin on STAT activity has been shown in different models. For instance, icariin has been shown to suppress Th1/Th17 responses through suppression of STAT1 and STAT3 activation leading to inhibit inflammatory responses in an animal model of colitis (Tao et al. 2013). In addition, it has been indicated that STAT3 inhibition by icariin leads to regulating Th17 activity and alleviates rheumatoid arthritis in a murine model (Chi et al. 2014). There are several studies indicating the effect of icariin on Th17 function without emphasizing the STAT activity. In this regard, it has been shown that icariin regulates Th17/Treg function in murine airways leading to reduce the expression of IL-6 and TGF-β (Wei et al. 2015).

Neutrophil infiltration to the lungs during SARS-CoV-2 infection has been shown to be closely related to lung injury (Wang et al. 2020a). Elevated expression of several adhesion molecules involved in neutrophil recruitment such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) has been detected in COVID-19 patients (Tong et al. 2020; Spadaro et al. 2021). Regarding the effect of icariin on neutrophil infiltration during inflammatory processes, it has been shown that icariin decreases neutrophil infiltration into the lung followed by lipopolysaccharide-induced acute inflammation in rats via NF-κB suppression (Xu et al. 2010). On the other hand, it has been demonstrated that icariin suppresses ICAM-1 expression via NF-κB inhibition leading to suppression of neutrophil recruitment and inhibiting lung injury in mice affected with cobra venom factor (Guo et al. 2018). In another study, it has been demonstrated that treatment of keratinocytes with icariin followed by TNF-α/IFN-γ-induced inflammation leads to inhibit the expression of IL-8, IL-1β, and ICAM-1 performing an anti-inflammatory effect (Kong et al. 2015). Additionally, icariin has been reported to suppress ICAM-1 and VCAM-1 expression and exhibits a protective effect against high glucose-induced inflammation in human umbilical vein endothelial cells (Sun et al. 2019).

One of the main consequences of cytokine storm is fibrosis in different organs especially the lungs (Grillo et al. 2021). In COVID-19 patients, Ang II-AT1R axis and elevated inflammatory cytokines are represented as the main cause of lung fibrosis (Brosnahan et al. 2020). In this case, it can be re-referred to the PI3K/AKT singling pathway, as it has been shown that Ang II-AT1R axis induces activation of this pathway leading to lung fibrosis induction (Hu et al. 2018). However, it has been demonstrated that icariin augments bleomycin-induced pulmonary fibrosis in rats by targeting the NF-κB pathway (Du et al. 2021). Based on this evidence, it can be said that negative regulation of the PI3K/AKT pathway by icariin may lead to suppression of lung fibrosis in COVID-19 patients and further studies in this regard may be constructive.

The other consequence of high levels of Ang II and cytokine storm in COVID-19 patients is blood coagulation which is closely related to the severity of the disease

(Han et al. 2020; Khezri and Ghasemnejad-Berenji 2021). Interestingly, it has been reported that platelets isolated from COVID-19 patients are over-activated due to over-activity of the PI3K/AKT signaling pathway (Pelzl et al. 2021). Since different studies have been conducted to suppress blood coagulation through inhibition of this pathway (Khezri et al. 2022), designing similar studies in order to clarifying the effect of icariin on platelet activity in COVID-19 patients can also be considered. However, previous studies have indicated the anti-platelet activity of icariin without emphasizing on mentioned factors. For instance, it has been demonstrated that icariin improves the imbalance between plasminogen activator inhibitor-1 and tissue-type plasminogen activator activities, suppresses platelet activity, and inhibits blood coagulation in rabbits fed a high-cholesterol diet (Zhang et al. 2013; Irfan et al. 2021). In addition, inhibitory effects of icariin on platelet activation have been reported in spontaneously hypertensive rats (Li et al. 2021).

