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Is hesperidin essential for prophylaxis and treatment of COVID-19 Infection?

Yusuf A. Haggag\textsuperscript{a,⁎},1, Nahla E. El-Ashmawy\textsuperscript{b}, Kamal M. Okasha\textsuperscript{c}

\textsuperscript{a} Department of Pharmaceutical Technology, Faculty of Pharmacy, Tanta University, Tanta, Egypt
\textsuperscript{b} Department of Biochemistry, Faculty of Pharmacy, Tanta University, Tanta, Egypt
\textsuperscript{c} Internal Medicine and Nephrology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

\textbf{A R T I C L E   I N F O}

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\textbf{A B S T R A C T}

SARS-CoV-2 or COVID-19 is representing the major global burden that implicated more than 4.7 million infected cases and 310 thousand deaths worldwide in less than 6 months. The prevalence of this pandemic disease is expected to rise every day. The challenge is to control its rapid spread meanwhile looking for a specific treatment to improve patient outcomes. Hesperidin is a classical herbal medicine used worldwide for a long time with an excellent safety profile. Hesperidin is a well-known herbal medication used as an antioxidant and anti-inflammatory agent. Available shreds of evidence support the promising use of hesperidin in prophylaxis and treatment of COVID 19. Herein, we discuss the possible prophylactic and treatment mechanisms of hesperidin based on previous and recent findings. Hesperidin can block coronavirus from entering host cells through ACE2 receptors which can prevent the infection. Anti-viral activity of hesperidin might constitute a treatment option for COVID-19 through improving host cellular immunity against infection and its good anti-inflammatory activity may help in controlling cytokine storm. Hesperidin mixture with diosmin co-administered with heparin protect against venous thromboembolism which may prevent disease progression. Based on that, hesperidin might be used as a meaningful prophylactic agent and a promising adjuvant treatment option against SARS-CoV-2 infection.

COVID-19 a public ongoing health disease

At the end of December 2019, pneumonia of unknown origin was detected in the hospitals of Wuhan city, China, and reported to the WHO country office for the first time \cite{1–3}. After a few days, the Chinese government has confirmed the human-to-human transmission of the new infectious respiratory disease \cite{4}. At the end of January 2020, the WHO declared the outbreak of severe acute respiratory syndrome (SARS), caused by a novel coronavirus (SARS-CoV-2), as an international public health emergency. The disease termed coronavirus 19 (COVID-19) rapidly transmitted from China to all over the world and subsequently the WHO declared it a global pandemic disease. The virulent virus structure is closely related to (SARS-CoV) strain with a single-stranded positive-sense RNA composition \cite{5}.

This pandemic disease is particularly of major importance to the whole world and especially to countries with a heavy population like Egypt. There is a critical need for emergent, continuous, and cost-effective health care delivery to infected people. Early detection and strategies for prevention of progression of COVID-19 would make a major difference for infected patients and would also be economically beneficial for a resource-constrained country.

People infected with COVID-19 may have no symptoms but still, act as a source of infection to other surrounding persons. The most common clinical manifestations following infection range from mild symptoms of (generalized fatigue, dry cough, low-grade fever, and sore throat) to severe symptoms of (typical severe acute respiratory distress syndrome (ARDS) and pneumonia) \cite{6}. Although the tremendous scientific research effort is focusing mainly on the use of antiviral drugs, certain drug repurposing, and vaccine production for the treatment of COVID-19 patients, there is no specific cure or vaccine for treatment up till now. New drug development is a time-consuming process so that drug repositioning may be the optimum solution to control this pandemic infection.

Hesperidin

Hesperidin is a common flavone glycoside found in citrus fruit such as lemons and sweet oranges \cite{7,8}. Hesperidin has several pharmacological activities such as anti-atherogenic, antihyperlipidemic, anti-diabetic, venotonic, cardioprotective, anti-inflammatory, and...
antihypertensive actions. The anti-inflammatory activity of hesperidin was mainly attributed to its antioxidant defense mechanism and suppression of pro-inflammatory cytokine production [7]. Hesperidin exhibited anti-viral activity against the influenza virus through a significant reduction of virus replication. Treatment of infected cells with hesperidin enhanced cell-autonomous immunity via activation and upregulation of p38 and JNK expression which is essential for cell defense mechanisms against influenza virus [9].

Hesperidin has been used as an herbal medicine for a long time. The safety of hesperidin was confirmed by FASEB (Federation of American Societies of Experimental Biology) upon request of the FDA. Toxicity studies have confirmed the high safety profile of hesperidin after oral intake. Results from oral toxicity studies showed the absence of adverse side effects after oral hesperidin ingestion of more than 2 g/kg [10].

Dafon 500 mg is a marketed tablet dosage form containing a micronized flavonoid mixture of 50 mg of hesperidin and 450 mg of diosmin which used as vasoprotective venotonic agent [10]. This hesperidin mixture is characterized by its high safety profile. Continues oral administration for hesperidin mixture to rats for 13 and 26 weeks, using a very high dose of 35-fold of the daily dosage showed no toxicity with a high LD50 value of more than 3 g/kg [10].

Fig. 1. Effect of hesperidin on prophylaxis and treatment of COVID-19.
severe infected cases [20].

A prophylactic dose of heparin (with low molecular weight, LMWH) is recommended for protection against venous thromboembolism in COVID-19 hospitalized patients [20]. In this context, it is essential to highlight the role of concomitant administration of hesperidin and diosmin mixture with heparin for protection against thromboembolism. Results from previous clinical trials that used Daflon 500 mg with LMWH confirmed the significant effect of this combination compared to LMWH alone in preventing the incidence of pulmonary embolism and deep vein thrombosis. Therefore, co-administration of LMWH and Daflon 500 mg can significantly inhibit clot formation and prevent disease progression [21].

Conclusions

Hesperidin is an old herbal medicine which has a long history of eating. Fortunately, it is a commonly available drug all over the world. Hesperidin used to treat vascular diseases in Europe and Australia and distributed with vitamin C as a dietary supplement in the USA. A drink powder of hesperidin was approved for health use in China and Japan. Hesperidin is a promising drug candidate for the prevention and treatment of COVID-19. To sum it up, hesperidin interferes with viral entry through ACE2 receptors, improves the host cellular immunity, minimizes the release of inflammatory mediators and its mixture protects against venous thromboembolism. We are planning to register a clinical trial on ClinicalTrials.gov to evaluate the clinical efficacy of hesperidin against COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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