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LETTER TO THE EDITOR

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Therapeutic potential of loureirin A against SARS-CoV-2 infection

To the Editor,

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an extraordinary threat to the global healthcare system. Coronavirus disease 2019 (COVID-19) is characterized by a wide clinical spectrum, the importance of which are coagulopathies and acute respiratory distress syndrome (ARDS) followed by a cytokine storm. Loureirin A, a flavonoid from the medicinal herb Dragon's Blood, is known for its antiinflammatory and anticoagulant properties. According to existing evidence, the mechanism of action of this flavonoid seems to interfere with some of the factors involved in the pathophysiology of COVID-19. Therefore, this letter aims to present loureirin A as a suitable treatment option in COVID-19 for further investigations.

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected the global health systems for more than 2 years. Although increased global access to vaccines has reduced the dissemination of the disease, no definitive cure has yet been found. New therapeutic strategies can be developed based on the mechanisms of the virus's cellular entry and the consequent pathophysiology of COVID-19. Loureirin A is a flavonoid extracted from the Chinese traditional medicine compound Dragon's Blood, which is historically used for antiinflammatory, antioxidant, and anticoagulant properties (Hu et al., 2020). Of note, Dragon's Blood has shown a high safety profile with no side effects or toxicities reported to date (Y. Liu et al., 2021). Based on the existing evidence, this letter is aimed to propose the possible effects of loureirin A for reducing the pathological effects of COVID-19.

Several cell entrance mechanisms have been introduced for the SARS-CoV-2 including angiotensin converting enzyme 2 (ACE2), CD147, furin, and TMPRSS2 (Khezri, Zolbanin, Ghasemnejad-Berenji, & Jafari, 2021). Among these, ACE2, which is a cell surface enzymatic receptor, has been shown as the main mechanism of cellular entry for SARS-CoV-2 (Yan et al., 2020). When bound to ACE2 via its Spike protein, SARS-CoV-2 is internalized via endocytosis along with the receptor. This contributes to reduced ACE2 levels on the cell surface, which leads to increased angiotensin II, a pro-inflammatory factor involved in lung fibrosis in COVID-19 patients (Khezri, 2021). Another intracellular pathway involved in regulation of SARS-CoV-2 entry to host cells is the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway, which regulates clathrin-mediated endocytosis of SARS-CoV-2 into the host cell (Sun et al., 2021). It is reported that this pathway is the downstream target of CD147 and furin, other SARS-CoV-2 receptors in host cells (Khezri, 2021). On the other hand, the PI3K/AKT signaling pathway is also involved in the activation of inflammatory factors such as nuclear factor kappa B (NF-κB) and activated protein 1 (AP-1) (X. Liu et al., 2014). Moreover, it is shown that activation of the PI3K/AKT signaling pathway induces fibrosis in different organs, including that of lungs (Saito et al., 2017). Relevant to this proposed effect of loureirin A on SARS-CoV-2, loureirin A is known as a general PI3K/AKT inhibitor (Hao et al., 2015; Hu et al., 2020). Although different isoforms of PI3K can have different activities in different organs, more studies are needed to determine the effect of this compound on different isoforms. It is shown that loureirin A suppresses the expression of inflammatory cytokines by inhibiting AKT/NF-κB in an animal model of osteoarthritis (Hu et al., 2020). Also, in this study, it was shown that loureirin A ameliorates IL-1β induced oxidative stress. Furthermore, oral treatment of myocardial infarction rats with Dragon's Blood led to reduced oxidative stress markers (i.e., superoxide dismutase) and inflammatory mediators (i.e., IL-6 and TNF-α) (Lyu et al., 2022). However, it can be speculated that PI3K/AKT inhibition by loureirin A, in addition to potentially beneficial antiinflammatory activities, may suppress SARS-CoV-2 entry into the host cells via ACE2 through blockade of clathrin-mediated endocytosis.

Moreover, one of the most serious complications of SARS-CoV-2 infection is blood coagulation, which is significantly associated with mortality (Ibrahim & Ellakwa, 2021). The PI3K/AKT signaling pathway plays a crucial role in coagulopathies during different pathologic conditions through inducing platelet activation and expression of coagulant factors (Khezri, Varzandeh, & Ghasemnejad-Berenji, 2022). Interestingly, it is shown that this pathway is involved in SARS-CoV-2-induced coagulopathy (Pelzl et al., 2021). In this regard, a study by Hao et al. (2015) indicates the antiplatelet activity of loureirin A (Hao et al., 2015). In this study, it was shown that the effect of loureirin A on platelet activation was directly mediated through PI3K/AKT inhibition. Additionally, in a clinical trial evaluating the effects of Dragon's Blood on thrombosis (Liang et al., 2021), Dragon's Blood showed antithrombotic properties, which is similar to that of low molecular weight heparin. These findings confirm the potential of loureirin A in treating coagulopathies with similar mechanistic backgrounds to that of COVID-19 infection.

Collectively, we hypothesize that loureirin A may have potentially beneficial effects on different pathologies of SARS-CoV-2 infection including the inflammatory and coagulation components, and propose that controlled preclinical and proof-of-mechanism studies in relevant models may be worthy of investigation.

CONFLICT OF INTEREST

There are no competing interests to declare.

AUTHOR CONTRIBUTIONS

Mohammad Rafi Khezri: Design and writing the manuscript; Donya Moloodsouri: Writing; Darya Hodaei: Revision and thought redirection; Morteza Ghasemnejad-Berenji: Revised 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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