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Vitamines C, D, and quercetin in the prevention and treatment of SARS-CoV-2

Vitamine C, D, và quercetin trong quá trình ngăn ngừa và điều trị SARS-CoV-2

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Abstract

The SARS-CoV-2 pandemic outbreak since December 2019 that causing COVID-19 disease is continuing to bring the world catastrophic consequences on human health and healthcare systems, not to mention many more serious social and economic issues. Different approaches have been used to combat the virus. While vaccines have been developed at unprecedented speed and urgently approved in many countries, different drugs have been tested or redirected for treatment at different stages of the diseases. However, these drugs only showed little or no efficiency. Alternatively, studies are demonstrating the roles of vitamins in the anti-inflammation, immune-boosting and prevention of SARS-CoV-2. This article resumes the latest discoveries about dietary supplements such as ascorbic acid (vitamin C), cholecalciferol (vitamin D) and quercetin in the prevention and treatment of SARS-CoV-2.

Keywords: SARS-CoV-2; COVID-19; quercetin; Vitamin C; Vitamin D.

Tóm tắt

Đại dịch SARS-CoV-2 bùng phát từ tháng 12 năm 2019 gây ra bệnh COVID-19 đang tiếp tục mang lại hậu quả thảm khốc cho thế giới đối với sức khỏe con người và hệ thống chăm sóc sức khỏe, cũng như nhiều vấn đề kinh tế và xã hội nghiêm trọng khác. Các cách tiếp cận khác nhau đã được sử dụng trong cuộc chiến với virus. Trong khi vắc-xin đã được phát triển với tốc độ chưa từng có và được cấp phép sử dụng khẩn cấp ở nhiều quốc gia, các loại thuốc khác nhau đã được thử nghiệm hoặc chuyển hướng điều trị ở các giai đoạn khác nhau của bệnh. Tuy nhiên, những loại thuốc này chỉ cho thấy hiệu quả đối với việc điều trị các triệu chứng. Bên cạnh đó, đã có những nghiên cứu chứng minh vai trò của vitamin trong việc tăng cường sức đề kháng và phòng ngừa SARS-CoV-2. Bài báo này tóm tắt các nghiên cứu mới nhất về các chất bổ sung trong chế độ ăn uống như axit ascorbic (vitamin C), cholecalciferol (vitamin D) và quercetin trong việc phòng ngừa và điều trị SARS-CoV-2.

Từ khóa: COVID-19; SARS-CoV-2; Vitamin C; Vitamin D; Quercertin

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1. Introduction

The severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2) pandemic outbreak now has counted more than 116 million cases and 2.5 million deaths worldwide. Despites of many strict measures to control the virus transmission, the situation is not at ease for many regions in the world, in particular for the United States (US), Brazil, India, Iran, Russia, Spain and the United Kingdom (UK). For those seven most affected countries, the reported cumulative number of cases by number of days since 10000 cases is reaching 30 millions while the cumulative number of deaths by number of days since 100 days is over 500000 for US (**Figure 1**), continuing breaking all records [1].

