



# Potential therapeutic effects of some flavonoids on coronavirus disease 2019

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## Dear Editor,

The novel coronavirus disease 2019 (COVID-19), or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in China (Guan et al., 2020). This coronavirus bind to the angiotensin-converting enzyme-2 (ACE2) receptor for infection the cells by transmembrane protease serine 2 on the surface of the host cell (Hoffmann et al., 2020). Following infection by SARS-CoV-2, a large amounts of pro-inflammatory mediators such as, interferon alpha, interleukin (IL)-1b, IL-6, IL-12, IL-18, IL-33, and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) are release by immune cells (Hoffmann et al., 2020).

Various biological compounded such as of flavonoids, have therapeutic effects including, anti-inflammatory and anti-asthmatic (Khazdair et al., 2019; Kianmehr and Khazdair, 2020), antioxidant and immunomodulatory effects (Khazdair et al., 2018; Khazdair and Boskabady, 2019). The anti-SARS coronavirus effects of phenolic compounds derivate of the plants were also reported (Lin et al., 2005). Therefore, the protective effects of some flavonoids including kaempferol and quercetin on SARS-CoV-2 are suggested.

The potency of kaempferol, for blocking of 3a channel (a cation channel) which expressed in the infected cells by SARS-CoV was showed. Kaempferol (20 $\mu$ M) blocked more than 50% of 3a channel in *Xenopus* oocyte by voltage-clamp techniques (Schwarz et al., 2014). Then, kaempferol by inhibiting of this ion channel can inhibit virus release. In an in vivo study, kaempferol (15mg/kg)

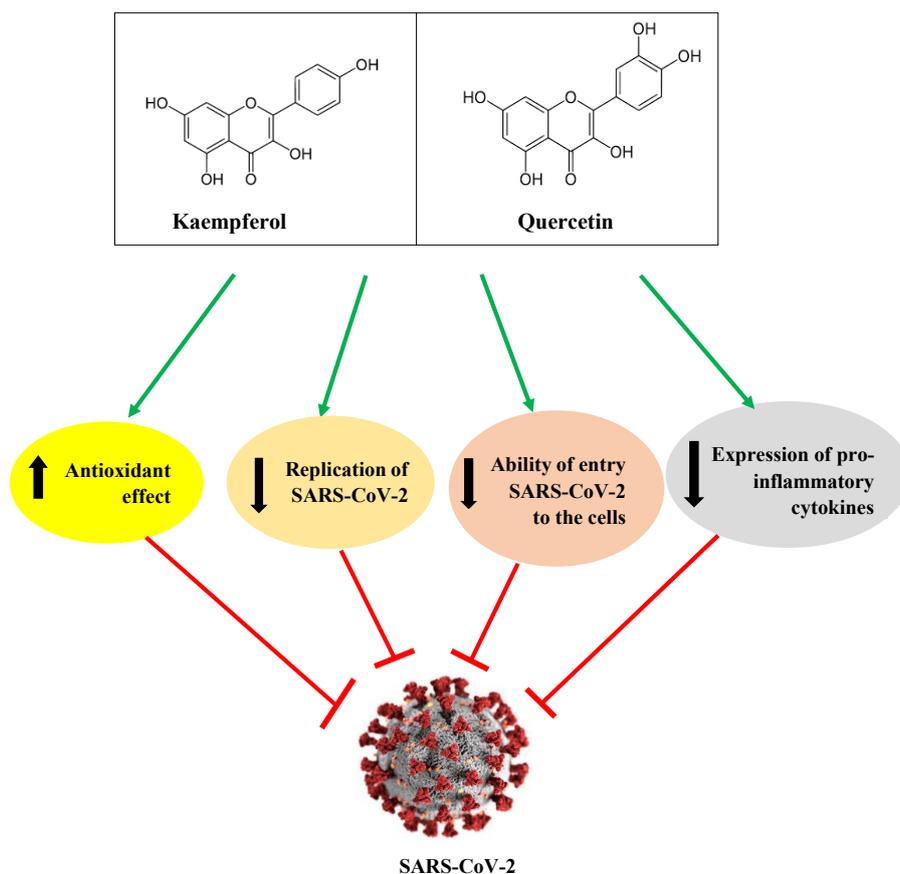
reduced pulmonary edema, permeability of pulmonary capillary and lung dry weight. Furthermore, kaempferol declined activity of myeloperoxidase, as well as the inflammatory cells in infected mice with H9N2 virus induced acute lung injury (Zhang et al., 2017). In addition, administration of kaempferol decreased production of reactive oxygen species (ROS) and malondialdehyde, reduced over production of IL-1b, TNF- $\alpha$  and IL-6, while increased the levels of antioxidant parameters such as, superoxide dismutase activity in H9N2 infected mice (Zhang et al., 2017).

The antiviral properties of the other flavonoid, quercetin have been reported. Administration of quercetin showed therapeutic effects on SARS-CoV-2 via acting on the pro-inflammatory mediators, caspase 3 and mitogen-activated protein kinase (MAPK)-1 activity and C type lectin receptor signaling pathway (Colunga Biancatelli et al., 2020). The results of a study showed that quercetin block the binding sites on the superficial spikes of the SARS-CoV-2 and to prevent the spread of the virus (Vijayakumar et al., 2020). The ability of quercetin for inhibiting main protease -3C $\text{pro}$ - from MERS-CoV and SARS-CoV-2 has also been documented (Abian et al., 2020). Alteration of human genes expression encoding proteins which is targeted by SARS-Cov-2 is also attributed to quercetin. The results of a silico modelling study showed that quercetin has high affinity for binding to the interface between viral spike protein of SARS-CoV-2 and the epithelial cell ACE2 protein (Williamson and Kerimi, 2020). It has been reported that quercetin

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**FIGURE 1.** Possible therapeutic effects of flavonoids on SARS-CoV-2.

and kaempferol presented in *Ficus benjamina* leaves inhibited Herpes Simplex Virus 1 (Yarmolinsky et al., 2012). Quercetin along with kaempferol has been proposed to bind the proteins of SARS-CoV-2 which is involved in inflammatory responses and modulation of immune system. They could affect the expression of cyclooxygenase 2, ILs, MAPKs and alter the signaling cascade related to toll-like receptors and JAK-STAT path way (Huang et al., 2020; Wang, 2020). According scientific evidences, quercetin and kaempferol derived from *Huoxiang zhengqi* could inactive SARS-CoV-2. This antiviral effect is associated with inhibition of replication of SARS-CoV-2 by affecting PI3K-Akt signaling pathway (Huang et al., 2020). It is also predicted that quercetin and kaempferol have a high affinity for SARS-CoV-2, 3CL hydrolase. These two flavonoids can join to ACE2 and affect intracellular signaling cascades including BCL2, PTGS2 and caspase 3 for inhibiting viral infectious resulting from hepatitis C, herpesvirus, measles and Epstein-Barr virus (Jimilihan, 2020). The possible therapeutic effects of flavonoids on COVID-19

is showed in Figure 1.

In conclusion, quercetin and kaempferol inhibited binding of viral spike protein of SARS-CoV-2 and the epithelial cell ACE2, protein replication of SARS-CoV-2 and virus release. Quercetin and kaempferol also decreased production of ROS and pro-inflammatory cytokines, while increased the levels of antioxidant parameters. Therefore, quercetin and kaempferol may be used as a potent drug for prevention and/or treatment of SARS-CoV-2.

**Conflict of interest**

The author declared no conflicts of interest in this article.

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