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COMMENTARY

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Immunomodulatory and anti-inflammatory potential of crocin in COVID-19 treatment

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Abstract

The current COVID-19 pandemic is one of the most devastating events in recent history. In the lack of a specific treatment and vaccine for this novel infection, finding effective drugs against this infection is crucial. We suggest the hypothesis that crocin, the main carotenoid of saffron, has the potential to limit the progression and severity of the SARS-CoV2 infection for several reasons: (a) crocin possesses powerful antioxidant properties, (b) crocin can alleviate the uncontrolled cytokine production responsible for acute lung injury, (c) crocin can upregulate PPARγ and downregulate NF-κB expression which leads to a wide range of immunomodulatory and anti-inflammatory effects, and (d) crocin can reduce the viral-induced oxidative stress and downregulates ACE2 expression by activating Nrf2 pathway. We hope our hypothesis, corroborated by preclinical evidence, will inspire further targeted studies to test crocin as a beneficial drug against the SARS-CoV2 infection.

Practical applications

Crocin is a natural antioxidant and the main active carotenoid components of saffron. We suggest the hypothesis that crocin has the potential to limit the progression and severity of the SARS-CoV2 infection because of its antioxidant and anti-inflammatory properties. Furthermore, this compound may prevent viral entry to host cells and reduce SARS-CoV2-induced lung injury. Therefore, we suggest further clinical studies on the effects of crocin against SARS-Cov-2 infection.

KEYWORDS

COVID-19, crocin, NF-κB, Nrf2, PPARγ, SARS-CoV2

Dear Editor,

Crocin is a natural antioxidant and the main active carotenoid components of Crocus sativus line (saffron). The carotenoid family has a polyene backbone containing conjugated double bonds in their molecular structure that is responsible for their strong antioxidant properties (Hashemzaei et al., 2020). Viral infections could evoke "cytokine storm" that leads to lung capillary endothelial cell activation, neutrophil infiltration, subsequent inflammation, and increased oxidative stress which may lead to lung cells apoptosis (Wang et al., 2010). Crocin has been shown to have an antioxidant, anti-inflammatory, and antiapoptotic effects. It has been shown that crocin can modulate NF-κB and Mitogen-activated protein kinase (MAPK) pathways and control the expression of genes encoding the inflammatory cytokines (e.g., TNF-α, IL-1, IL-2, and IL-6) (Zeinali et al., 2019). It is believed that excess oxidative stress plays a key role in the pathogenesis of SARS-CoV-2 infection by unbalancing the immunological tolerance, increasing inflammatory mediators, and inducing apoptotic cell death (Delgado-Roche & Mesta, 2020). A recent study has shown that crocin could protect lung tissue against cigarette smoke-induced oxidative stress by nuclear erythroid-related factor 2 (Nrf2) modifications (Dianat et al., 2018). Furthermore, it has been reported that crocin ameliorates bleomycin-induced pulmonary fibrosis by its anti-inflammatory, antioxidant, and immunomodulatory properties (Zaghloul et al., 2019). Furthermore it