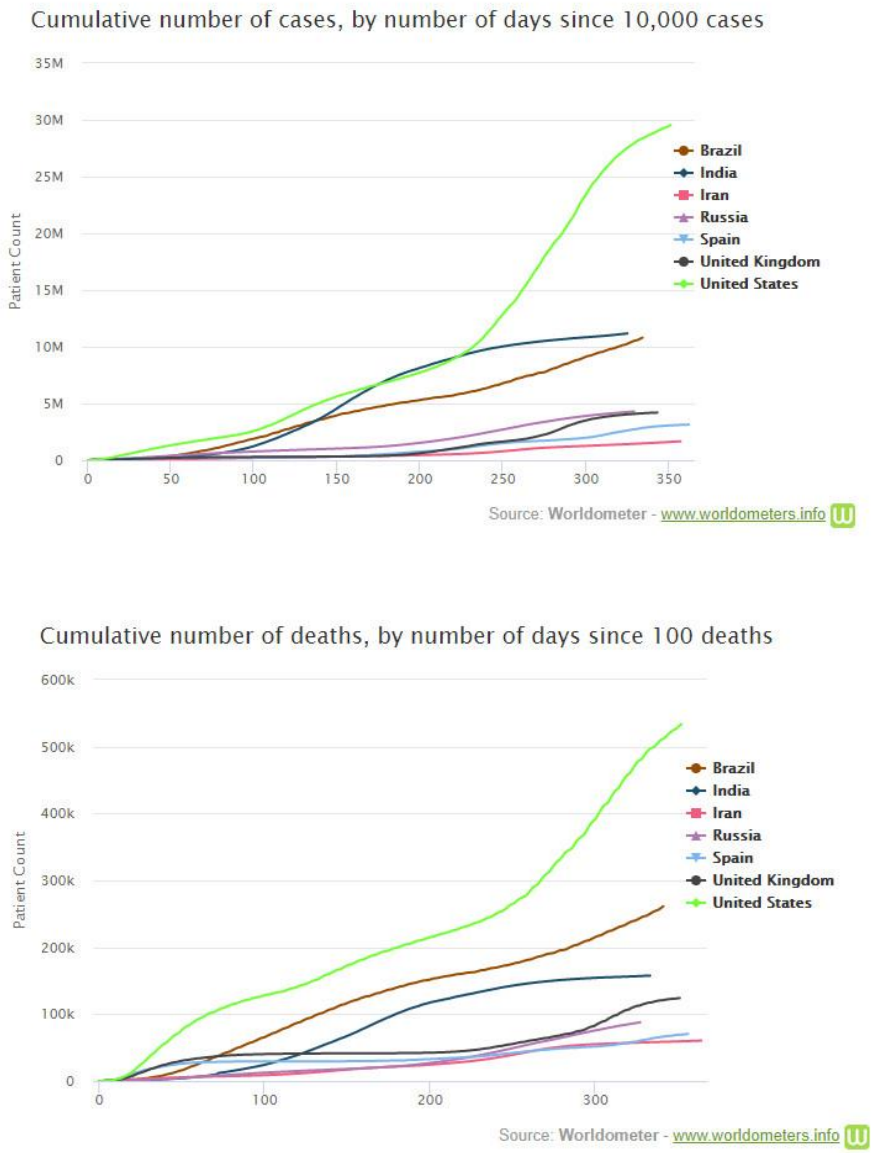

Figure 1. The cumulative number of cases by number of days since 10000 cases (top) and cumulative number of deaths by number of days since 100 deaths (bottom) of 7 most affected countries. Data were taken from www.worldometer.com the March 2nd 2021.

Different approaches have been taken to control the virus transmission. The first one, as we most expect, is vaccines. Actual vaccines have been developed using three different

approaches: (i) a whole virus or bacterium (whole-microbe approach), or (ii) parts that trigger the immune system (subunit approach), or (iii) just the genetic material (nucleic acid vaccine/m-RNA and DNA approach). As of February 2021, at least seven vaccines from different companies such as Pfitzer and BioNTech, AstraZeneca, Moderna, Johnson and Johnson, are authorized on use and about 200 others are under different stages of trial [2]. However, rapid development, emergent approved, unidentified long-term effects to human health can raise concerns, not to mention the safety and effectiveness of the vaccines against virus mutations.

On the other hand, dozen of drugs have received FDA approval for the use against SARS-CoV-2, such as antiviral drug (remdesevir, oseltamivir, lopinavir, darunavir...), antiparasitic (chloroquine, hydroxychloroquine, ivermectin), and anti-inflammatory medications (fingolimod, sarilumab) individually or in combination for the treatment of SARS-CoV-2 in a specific state of the patient. However, the effectiveness of the drugs is not clear. As reported by World Health Organization (WHO), hydroxychloroquine has shown no benefit for the treatment of COVID-19, while remdesivir, lopinavir/ritonavir and interferon showed little or no effect on 28-day mortality or the in-hospital course of COVID-19 patients. Dexamethasone is the only one that was reported helping to reduce the time of ventilator and save lives of patients with severe and clinical illness [3] [4].

While waiting for the vaccines or drugs to take effect, a series of measures attempting the prevention of virus transmission such as social distancing, avoid gathering and in close contact, mask-wearing, good hygiene are imposed or recommended in different parts of the world.

Moreover, a balanced and healthy diet is important in supporting the immune system. The European Society for Clinical Nutrition and Metabolism (ESPEN) proposes 10 practical recommendations focusing on the intensive care unit (ICU) patients and/or in the presence of older age and polymorbidity. In that guidance, the third statement indicates that supplement of micronutrients such as vitamins A, D, B, C, omega-3 as well as another micronutrients as zinc, iron and selenium can help to reduce adverse clinical outcomes during viral infection [5]. Other studies suggest the effectiveness of natural products and vitamins in the inhibitory antiviral activities *vs.* SARS-CoV-2 [6]. Herein, we resume the latest discoveries with vitamins C, D and quercetin in the prevention and treatment against the SARS-CoV-2.