Antioxidant effects of icariin

Disturbing the balance between free radicals' generation and the ability of cells to their elimination leads to oxidative stress induction (Pizzino et al. 2017). Reactive oxygen species (ROS) play a central role in alterations in pulmonary and red blood cell activity and contribute to hypoxic respiratory failure in severe cases of COVID-19 (Laforge et al. 2020). Since oxidative stress plays a crucial role in pathogenesis of respiratory viruses, especially SARS-CoV-2, therapeutic interventions to modify oxidative stress represent a rational approach for the treatment of lower respiratory tract infections (Karkhanei et al. 2021). However, there are several intracellular factors which can be examined here. Nuclear factor erythroid 2–related transcription factor (Nrf2) is one of the main transcription factors of antioxidant enzymes which its activation exhibits protective effects against different pathologies (Liu et al. 2019). Therefore, therapeutic interventions to activate it in SARS-CoV-2 infection have been highly regarded as a treatment option (Cuadrado et al. 2020). Regarding the Nrf2-activating effects of icariin, it has been shown that icariin augments cigarette smoke–induced oxidative stress in lung human epithelial cells through Nrf2 activation, increased glutathione levels, and suppression of ROS generation (Wu et al. 2014). Additionally, protective effects of icariin on hypoxia/reoxygenation-induced oxidative stress have been shown to be mediated by Nrf2-heme oxygenase 1 (HO-1) activation in cardiomyocytes (Sun et al. 2021). Also, it has been reported that icariin inhibits carrageenan-induced acute inflammation and oxidative stress in rats through increasing the Nrf2 expression and reducing NF-κB expression (El-Shitany and Eid 2019).

Hypothesis of possible effect of icariin on SARS-CoV-2 entry to the host cells

In order to study the effect of a compound on COVID-19, it is necessary to first explain its potential ability to suppress entry of the SARS-CoV-2 into the host cell. So far, four main factors are presented mediating the SARS-CoV-2 entry to host cells, including angiotensin-converting enzyme 2 (ACE2), transmembrane Serine Protease 2 (TMPRSS2), furin, and cluster of differentiation 147 (CD147).

ACE2 is an enzymatic receptor on cell surface which has been introduced as the main SARS-CoV-2 receptor because of its high expression on respiratory system cells (Jiang et al. 2022). In addition to the respiratory system, high expression of ACE2 has been shown in different other organs, including the intestine, skin, and testes (reviewed by Khezri et al. (2021)). Regarding the mechanism of SARS-CoV-2 entry to host cells through ACE2, it has been shown that clathrin-mediated endocytosis is involved (Bayati et al. 2021). In a closer inspection, it has been indicated that phosphorylation of AP2M1 which encodes the μ2 subunit of AP2 complex, an adapter protein complex for clathrin, is involved in clathrin-mediated SARS-CoV-2 endocytosis (Wang et al. 2020b). One of the main regulators of the clathrin-mediated endocytosis is the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway which is involved in entry of different viruses that use clathrin-mediated endocytosis to infect host cells (reviewed by Khezri et al. (2021)). Interestingly, the PI3K/AKT signaling pathway suppression has been shown to suppress SARS-CoV-2 entry to host cells (Sun et al. 2021). In a closer inspection, existing evidence suggests that the association between the PI3K/AKT signaling pathway and clathrin-mediated endocytosis of SARS-CoV-2 may be mediated by AP2M1. In this regard, it has been shown that activation of the PI3K/AKT signaling pathway in acute myeloid leukemia stem cells contributes to induce AP2M1 expression (Yu et al. 2021). In addition, it has been reported that sunitinib, a PI3K/AKT inhibitor, reduces SARS-CoV-2 infection via inhibiting AP2M1 phosphorylation (Wang et al. 2020b). Based on this evidence, it can be said that the effect of a compound on the activity of this pathway can affect the entry of SARS-CoV-2 into the cell. It is clearly understood that icariin suppresses the PI3K/AKT signaling pathway. In this case, it has been shown that icariin augments lipopolysaccharide-induced inflammation in rat lung tissue through inhibition of the PI3K/AKT signaling pathway (Xu et al. 2010). In addition,

it has been shown that icariin induces apoptosis of human lung adenocarcinoma cells through suppression of the PI3K/AKT pathway (Wu et al. 2019). This data suggests the probable inhibitory effect of icariin on SARS-CoV-2 through suppression of clathrin-mediated endocytosis by inhibition of the PI3K/AKT/AP2M1 pathway.

