

## COMMENTARY

# Hesperetin and the PI3K/AKT pathway: Could their interaction play a role in the entry and replication of the SARS-CoV-2?

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**Abstract**

Hesperetin, mainly found in citrus honey, has antioxidant, anti-inflammatory, and antiviral properties. Recently, the effect of hesperetin on different aspects of SARS-CoV-2 infection such as viral entry, replication, and inflammatory responses has attracted a lot of attention. However, the exact molecular mechanism for its effects on SARS-CoV-2 infection is not stated. The PI3K/AKT signaling pathway is an intracellular pathway involved in cell proliferation, protein synthesis, and response to environmental changes. Since the role of this pathway in the pathogenesis of SARS-CoV-2 has recently been considered, this letter assumes the probable role of this pathway in the function of hesperetin against SARS-CoV-2 infection.

**Practical applications**

In this paper, we have discussed the therapeutic effects of hesperetin on SARS-CoV-2 infection. Additionally, we have hypothesized the molecular mechanism of hesperetin in suppression of SARS-CoV-2 entry to the host cells, its replication and inhibition of inflammatory responses. Based on this evidence, the pharmacological properties of hesperetin make this natural compound a potential treatment for suppression of SARS-CoV-2 entry into host cells and the subsequent replication of viral particles.

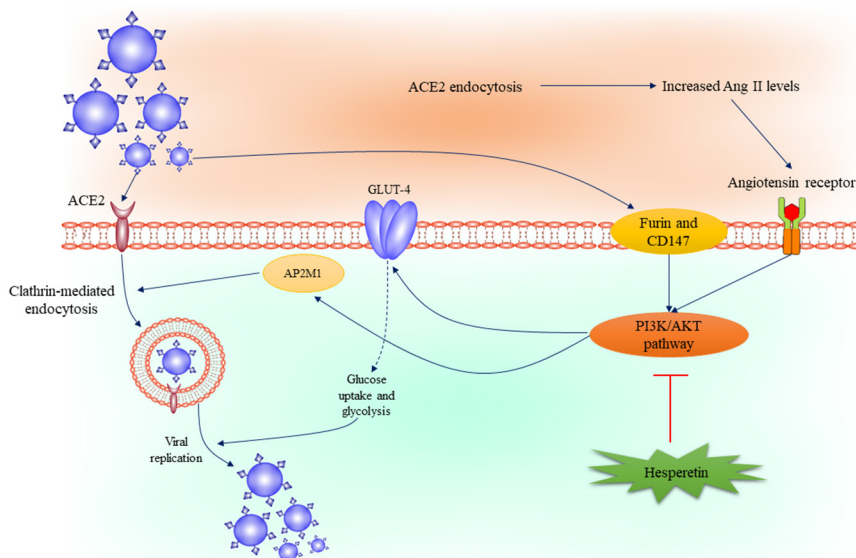
**KEYWORDS**

COVID-19, hesperetin, PI3K/AKT, SARS-CoV-2

Hesperetin is a bioactive compound which is mainly found in different food sources, especially oranges, grapefruit, lemon, and tangerines, and recently, its effects on SARS-CoV-2 have received much attention. Extensive studies have examined its role in various pathophysiological aspects of SARS-CoV-2 infection, including virus entry, inflammatory response, and oxidative stress. However, there are gaps in the expression of its exact molecular mechanism that are addressed in this letter.

Several major routes for SARS-CoV-2 entry to the host cell have been identified, including angiotensin-converting enzyme 2 (ACE2), furin, TMPRSS2, and CD147 (Khezri et al., 2021). Among these, ACE2 and TMPRSS2 have attracted more attention due to their high expression in different organs. The mechanism underlying SARS-CoV-2 entry into the host cells through ACE2 has been well studied. In this regard, it has been shown that ACE2/SARS-CoV-2

complex enters the host cell via a clathrin-mediated pathway (Bayati et al., 2021). In a closed inspection, sunitinib, a tyrosine kinase inhibitor, has been shown to suppress the phosphorylation of AP2M1, which encodes an adapter protein complex for clathrin, AP2, leading to suppress SARS-CoV-2 entry into host cells (Wang et al., 2020). On the other hand, it has been demonstrated that the PI3K/AKT signaling pathway is involved in expression of AP2M1 (Yu et al., 2021). Since sunitinib is known as a PI3K/AKT inhibitor (Makhov et al., 2012), it can be said that its effect on inhibition of SARS-CoV-2 entry to host cells may be mediated by the PI3K/AKT/AP2M1 pathway. In this case, there are several studies which indicate that inhibition of the PI3K/AKT pathway contributes to suppress entry of different viruses using the clathrin-mediated pathway (Khezri et al., 2021). There are similar studies on SARS-CoV-2, which have shown that the PI3K/AKT pathway inhibition by capivasertib