2. Vitamin D

Vitamin D is a prehormone that can be synthesized in the skin by exposure to sunlight or obtained through diet and supplements. Vitamin D is known essential for good health that contributes to prevent several chronic diseases such as diabetes, cardiovascular and chronic kidney diseases by regulation of oxidative stress [7] [8]. Lanham-New *et al.* (UK, May 2020) in a brief report for British Medical Journals (BMJ), discuss the role of vitamin D and/with SARS-CoV-2/COVID-19 disease, in which the authors declare that vitamin D should be considered not as a “magic bullet” but as part of a healthy life-style to ensure the best position of the public against the pandemic [9]. It is noteworthy that in many country in the North, vitamin D defficiency is quite common, particularly in winter and during the indoor-confinement. There have been an observation that the highest mortalities is relatively low for the countries below 35-degree latitude and highest for the European

countries with the highest incidence of severe vitamin D deficits. Vitamin D supplements are recommended by many governments for the general public with different doses: 400 IU/day for the UK, 600 IU/day for the US and EU, and up to 800 IU/day for > 70 years. However, vitamin D intake greater than 4000 IU/day may be harmful and must be taken with the advice of a professional healthcare agent. High dose of vitamin D may complicate the cases of COVID critical ill [10]. Vitamin D status was suggested to impact the mortality from SARS-CoV-2 infection [11]. In particular, there is on-going scientific evaluation for the impact of vitamin D deficiency on the COVID-19 disease [12].

3. Vitamine C

Vitamin C is known for decades to have antioxidant activity and helpful to boost the immune-system [13]. Antiviral activity of vitamin C against some influenza H3N1 [14] and H1N1 virus [15] in mice is also reported. Different roles and mechanisms of action of vitamin C were proposed such as lynphocyte-supporting activity, improving the production of α-interferon, cytokines modulation, inflammatory reduction and improving endothelial dysfunction as well as restoring mitochondrial function [16]. For SARS-CoV-2, Chiscano-Camon *et al.* (2020) proposed the first study of vitamin C deficient in a group of a small number of patients with SARS-CoV-2-associated with sepsis-related acute respiratory distress syndrome (ARDS), which indicate the undetectable level of vitamin C in those patient (17/18 patients, 94.4%) vs only 1/18 has a low level of vitamin C (2.4 mg/L) [17]. Although there is no direct evidence of vitamin C in the treatment of SARS-CoV-2 disease, vitamin C as well as other micronutrients are recommended for promoting a good function of the immune system and help to defense as an antioxidant, anti-inflammation and anti-viral.

4. Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the most common flavonoid compounds and is known for human-health benefice such as anti-inflammation, antibacterial, anticancer, antioxidation, antiviral activities [18]. The use of quercetin is popular in Chinese traditional medicines, through medicinal plants.

Quercetin and many of its derivatives have been reported for having an impact on different steps of viral life circles of the influenza virus [19]. Luo *et al.* (2020) from Wuhan, studied herbs with high quercetin content on 54 patients with novel coronavirus pneumonia. The authors of this study reported for shortening the days' hospitalization and improve the symptoms of the patient [20]. Onal *et al.* reported a clinical study on the treatment of COVID-19 patients with quercetin in a single-centre, randomized, controlled trial for 447 patients with at least one chronic disease and moderate-to-severe respitory symptoms. Although the supplementation of QCB (quercetin, vitamin C and bromelain) did not reduce the risk of events, it is shown to have a positive effect on laboratory recovery by providing a stable blood level while using QCB [21].

Besides, numerous docking studies are suggesting that quercetin is a potential molecule that can inhibit the proteins of SARS-CoV-2 and should be considered for a clinical trial. For example, early studies of Abian *et al.* screened a small library of 150 small molecules for the inhibition of **3CL^{pro}** protein of SARS-CoV-2 and identified quercetin as a reasonable inhibitor (Ki ~ 7μM) [22]. A computational study by molecular docking by Alrasheid *et al.* evaluated the medicinal plants' compounds for the inhibition of SARS-CoV-2 and showed that gallic acid, quercetin, naringin, capsaicin,

psychotrine, among others, with binding energy ranging from -17.5 to -13.8 kcal/mol, are potential sources for the drug design against COVID-19 [23]. Hussen's docking study screened 9 flavonoids and 14 FDA approved antiviral drugs binding with COVID-19 main protease 6L7U, a COVID-19 main protease with N3 as an inhibitor [24]. In this study, naringin and quercetin showed the lowest binding energy (-10.2 and -8.0 kcal/mol) and therefore higher binding affinity than the other flavonoids. The authors show that for naringin, five hydrogen bonding interactions (NH and OH) formed with residues His163, Glu166, Asn142, His41 and Gln189 while quercetin may have hydrogen bonding interaction with the His163, Gln189, His41, Glu166 and His164. The study also suggested that two natural molecules overperformed all 14 FDA antiviral drugs in terms of docking score. Similarly, the active constituents of *Cressa cretica* plant were considered to treat COVID-19 by molecular dynamic simulation [25]. The 3,5-dicafeoylquinic acid and quercetin outperformed the standard antiviral drug remdesivir by showing better affinity toward **M^{pro}** receptor of the SARS-CoV-2 virus.

