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Opinion

Use of Quercetin for Therapeutic Purposes in COVID-19 Infections: The Opinion of the Geriatrician Doctor

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Abstract

The COVID-19 epidemic has put health systems around the world in distress, at the same time stimulating global research in an attempt to discover new therapeutic strategies against this virus. In this opinion we analyze the characteristics of a flavonoid, quercetin, trying to better understand its usefulness in the treatment of coronavirus infection.

Keywords: quercetin, elderly patient, COVID-19, infection, receptors

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1 INTRODUCTION

The COVID-19 epidemic has affected the Italian healthcare system on various levels, including the organization of hospital and territorial systems[1], the costs of diagnosis and follow-up (tampons)[2] as well as curative strategies (monoclonal and antiviral drugs) [3] and preventive (vaccines)[4]. In order to have the widest possible, accessible and low-cost therapeutic armament, clinical research has moved in various fields and together with the traditional pharmacopeia other molecules and active ingredients have been investigated that could be used in the fight against the virus and that could be therefore used alongside drugs and vaccines already tested and approved by drug regulatory bodies [Food and Drug Administration; European Medicine Agency; Italian Medicine Agency (Agenzia Italiana del Farmaco)][5-7]. Recent disappointments, such as in the case of molnupinavir (which, beyond its proven safety, has not convinced regulatory bodies in terms of efficacy on symptoms and hospitalizations)[8-10] have convinced scientists to try to find new ways to fight the virus. So, nucleoside antivirals[11], ensitrelvir - a noncovalent nonpeptidic agent with potential strong broad-spectrum anticoronaviral activities[12], antioxidant polyphenolic 1,3,4-oxadiazole compounds[13], polyphenolics and 1,3,4-oxadiazoles - like Taroxaz-104[14], molecules with a potential inhibitory activities RNA polymerase (nCoV-RdRp) protein - like the teriflunomide or synthetic nitrogenous heterocyclic antivirals[15,16], analogues and derivatives of natural nucleosides / nucleotides[17], topped the scene as top options for the treatment of coronavirus. In parallel, research has turned its interest towards compounds of natural origin, which could have antiviral properties and be useful in the fight against the virus. Among several molecules (curcumin, naringenin, luteolin, hesperidin, mangiferin, and gallic acid),

quercetin has aroused particular interest[18].

2 QUERCETIN: CHEMICAL PROPERTIES AND DIETARY INTAKE

Quercetin is a flavonoid contained in numerous plants and foods. It too has strong antioxidant and anti-inflammatory properties, and has even been studied in cancer trials. This flavonoid is one of the most common present in nature as it can be isolated from numerous plant species. In fact, it is found in capers, asparagus, onions and red grapes / red wine, tomatoes and green tea; in berries; in citrus fruits and broccoli; in blueberries; in the apple; into the celery (Figure 1)[19,20]. For these reasons, foods rich in quercetin are recommended in the diet and products used as dietary supplements of the same are regularly found on the market. The anti-inflammatory and free radical fighting properties are well known and studied in the literature; the molecule also inhibits numerous phases that lead to the release of histamine and the production of prostaglandins and leukotrienes with a pro-inflammatory action, as well as the enzymes 5-lipoxygenase and phospholipase A2[21-23]. Due to its heterogeneous and diverse beneficial properties, quercetin has been studied for a long time in order to better understand its possible uses in the clinical setting[24].