**FIGURE 1** The probable molecular mechanism of hesperetin against SARS-CoV-2 entry to the host cells and its replication

suppresses virus entry into the host cells (Sun et al., 2021). Although the effect of hesperetin on ACE2 and TMPRSS2 and inhibition of SARS-CoV-2 entry to host cells has been shown in various studies (Agrawal et al., 2021), none of these studies specify the exact mechanism. Numerous studies have suggested the role of hesperetin as an inhibitor of the PI3K/AKT pathway. For instance, it has been demonstrated that hesperetin ameliorates hepatic oxidative stress and inflammation via the PI3K/AKT pathway in oleic acid-induced HepG2 cells (Li et al., 2021). Therefore, based on the available evidence, it can be concluded that the effect of hesperetin on inhibiting SARS-CoV-2 entry into the cell may be due to its effect on the PI3K/AKT/AP2M1 pathway, and further studies in this field to identify the exact mechanism can be constructive.

In addition to entry of SARS-CoV-2 into the host cell, the effect of hesperetin on its replication may be interesting. In this context, the association between cell metabolism and viral replication can be examined. It has been demonstrated that SARS-CoV-2 affects human aortic adventitial fibroblasts through its nucleocapsid protein which leads to increased expression of glucose transporter 4 (GLUT-4) (Freda et al., 2021). On the other hand, increased GLUT-4 level is associated with increased glucose uptake by SARS-CoV-2 infected cells leading to stimulated glycolysis process, and eventually, viral replication (Malgotra & Sharma, 2021). Since the PI3K/AKT signaling pathway is involved in expression of GLUT-4, and the activation of a group of SARS-CoV-2 receptors such as CD147 activates this pathway (Khezri et al., 2022), it can be concluded that the increase in GLUT-4 expression by the virus can be mediated by the PI3K/AKT pathway. On the other hand, it has been demonstrated that hesperetin impairs glucose uptake in breast cancer cells through inhibition of GLUT-4 translocation into cell membrane via AKT inhibition (Yang et al., 2013). This mechanism can be studied in relation to the effect of hesperetin on SARS-CoV-2 replication in host cells through glucose metabolism.

Another aspect of the therapeutic role of hesperetin in COVID-19 that has not been studied is its effect on angiotensin II (Ang II), a pro-inflammatory factor involved in lung fibrosis (Khezri, 2021). Endocytosis of ACE2 along with SARS-CoV-2 contributes to increase Ang II levels, as it has been shown in patients with COVID-19 (Khezri, 2021). The effects of Ang II in inflammation and fibrosis induction are mediated by the PI3K/AKT pathway induction (Khezri, 2021). In this regard, it has been reported that hesperetin blocks the proliferation of cardiac fibroblasts induced by Ang II through AKT suppression (Yuan & Tang, 2014). Also, it has been demonstrated that hesperetin attenuates Ang II-induced collagen expression in cardiac fibroblasts (Liu et al., 2014).

In addition to mentioned points, the PI3K/AKT signaling pathway is involved in other important aspects of COVID-19 pathophysiology such as blood coagulation (Khezri et al., 2022), inflammatory responses, and oxidative stress (Khezri et al., 2021), which can be studied to investigate the antiviral effects of hesperetin. Figure 1 depicts the probable role of hesperetin in reduced SARS-CoV-2 entry into host cells and the subsequent replication of viral particles.

#### CONFLICT OF INTEREST

There are no competing interests to declare.

#### AUTHOR CONTRIBUTIONS

**Mohammad Rafi Khezri:** Design and writing manuscript; **Donya Moloodsouri:** Writing; **Morteza Ghasemnejad-Berenji:** Revise the manuscript.