A similar study by Verma and Pandey suggests that quercetin displayed the highest binding energy of -8.31 kcal/mol to SARS-CoV-2-**M^{pro}** and hydrogen interaction between quercetin and 6 residues Gln127, Cys128, Lys137, Asp289 and Glu290 were observed [26]. High stability of **M^{pro}**-quercetin complex as well as the allosteric inhibitory effect of quercetin was observed for a short essential peptide sequence (AVLQSGFR) of polypeptide 1a and 1ab at the enzyme active site. In another study, *in silico* virtual screening of natural compounds from *Cassia alata* and *Dendrophthoe petandra* was studied against **M^{pro}** and **3CL^{pro}** proteases. The binding energies from molecular docking results indicated quercetin, kaemferol and aloe-emodin as the most potent inhibitors of COVID-19 [25].

The quercetin, along with ten other analogous compounds was *in silico* identified to lead in a study from 100 compounds isolated from the Mexican medicinal plants. Docking analysis showed that the three compounds quercetin, riolozatrione and cichoriin can target the key proteins of SARS-CoV-2. For example, the best targets of cichoriin are RdRp (RTP site), Nsp14 (ExoN), Nsp3 (207-379, AMP site) and papain-like protease. Futhermore, only cichoriin appears to be safe with ADME properties and physiologically based pharmacokinetic (PBPK) that reach higher concentration in the lung intracellular than other compartment, with a level of 100 mg/Kg [27]. The authors suggested that the effects of cichoriin on SARS-CoV-2 may result from the anti-inflammatory and antioxidant effect of the compound, mediated *via* NF-κB, Akt and the MAP-kinases MEK and ERK, consequently target the chronic proinflammatory cytokine storm in the COVID-19 patient. Recently, Milanovic *et al*. showed that the inhibition effects of the dominant acid-base forms of quercetin and its oxidative metabolite 2-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxy-3(2H) benzofuranone derivative towards two important targets of SARS-CoV-2, *i.e.* the FURIN enzyme and spike protein. The affinity of the natural molecules is comparable to chloroquine and hydrochloroquine, even for the two most active forms CQ^{2+} and HCQ^{+} [28]. Derosa analyses the role of quercetin in COVID-19 in the interference of the virus replication, showing the ability of quercetin to inhibit the **3CL^{pro}** and **PL^{pro}** with docking binding energy of -6.25 and -4.62 kcal/mol, respectively [29].

In the combination approach, the anti-HIV drug darunavir and phyto-flavonoid quercetin-3-rhamnoside were combined in use against SARS-CoV-2 [30]. Perceptibly, the docking complex has actively interacted with eight strong H-bonds with stability better than the individual component against SARS-CoV-2-**M^{pro}**, based on RMRD-, RMSF-Rg-plots and MM/PBSA-binding energy calculation during 100 ns. Furthermore, the use in combination of quercetin and vitamin D and estradiol were identified as top-scoring candidate therapeutics in a docking study using SUMMIT supercomputer [31]. A hypothetical combination of quercetin/vitamin D/estradiol may affect the expression of 73% of human genes encoding SARS-CoV-2 targets. Similarly, quercetin and vitamin C were suggested for use as synergistic therapy for the prevention and treatment of SARS-CoV-2 [32]. Mc Cullough *et al.* suggested the quick response to the pandemic *via* multidrug strategy using Zinc, Vit C, Vit D and quercetin, alternatively [33].

5. Conclusions

In conclusion, at the present, there is no direct evidence of the effect of quercetin and vitamins D and C in the treatment of COVID-19 disease, particularly for patients with a severe and critical illness, although some of the studies aiming to set up this relationship are on-going. However, there are many computational studies determined with the potential of quercetin and flavonoids in the treatment of SARS-CoV-2. The vitamins C and D, in parallel, is known important for the immune system which helps to prevent and defense numerous disease, including viral-transmission ones. The clinical trial in the future will be the best answer and it should be done quickly for such easy and readily chemicals.

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