3 CLINICAL EVIDENCE OF THE BENEFICIAL EFFECTS OF QUERCETIN IN THE MEDICAL FIELD

As highlighted in a work by Jafarinia et al.[25], quercetin modulates the immune system in various ways: It decreased allergic airway inflammation and hyperresponsiveness due to the alteration of Th1/Th2 differentiation, it reduced the increased levels of IL-4, increased interferon (IFN)-ɣ, reduced the eosinophil recruitment, IL-4 and IL-5 levels in the bronchoalveolar lavage fluid, as well as, inhibited the nuclear transcription factor-kappa B activation, P-selectin expression and the mucus production in the lung. Such actions can be useful not only in allergic pathologies but also in the case of COVID or when there is an overlap between allergies, asthmatic disease and coronavirus infection. Quercetin shows, as evidenced in the work of Deng et al.[26] number actions on inflammatory mediators that underlie atherosclerotic plaque imbalance [the production of tumor necrosis factor alpha, interleukin 1 beta, IL-6, prostaglandin E2, mitogen-activated protein kinase, Janus kinase / signal transducers and activators of transcription decreases while 5' AMP-activated protein kinase, Cathepsin production increases, just as it increases that of superoxide dismutase, glutathione and nuclear factor erythroid-derived 2-like 2(Nrf2)]. It has also been seen that quercetin can increase the activity of the Na-K-Cl cotransporter 1, by modifying the concentration of chloride ions[27]. This event, by first modifying the expression of chloride channels at the gene level and then at the protein level, leads to a reduced reabsorption of sodium, for which has a reduced blood volume and therefore a consequent drop in blood pressure. All these actions not only make quercetin a good pharmacological agent that can be used in cardiovascular pathology, but they can also be of great help in the COVID phase, whose increase in deaths is both greater in the general population due to cardiovascular causes and in cardiovascular patients[28,29]. In the same way[30], similar benefits can be obtained by using quercetin in patients with diabetes, infected with COVID: Together with the cardiovascular effects already mentioned, quercetin stimulates glucose uptake through the mechanism of insulin-dependent MAPK, with translocation of the glucose transporter type 4 in skeletal muscle. In the treatment of dyslipidemia, Talirevic et al.[31], quercetin with its antioxidant effects has been shown to contribute both to a reduction in lipid levels but above all to an intervention in the oxidation mechanisms of LDL, therefore with an anti-atherogenic profile[32]. Based on the available evidence, it is recommended by a panel of experts that safe but stringent control of blood glucose, blood pressure, and lipids be carried out in patients with type 2 diabetes, measures that could potentially serve to decrease the severity of COVID-19 should these patients contract the viral infection[33]. So the use of quercetin can be useful for this purpose. Multiple effects of quercetin, investigated in the literature, have concerned other pathologies causing fragility and vulnerability both taken individually and in the case of COVID-19 infection, such as tumors, osteoporosis, urinary obstruction and cognitive impairment[34-38], pathologies often present, individually or not, in the elderly patient.

4 USE OF QUERCETIN IN THE FIELD OF INFECTIOUS DISEASES: BACTERIA, FUNGI AND PARASITES

Quercetin has been seen to exert numerous actions both *in vitro* and *in vivo* against various infectious agents, both bacterial and fungal: it inhibits the synthesis of nucleic acid with interference with the plasma membranes of various bacteria (Pseudomonas aeruginosa, Salmonella typhimurium, Escherichia coli, Enterococcus faecalis)[39,40]. It has also potential anti-biofilm properties[41]. At the fungal level, it has been seen that at different concentrations of the drug there is an ability to inhibit the crestica of various fungal species as well as a synergy of the molecule with antifungal pharmacological agents such as fluconazole and amphotericin against Candida albicans, parapsilosis and Tropicalis, Aspergillus flavus and Cryptococcus neoformans[42,43]. Quercetin has been shown to be important in the fight against parasites and has been demonstrated in different clinical trials, such as those against Leishmania, Trypanosoma, and Plasmodium[44,45].