Another aspect of the study of ACE2 in COVID-19 is related to its shedding which contributes to form soluble ACE2 (sACE2) (Zoufaly et al. 2020). It is clearly understood that increased sACE2 levels suppress SARS-CoV-2 infectivity through binding to its Spike protein (Zoufaly et al. 2020). One of the main enzymes involved in ACE2 shedding is a disintegrin and metalloprotease 17 (ADAM17) which its role in suppression of SARS-CoV-2 infectivity has also been studied (Jiang et al. 2022). In this regard, although there is no evidence indicating the effect of icariin on ADAM17 expression and activity, its effect on pathways involved in ADAM17 expression can be examined. Mitogen-activated protein kinase (MAPK) is an intracellular factor which regulates ADAM17 expression positively and is involved in ACE2 shedding by mediating of ADAM17 (de Queiroz et al. 2020). On the other hand, it has been shown that icariin induces mesenchymal stem cell differentiation via MAPK activation (Wu et al. 2015). Therefore, studies can be designed to investigate the effect of icariin on the MAPK/ADAM17 pathway, ACE2 shedding, and subsequently suppression of virus infectivity.

TMPRSS2 is involved in SARS-CoV-2 fusion into the cell (Matsuyama et al. 2020). Extensive expression of TMPRSS2 in various tissues and cells introduces it as a candidate for therapeutic interventions to prevent the SARS-CoV-2 entry and replication in the host cell. Regarding the association between icariin and TMPRSS2, in a computational study, it has been shown that icariin has a strong binding affinity to TMPRSS2 which introduces it as a potential inhibitor of SARS-CoV-2 entry to host cells (Chikhale et al. 2020).

CD147 is the other known receptor for SARS-CoV-2 to enter the host cells (Ulrich and Pillat 2020). It seems that this receptor is involved in SARS-CoV-2 infectivity in cardiomyocytes as it has been reported that melatonin augments myocardial injury caused by SARS-CoV-2 through CD147 (Loh 2020). In this case, it has been indicated that icariin suppresses CD147 expression and exhibits a protective role against apoptosis in myocardial cells and it can also be considered in the case of SARS-CoV-2 infection (Shi et al. 2018).

In addition to the mentioned factors, furin and different forms of cathepsins including cathepsins B, L, and K are involved in SARS-CoV-2 Spike protein cleavage leading to its fusion to the cell (Bollavaram et al. 2021). There is no data indicating the effect of icariin on furin activity, but it serves as a cathepsin K inhibitor in different tissues. For instance, it has been shown that icariin inhibits bone degradation in an animal model of arthritis through suppression of cathepsin K (Sun et al. 2013).

Although there is not any study on the effects of icariin on the mentioned factors, in an in-silico study, it has been reported that icariin could interact with the catalytic residues of the RBD of the spike glycoprotein (Tyr505, Asn501, Ser494, Gln493, and Leu455). In addition, it was shown that icariin extensively interacts with the active amino acid residues of cathepsin B (Istifli et al. 2021).

Collectively, this data introduces icariin as a strong candidate to investigate its effects on SARS-CoV-2 infectivity through different mechanisms and designing studies in this case can be constructive.

Icariin in clinical trials

Double-blinded, placebo-controlled randomized trial studies used the purified extract of EP to examine its safety, pharmacokinetics in healthy people, and its effect on osteoporosis in post-menopausal women. The results showed no substance-related adverse effects, and the drug was well tolerated. The serum levels of EP metabolites were measured, while icariside I and icariin serum levels were undetectable (Teo et al. 2019; Yong et al. 2021). Additionally, treating late menopausal osteopenia women (lumbar spine bone densitometry T score of − 2 to − 2.5) with daily ingestion of icariin in a 24-month randomized trial showed significant improvement in bone loss prevention (Zhang et al. 2007). We found no evidence of icariin application for viral diseases in humans, while in animal studies, icariin showed survival effects for duck viral hepatitis in ducklings (Xiong et al. 2014). Collectively, these studies suggest that purified icariin can be evaluated in the design of clinical trials to evaluate its various benefits in COVID-19 patients.