#### DATA AVAILABILITY STATEMENT

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

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## REFERENCES

- Agrawal, P. K., 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. *Natural Product Communications*, 16(10), 1934578X211042540.
- Bayati, A., Kumar, R., Francis, V., & McPherson, P. S. (2021). SARS-CoV-2 infects cells after viral entry via clathrin-mediated endocytosis. *Journal of Biological Chemistry*, 296, 100306.
- Freda, C. T., Yin, W., Ghebrehiwet, B., & Rubenstein, D. A. (2021). SARS-CoV-2 proteins regulate inflammatory, thrombotic and diabetic responses in human arterial fibroblasts. *Clinical Immunology*, 227, 108733.
- Khezri, M. R. (2021). PI3K/AKT signaling pathway: a possible target for adjuvant therapy in COVID-19. *Human Cell*, 34(2), 700–701.
- Khezri, M. R., Varzandeh, R., & Ghasemnejad-Berenji, M. (2022). The probable role and therapeutic potential of the PI3K/AKT signaling pathway in SARS-CoV-2 induced coagulopathy. *Cellular & Molecular Biology Letters*, 27(1), 1–10.
- Khezri, M. R., Zolbanin, N. M., Ghasemnejad-Berenji, M., & Jafari, R. (2021). Azithromycin: Immunomodulatory and antiviral properties for SARS-CoV-2 infection. *European Journal of Pharmacology*, 905, 174191.
- Li, J., Wang, T., Liu, P., Yang, F., Wang, X., Zheng, W., & Sun, W. (2021). Hesperetin ameliorates hepatic oxidative stress and inflammation via the PI3K/AKT-Nrf2-ARE pathway in oleic acid-induced HepG2 cells and a rat model of high-fat diet-induced NAFLD. *Food & Function*, 12(9), 3898–3918.
- Liu, Y., Tang, Q., Li, L., Liu, W., Jiao, R., & Deng, W. (2014). Hesperetin attenuates angiotensin II-induced collagen expression in cardiac fibroblasts in vitro. *Zhonghua Yi Xue Za Zhi*, 94(36), 2852–2856.
- Makhov, P. B., Golovine, K., Kutikov, A., Teper, E., Canter, D. J., Simhan, J., Uzzo, R. G., & Kolenko, V. M. (2012). Modulation of Akt/mTOR signaling overcomes sunitinib resistance in renal and prostate cancer cells. *Molecular Cancer Therapeutics*, 11(7), 1510–1517.
- Malgotra, V., & Sharma, V. (2021). 2-Deoxy-D-glucose inhibits replication of novel coronavirus (SARS-CoV-2) with adverse effects on host cell metabolism.
- Sun, F., Mu, C., Kwok, H. F., Xu, J., Wu, Y., Liu, W., Sabatier, J. M., Annweiler, C., Li, X., Cao, Z., & Xie, Y. (2021). Capiwasertib restricts SARS-CoV-2 cellular entry: A potential clinical application for COVID-19. *International Journal of Biological Sciences*, 17(9), 2348–2355.
- Wang, P.-G., Tang, D. J., Hua, Z., Wang, Z., & An, J. (2020). Sunitinib reduces the infection of SARS-CoV, MERS-CoV and SARS-CoV-2 partially by inhibiting AP2M1 phosphorylation. *Cell Discovery*, 6(1), 1–5.
- Yang, Y., Wolfram, J., Boom, K., Fang, X., Shen, H., & Ferrari, M. (2013). Hesperetin impairs glucose uptake and inhibits proliferation of breast cancer cells. *Cell Biochemistry and Function*, 31(5), 374–379.
- Yu, D.-H., Chen, C., Liu, X.-P., Yao, J., Li, S., & Ruan, X.-L. (2021). Dysregulation of miR-138-5p/RPS6KA1-AP2M1 is associated with poor prognosis in AML. *Frontiers in Cell and Developmental Biology*, 9, 270.
- Yuan, L., & Tang, Q. (2014). GW25-e3242 Hesperetin blocks the proliferation of cardiac fibroblast cells induced by Ang II through AKT/GSK3 $\beta$  signaling pathway. *Journal of the American College of Cardiology*, 64(16S), C15.

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