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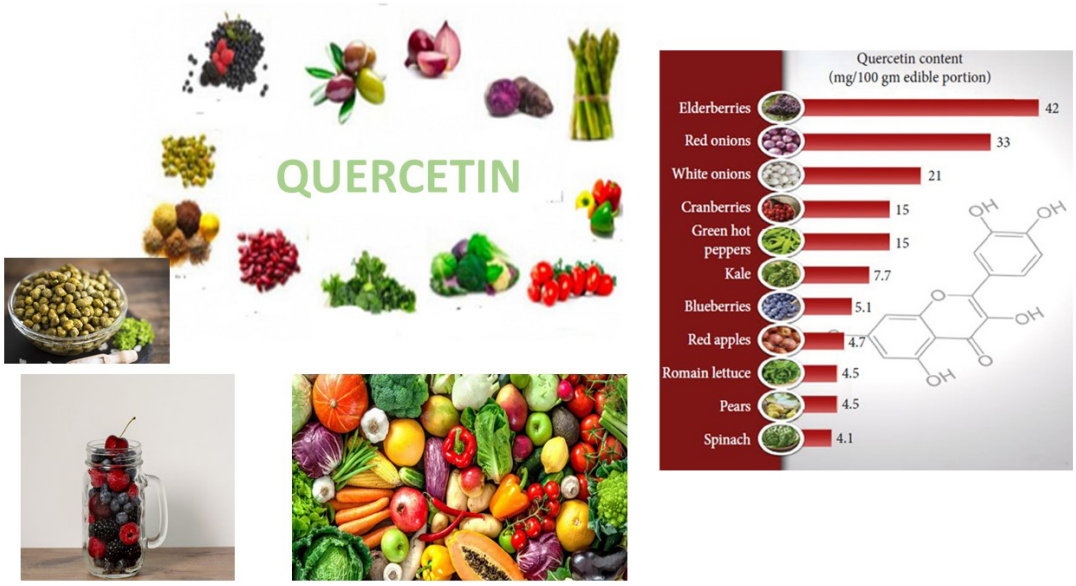

Figure 1. Quercetin content.

5 ANTIVIRAL ACTIONS OF QUERCETIN

An interesting and recent meta-analysis by Brito et al.[46] well describes the action of quercetin in the lung affected by a virus that has caused inflammation: the use of the flavonoid in various forms of administration leads to a decrease in the activation of the viru-related pro-inflammatory cytokine and chemokine cascade, to a lower production of mucus, with reduction of airway resistance and increase in vital capacity. The final effect is clinical improvement and reduction of mortality in animals. It is known that the effect of the vaccine in the human body is to generate an immune response that causes the formation of neutralizing antibodies directed against the spike protein of the coronavirus. The spike protein covers the external surface of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with protuberances and is precisely one of the peculiar characteristics of the family to which this virus belongs, the coronaviruses, which thanks to the protuberances of the spike proteins on their surface, when viewed under an electron microscope, resemble crowns. The spike protein of SARS-CoV-2 is the main mechanism that the virus uses to infect target cells. The spike protein of SARS-CoV-2 is one of the most studied drug targets. In fact, blocking its functioning quercetin was identified as being between the top scoring ligands for the spike protein: Angiotensin-converting enzyme 2 (ACE2) receptor interface would mean preventing the virus from infecting target cells, thus making it harmless[47]. Spike protein of SARS-CoV-2 binds with human ACE2 protein, a component of renin-angiotensin-aldosterone system involved in regulation of blood pressure. It also plays an important role in the initiation of pulmonary hypertension-like complications in COVID-19 patients. The major druggable targets of SARS-CoV-2, in addition to the spike protein mentioned above, include the 3-chymotrypsin-like protease ($3CL^{pro}$) and the papain-like protease (PL^{pro}), RNA-dependent RNA polymerase. So, quercetin can target ACE2 expression by interfering with Spike-ACE2 binding and interacting with PL^{pro}. Among all the potential protein targets within coronaviruses, the main protease (M^{pro} or $3CL^{pro}$) stands out as a highly conserved gene, making $3CL^{pro}$ a good target for developing effective drugs against SARS-CoV-2. Together with PL^{pro}, $3CL^{pro}$ is responsible for the processing of the viral polyproteins synthesized from the viral RNA after infection, rendering the individual viral proteins active and functional. Quercetin binds to SARS-CoV-2 $3CL^{pro}$ active site. Several studies showed a significant inhibition by quercetin of $3CL^{pro}$and PL^{pro}[48-50]. An italian 2-week, randomized, open-label and controlled clinical study, that had enrolled only 42 COVID-19 outpatients: in this study, quercetin in phytosomal form was able not only to accelerate the negativity of patients but was also able to intervene favorably on various blood parameters, decreasing many inflammatory and pro-thrombotic indices, such as C-reactive protein and D-dimer[51]. An equal prospective study on a much greater number of patients (over 400) confirmed the benefits in terms of improvement of various laboratory parameters, although there was great uncertainty about the dose of quercetin capable of giving these benefits[52]. Saeedi-Boroujeni et al.[53] have seen that this effect on inflammatory parameters is mediated by the action that quercetin has on inflammasomes. Inflammasomes are cytosolic multiprotein oligomers of the innate immune system responsible for the activation of inflammatory responses. Inflammasome activation (for example the cytoplasmic nod-like receptor, family pyrin domain containing 3 - NLP3) and assembly promotes proteolytic cleavage, maturation and secretion of pro-inflammatory cytokines, generating active forms of