Conclusion

Based on the existing evidence, icariin has been approved to be an anti-inflammatory and antioxidant agent in different pathologies. These effects have been associated with its effects on different inflammatory factors (i.e., NF-κB and STATs) which contribute to inducing the expression of pro-inflammatory cytokines, the most important of which are TNF-α, IL-1, and IL-6. These factors are involved in the induction of fibrosis in various organs, and the effect of icariin on their expression has been shown to inhibit organ fibrosis in various models. Since the role of the mentioned factors in the pathophysiology of COVID-19 has been shown, the positive effects of icariin in this disease can be considered. On the other hand, the interplay between

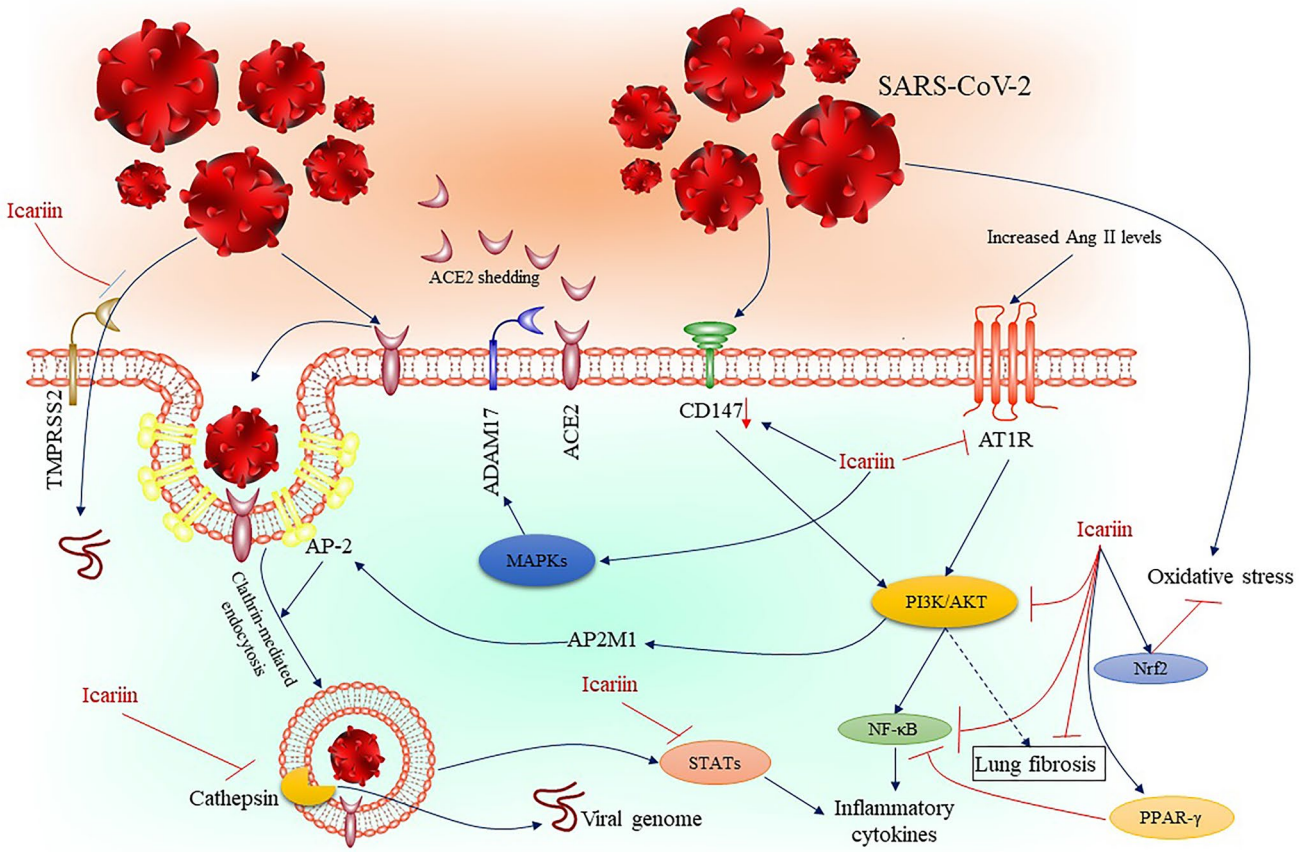

Fig. 1 The probable molecular mechanism of icariin which may be involved in hypothetical anti-SARS-CoV-2 effects

icariin and intracellular pathways involved in the entry of SARS-CoV-2 into the host cells has been investigated in non-COVID-19 models, which offers hypotheses for the beneficial effects of this compound on the disease. However, it seems that designing studies to investigate these effects in SARS-CoV-2 infection can be considered as a treatment option. Figure 1 depicts the molecular mechanisms of icariin interfering with SARS-CoV-2 infection.

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Declarations

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