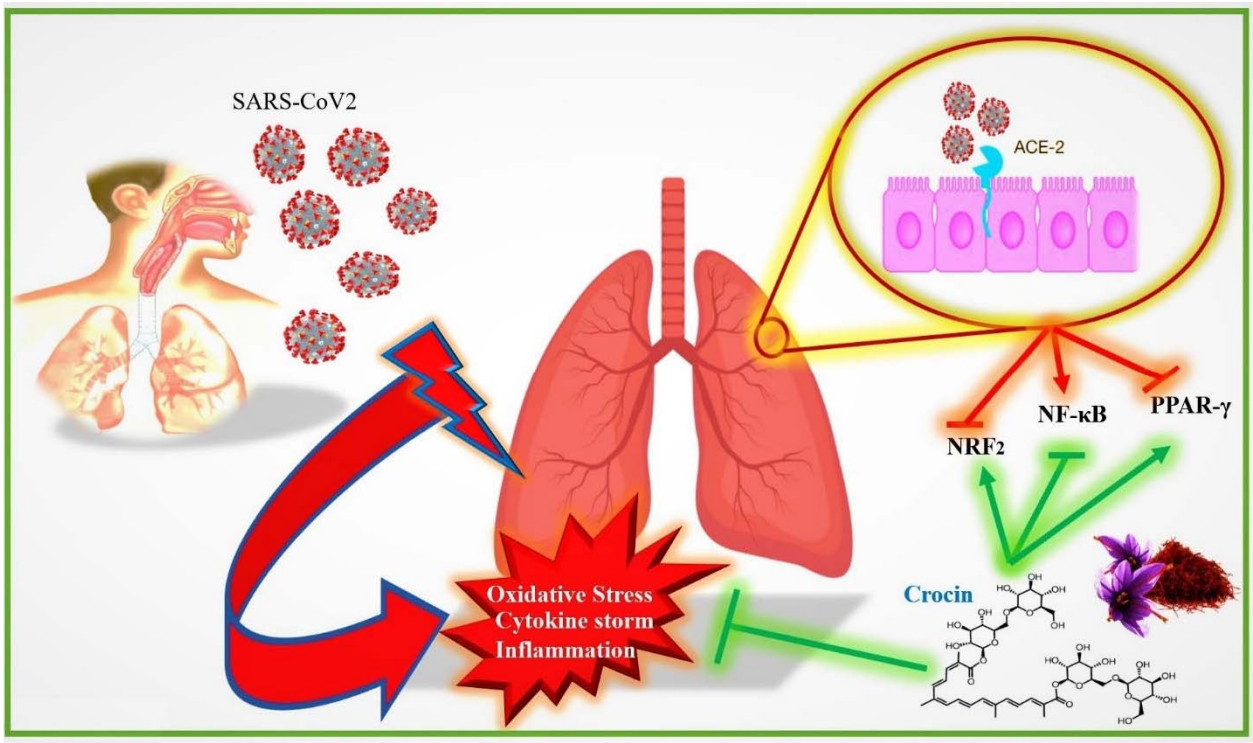

FIGURE 1 The potential of Crocin in SARS-CoV2 infection. The SARS-CoV2 induces cytokine storm, oxidative stress, and inflammation by activating NF-κB and inhibiting NRF2 and PPAR-γ. Crocin recognizes several receptor targets and displays a multifaceted immunomodulatory, anti-inflammatory, and anti-oxidative activity that could limit the severity of SARS-CoV2 infection. Crocin could downregulate NF-κB and upregulate PPAR-γ and Nrf2 expression which lead to repression in oxidative stress, cytokine storm, and subsequent inflammation

downregulates NF-κB activation in lung tissue and T cells (Du et al., 2018). The stimulation of Nrf2 plays a key role in protecting lung from severe injury. It has been reported that, crocin induces the upregulation of Nrf2 (Akbari et al., 2017). Since the NF-κB and Nrf2 are involved in the CoV-induced acute lung injury (Cecchini & Cecchini, 2020), therefore, crocin may inhibit viral-induced inflammation by inhibiting NF-κB and enhance the capacity of the oxidative stress defense system of the body by the activation of Nrf2. A recent study has indicated that Nrf2 activation downregulates ACE2 expression, and its deficiency upregulates the ACE2 receptor (McCord et al., 2020). The entry of SARS-CoV-2 into human cells is facilitated by the interaction of a receptor-binding domain in its viral spike glycoprotein ectodomain with the ACE2 receptor, therefore, activation of Nrf2 by crocin may reduce the expression of ACE2 which could be beneficial in preventing viral entry to host cells. Furthermore, since crocin represses the inflammatory process by reducing cytokine production and oxidative stress; it might play a similar role in protecting against lung injury associated with COVID-19 (Figure 1). In addition to directly causing an improvement in lung dynamics, crocin could significantly counteract the onset of the cytokine storm from resident macrophages. Therefore, crocin may potentially block acute effects of COVID-19, and its beneficial effects may extend to protecting other organs from the cytokine storm and reducing mortality. Another possible beneficial effect of crocin on COVID-19 could be related to the ability of this natural compound on upregulating of PPAR-γ expression. PPAR-γ acts on the transcription of the upstream inflammatory genes, thus preventing the cytokine over-production and becoming an attractive target for immunomodulatory (Esposito et al., 2020). It has been reported that stimulation of PPAR-γ can exert a regulatory role on the cytokine storm induced by viral infections. Reductions in PPAR-γ from SARS-CoV-2 may be an important effector of pulmonary inflammation and mechanistically involved in the pathogenesis of acute lung injury (Ciavarella et al., 2020). As such, use of crocin may serve a useful therapeutic role by helping to reverse the inflammatory changes induced by SARS-CoV-2. Overall, the well-documented anti-oxidative, anti-inflammatory, and immunomodulatory effects of crocin along with the anti-fibrotic and pulmono-protective effects of this phytochemical make it a potential herbal candidate as adjuvant therapy for patients with COVID-19. The importance of this letter is due to the fact that crocin is a nutraceutical that could be safely used in patients with COVID-19. Therefore, we suggest further clinical studies on the effects of crocin against SARS-Cov-2 infection.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Morteza Ghasemnejad-Berenji: Conceptualization; Writing-original draft.

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