Quercetin as a potential nutraceutic against coronavirus disease 2019 (COVID-19)

La Quercetina como un potencial nutracéutico contra la enfermedad por coronavirus 2019 (COVID-19)

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Resumen

Introducción: La enfermedad del coronavirus 2019 (COVID-19) es una enfermedad viral que afecta a varios órganos y sistemas. Los tratamientos preventivos o profilácticos son especialmente útiles en enfermedades infecciosas emergentes como COVID-19 porque reducen la necesidad de hospitalización y el gasto en salud pública. Aunque el efecto preventivo del SARS-CoV-2 de varios agentes terapéuticos (e.g., hidroxicloroquina/cloroquina, remdesivir, lopinavir y ritonavir) se ha evaluado ampliamente, ninguno de ellos ha demostrado una gran eficacia clínica.

Método: Por lo tanto, aquí nuestro objetivo es abordar y discutir los estudios publicados recientemente sobre el potencial quimioprofilático de la quercetina contra el SARS-CoV-2. Metodología: Se realizó una búsqueda de la literatura en bases como PubMed/MEDLINE, Scielo, Scorpus, Web of Science, Cochrane Library y Clinical Trials.gov. Se incluyeron y evaluaron críticamente estudios que abordan la quercetina contra el SARS-CoV-2 u otros tipos de coronavirus.

Resultados: Algunos estudios han demostrado que la quercetina, un flavonoide aprobado por la FDA que se utiliza como agente antioxidante y antiinflamatorio, inhibe la entrada del coronavirus (SARS-CoV) en la célula huésped. Además, un estudio in silico mostró que la quercetina es un potente inhibidor de la proteasa principal del SARS-CoV-2 (Mpro), lo que sugiere que este flavonoide también es activo contra COVID-19.

Conclusiones: Debido a que la quercetina podría prevenir y disminuir la duración de las infecciones por SARS-CoV-2, es plausible suponer que el uso profiláctico de este flavonoide produce varios beneficios clínicos. Pero, estas pruebas preliminares deben ser confirmadas mediante ensayos in vitro y, posteriormente, en un ensayo clínico aleatorizado.

Palabras clave: Quercetina; Nutracéutico; Coronavirus; COVID-19; SARS-CoV-2.

Abstract

Introduction: The coronavirus disease 2019 (COVID-19) is a viral disease that affects several human organs and systems. Preventive or prophylactic treatments are specifically useful in emerging infectious diseases such as COVID-19 because they reduce the need for hospitalization and public health spending. Although the SARS-CoV-2 preventive effect of several therapeutic agents (e.g., hydroxychloroquine/chloroquine, remdesivir, lopinavir, and ritonavir) has been extensively evaluated, none of them have demonstrated significant clinical efficacy.

Method: We aim to address and discuss the recently published studies on the chemoprophylactic potential of quercetin against SARS-CoV-2. A literature search was carried out on different databases, such as PubMed/MEDLINE, Scielo, Scopus, Web of Science, Cochrane Library, and Clinical Trials.gov. Studies that report the effect of quercetin against SARS-CoV-2 or other types of coronaviruses were included and critically evaluated.

Results: Studies have shown that quercetin, an FDA-approved flavonoid used as an antioxidant and anti-inflammatory agent, inhibits the entry of coronavirus (SARS-CoV) into the host cell. Moreover, an in silico study showed that quercetin is a potent inhibitor of the SARS-CoV-2 main protease (Mpro), suggesting that this flavonoid is also active against COVID-19.

Conclusions: Because quercetin might prevent and lessen the duration of SARS-CoV-2 infections, it is plausible to assume that the prophylactic use of this flavonoid produces several clinical benefits. However, this preliminary evidence needs to be confirmed by in vitro assays and, posteriorly, in randomized clinical trials.

Keywords: Quercetin; Nutraceutic; Coronavirus; COVID-19; SARS-CoV-2.

Introduction

The COVID-19 pandemic, caused by the betacoronavirus SARS-CoV-2, has severely compromised the health system and the economy of several countries worldwide. Currently, the overall lethality rate of COVID-19 is approximately 5%, and this infection has affected more than 9,700,000 people in 209 countries and caused more than 490,000 deaths[1].

Due to the public health crisis created by COVID-19, researchers have focused on the identification of drugs with therapeutic or prophylactic potential for the treatment and control of this viral infection. In this context, several studies have highlighted the advantages of the drug repurposing strategy, which aims to identify new uses for FDA-approved drugs. For instance, some research groups have reported the promising therapeutic effects of hydroxychloroquine/chloroquine, remdesivir, lopinavir, and ritonavir against severe COVID-19[2-4].

