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Potential effects of a flavonoid, hesperidin on SARS-CoV-2 disease

To the Editor

The novel coronavirus, COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in China in December 2019 [1].

SARS-CoV-2 uses the receptor angiotensin-converting enzyme 2 (ACE2) for infection by the transmembrane protease, serine 2 (TMPRSS2) on the surface of the host cell entry [2]. SARS-CoV-2 is not only rapidly spreading but has become a global pandemic that may challenge the economic, medical and public health of the world [3]. Following infection by SARS-CoV-2, cytokine storm is mediated by the release of large amounts of IFN-α, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc. by immune effector cells [4, 5]. Various biological compounds such as of flavonoids, have been showed as anti-asthmatic [6, 7], therapeutic, antioxidant, antiviral and with other properties in nature [8, 9]. Anti-SARS coronavirus 3C-like protease effects of plant-derived phenolic compounds were also reported [10]. Hesperidin is a common flavone glycoside found in citrus fruit such as lemons [11]. The virions load in hesperidin-treated Madin-Darby canine kidney (MDCK) cells were 148-fold less than that of the untreated MDCK cells infected by influenza virus. Hesperidin (100 μM) also decreased viral RNA level and enhanced antiviral state-associated genes expression in the uninfected A549 cells [12].

The inhibitory effect of hesperidin (0–25 mM) on influenza A virus (IAV) infected MDCK cells induced distinct reduction in IAV replication. Hesperidin had no cytotoxic effects on MDCK cells [13]. It is the compound that could target the binding interface between SARS-CoV-2 Spike and ACE2 human receptors [14]. It has been reported that hesperidin strongly binds to the active site of RNA dependent RNA polymerase (RdRp), which catalyzes SARS-CoV-2 RNA replication [15].

Hesperidin (2.0 mg/mL) significantly reduced expression of pro-inflammatory cytokines in human osteoarthritis (OA) chondrocytes [16].

The effects of hesperidin (5, 10, 50 and 100 μM) on hydrogen peroxide (H_2O_2) induced oxidative stress damages to chondrocytes, downregulated the mRNA levels of COX-2, IL-1β, TNF-α, MMP-3, MMP-9, and upregulated IL-10, TIMP-1, SOX9 [17]. Treatment of *Aeromonas hydrophila*-infected mice with hesperidin (250 mg/kg b.wt.), significantly suppressed inflammatory response through reduction of reactive oxygen species (ROS) production and adhesion molecules expression, as well as an increase of CD4+/CD8+ cell ratio [18]. Hesperidin (100 mg/kg. b.w) also reduced lipid peroxidation and inflammatory mediators (IL-1 β and TNF-α), while increased anti-inflammatory cytokines (IL-4 and IL-10) in induced Parkinson's disease in male C57BL/6 mice [19].

Nitric oxide (NO) has the potential therapeutic effects on acute respiratory distress syndrome in patients with COVID-19, and inhaled nitric oxide may become an alternate rescue therapy in patients with COVID-19 [20]. NO may inhibit the early stage in viral replication and could prevent viral spread, and recovery of patients [21]. Treatment of bovine aortic endothelial cells (BAEC) with hesperedin (10 μM for 5 h) stimulated production of NO [22]. The effect of hesperidin (15 and 30 mg/kg) on cardiovascular remodeling in rats significantly reduced oxidative stress markers, TNF-α, TGF-β1, and enhanced plasma

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nitric oxide metabolite (NOx) in L-NAME-induced hypertension in rats [23]. The results of a review of different studies in China showed that less than 10% of smokers infected with COVID-19 [24]. The intermittent bursts of high NO concentration in cigarette smoke may be a protective mechanism against SARS-CoV-2 [25].

Hesperidin may be used as a promising drug candidate for the prevention and treatment of SARS-CoV-2 due to antiviral, anti-inflammatory and antioxidant properties. Furthermore, hesperidin interferes with viral entry through ACE2 receptors, release of NO into the blood stream and improved immune system.

Conflict of interest

The author declares no conflicts of interest.

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