cytokines (IL-1β and IL-18). The activation or inhibition of the inflammasome NLRP3 is affected by regulators such as Nrf2 cited in this article: affecting the regulator Nrf2, quercetin suppresses the NLRP3 inflammasome. The Nfr2 agonists abrogate replication of SARS-CoV-2 in lung cells; quercetin has been shown to be an agonist of Nfr2 and several experimental evidences have shown that this results in a lower production of reactive oxygen species[54,55]. It transduces with anti-fibrotic effects in a mouse model of bleomycin-induced pulmonary fibrogenesis through Nrf2-dependent restoration of redox imbalance[56]. These characteristics are important since there is not only acute damage caused by the virus, through an inflammatory response, but there are also consequences that are felt even after some time and damage that anatomically remains in the lung, even once the infection is finished. An anti-fibrotic action of quercetin is therefore of extreme interest. Since the harmful action of the coronavirus infection takes place at the level of the circulation, with a virus-induced pro-thrombotic effect[57], the anti-thrombotic properties of quercetin have been highlighted both *in vitro* and in animal models[58,59]. An high percentage of hospitalized patients with COVID-19 have hematologic changes in coagulation tests (elevated D-dimer, prolonged prothrombin time, thrombocytopenia and / or low fibrinogen levels) with a procoagulant response of the infection itself[60]. Quercetin inhibits agonists (ADP, collagen, and thrombin) of the platelet aggregation and granule secretion, it inhibits platelet activation by inhibiting various components, like the collagen; it also inhibits fibrin production in several histopathological and mouse experimental models[50], through inhibition of the activation of factor X (inactive) to factor Xa (active). Zhang et al.[61] reviewed ongoing clinical trials in which quercetin is used alone or in association with other drugs / dietary supplements against COVID-19: the results of these and other studies will allow us to better understand the practical extent of the properties of quercetin and its possible real applications in the therapeutic field against this virus.

6 CONCLUSION

The need to find new weapons to use in the fight against the coronavirus has prompted research to deal with the properties of medicinal substances present in nature. Among these, quercetin appears very promising and its effects in patients both suffering from comorbidities and infected with coronavirus have prompted the launch of several researches and clinical trials. Recent scientific works published up to 2023 and a very recent meta-analysis continue to confirm its beneficial properties and possible implications as a therapeutic agent against COVID[62-65]. Many questions currently remain to explain about the dose to be used, the significance in practice of the clinical and laboratory effects already highlighted on models and guinea pigs as well as the best therapeutic scheme (alone, together with other substances, together with other drugs already in use) to guarantee maximum benefit to patients. There are still few studies in humans to be able to infer clinically significant effects and hospitalizations. At the same time, from the literature consulted, the molecule up to now would appear to be quite safe, as no significant toxic effects on humans at the doses used and important interactions with other drugs would have been seen, so as to increase adverse events. Further studies on the subject, clarifying these points, will certainly contribute to the progress of treatments and the fight against this terrible virus.

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Conflicts of Interest

The author declared no conflict of interest.

Author Contribution

Magro VM was the primary researcher and wrote the manuscript. Magro VM provided research and editing assistance to the manuscript. Magro VM contributed to overall article design, data collection as well as revising and approving the manuscript.

Abbreviation List

$3CL^{pro}$, 3-chymotrypsin-like protease
ACE2, Angiotensin-converting enzyme 2
Nrf2, Nuclear factor erythroid-derived 2-like 2
PL^{pro}, Papain-like protease

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