Preventive or prophylactic treatment reduces the incidence of the disease, the need for hospitalization, and the public health spending[5]. However, the prophylactic use of pharmacological agents can be limited and remains controversial. Additionally, the side effects produced by some of these drugs, especially hydroxychloroquine/chloroquine and the impact of their indiscriminate use, must be taken into account. Then, the use of nutraceuticals is a safe alternative for chemoprophylaxis of SARS-CoV-2 infections.

Methods

We performed a narrative and critical review of biomedical literature. PubMed/MEDLINE, Scielo, Scopus, Web of Science, and Cochrane Library databases were searched for articles published in English, Spanish, French, and Portuguese (until May 29, 2020) using the following Medical Subject Heading (MeSH) terms and keywords: ("COVID-19" OR "Coronavirus" OR "SARS-CoV-2") AND "Quercetin". The reference list of all included studies were also screened to identify potentially eligible studies. Furthermore, we used the Web of Science to search citations in the included articles to identify other eligible articles. Finally, we searched the ClinicalTrial.gov website and the United States Patent and Trademark Office (USPTO) to identify ongoing Clinical trials and patents on quercetin against SARS-CoV-2.

The general eligibility criteria of studies was defined as original studies describing clinical and pre-clinical tests (in vitro, in vivo, and in silico) on the use of quercetin against SARS-CoV-2. Review papers, notes, emails, editorials, letters, studies presented in scientific events, and papers that did not present original material were excluded. Moreover, other articles were excluded based on the following criteria: (i) studies that include quercetin derivatives (such as their heterosid analogues); and (ii) studies describing the chemoprophylactic effect of quercetin on other respiratory viruses. In cases where the article was in accordance with the inclusion criteria but the full-text was not available, the corresponding author was contacted by e-mail 3 times (with 14-day intervals between them), and the articles were included.

Results and Discussion

Nutraceuticals comprise any food or part of foods that provide health benefits, including prevention or treatment of a disease. Quercetin (3,5,7,3'- 4'-pentahydroxy flavone) is a nutraceutical compound with well-known preventive activity against viral respiratory infections. This compound is a flavonoid commonly found in several fruits and plants, such as red grapes, citrus fruits, tomatoes, broccoli, and green leafy vegetables[6,7]. It is generally isolated from foods as a glycosylated molecule, which enhances its absorption by the body[8,9]. Importantly, quercetin has low toxicity, and its oral use is considered safe. In 1998, the International Agency for Research on Cancer evaluated the carcinogenic effect of quercetin and assigned it to the Group 3 of mutagenicity, suggesting the absence of carcinogenicity in humans at safe doses (500 mg twice daily for 12 weeks)[10,11].

Quercetin is popularly known due to its potent antioxidant properties; however, this flavonoid has also shown promising antiviral activity. Studies have demonstrated that quercetin is active against several viruses, including human immunodeficiency virus (HIV), Herpes simplex virus (type 1 and 2), Poliovirus (type 1), Parainfluenza (type 3), Hepatitis C virus, Human respiratory syncytial virus, Sindbis virus, Vaccinia virus, and coronavirus (SARS-CoV)[12-17]. Furthermore, the use of quercetin as a prophylactic agent against infections caused by respiratory viruses, such as avian influenza (H5N1) and rhinovirus (US7,671,086 and US7,479,498) was described in two patents[18,19].

COVID-19 is more fatal in patients with advanced chronological age and two receptors pointed at infection by SARS-CoV-2, CD26 and ACE-2 (angiotensin-converting enzyme 2) present correction with senescence and interestingly quercetin, an antioxidant molecule significant senolytic activity[20]. Quercetin inhibits the entry of SARS-CoV into the host cell. Because this is the initial stage of viral infection, quercetin is a promising drug for the chemoprophylaxis of COVID-19[17]. The concentration of quercetin required to inhibit 50% of SARS-CoV (EC50) was 83.4 µM, which is considerably lower than the concentration reached in human blood (418 µM for a daily dose of 500 mg during 12 weeks)[21].

Furthermore, an in silico study showed that quercetin is a potent inhibitor of the SARS-CoV-2 main protease (Mpro) due to the presence of a pharmacophore similar to that found in nelfinavir[22]. This enzyme is essential for viral replication and has become a molecular target in the development of anti-SARS-CoV-2 drugs. Additionally, because the glycosylated quercetin is more soluble and highly bioavailable in the lumen of the gut[23], its use could be more beneficial than the use of the aglycone form. There is currently a clinical trial recruited in Turkey, NCT04377789, entitled quercetin for the prophylaxis and treatment of COVID-19. This study justifies that COVID-19 accompanies an excessive immune reaction of the human body in severe cases, and due the strong anti-oxidant and anti-inflammatory quercetin activity, it can be effective both in prophylaxis and in the treatment of COVID-19 cases.

Acknowledgments

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