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Editorial

Nutraceuticals and dietary supplements should not be used as pharmaceuticals to treat COVID-19



A recent preprint by Lordan and Rando reviewed the use of dietary supplements and nutraceuticals in the management of coronavirus disease 2019 (COVID-19). Despite the bulk of evidence supporting a role for natural compounds in COVID-19, the authors reported paucity in the clinical evidence of tested compounds such as probiotics, vitamins, polyunsaturated fatty acids (PUFAs), and zinc in treating COVID-19. They determined that if an improvement is observed, it is only due to the individual's optimal nutritional status, which is able to prime their own immune system and boost a rapid clearance response against the virus [1]. Despite some evidence showing the beneficial action of ω -3 PUFAs in preventing COVID-19 [2], the use of nutraceuticals to treat mild or severe forms of COVID-19 raises several controversial issues.

A recent survey with 372,270 UK participants, of whom 175,652 were nutritional supplement users, reported that a very modest association might exist between lower risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)-positive and diets enriched with probiotics, multivitamins, vitamin D, and ω -3 fatty acids, despite the study results being positive only for women [2]. Clinical trials are crucial to assess any purported effect.

Phytochemicals sold as dietary supplements should be used only to potentiate and improve the nutritional status of an individual and prevent further damage due to the onset of an inflammation or an exacerbated immune and stress response, particularly when there are micronutrient deficiencies. Interestingly, Lordan and Rando's contribution did not address polyphenolic compounds from plants, despite their widespread use as nutraceuticals [1].

About 250 articles on "flavonoids AND COVID-19" on Pubmed/Medline deal with the use of natural phytochemicals in addressing the COVID-19 pandemic. Most of the phytochemicals are purported to have a specific role in targeting virus entry, budding, replication, and life cycle of SARS-CoV2, with high specificity [3]. This would erroneously suggest the naive thesis that nature-derived phytochemicals may act pharmacologically.

For example, the flavanone glycoside hesperidin, usually found in citrus fruits, has been considered, in some clinical trials, a possible compound to treat COVID-19, yet only 35 papers retrieved on Pubmed (Medline MESH term "hesperidin AND COVID") failed to contain any experimental study on humans or in animal models, except from *in silico*, docking, and computational methods on SARS-CoV2 targeting. The content of hesperetin, the aglycone flavanone of hesperidin (i.e., the 4'-methoxy derivative of eriodictiol), ranges from 2.20 to 36.14 mg for 100 mL of orange juice, a mean of 12.80 mg/100 mL [4], whereas other studies reported an

average amount of 23.70 mg/100 mL [5], suggesting that four glasses of orange juice might contain the level of hesperidin usually available on the market as a dietary supplement. Although it may appear foolish to think that orange juice can alleviate the early symptoms of COVID-19, thus returning the individual to their previous health status, research is continuing to promote hesperidin as a possible pharmaceutical compound against COVID-19 [6].

There are a number of reasons to expand even gentle criticism about this perspective.

First, it is widely known that the actual bioavailability of any polyphenolic compound from either raw food or nutritional supplements is difficult to assess, as flavonoid pharmacokinetics are greatly affected by the gut microbiome composition, and therefore it is quite impossible to establish a reliable dosage and a reliable dose-effect on the patient. Second, the panoply of actions toward oxidative stress signaling is highly complex and depends on a large number of factors related with disease progress and the host's response. Third, the activity of a polyphenolic compound, such as a flavonoid, may be completely reversed or attenuated by other phytochemicals coming from diet, usually in a way that is difficult to fully elucidate.

The equivocal belief that flavonoids in nutritional supplementation may act in a pharmacological way is related to the numerous *in vitro* reports showing the ability of aglycone flavonoids to either suppress, or enhance, or modulate many cell molecular pathways, usually those targeting defined signaling systems or receptors or other macromolecular complexes in a fashion very close to pharmaceuticals. Despite this perspective appearing convincing, flavonoids are highly pleiotropic, and their activity can be perfectly restricted to the simple survival system of the oxidative stress response. Fundamentally, any phytochemical from plants is a toxic compound, which, in a narrow range of dosage, can trigger an oxidative stress response able to activate cell survival, via the production of reactive oxygen species (ROS) as signaling molecules. The correct dose to elicit a benefit is usually established by a certain empiricism, as flavonoid pharmacokinetics is very complex, and adverse effects due to the compound subclinical toxicity may be incurred by the patient. In this context, clinical trials are crucial but the introduction of a nutraceutical form of a flavonoid can be affected by the introduction of the same flavonoid (or other antagonists) from food. What the researcher probably observes is a beneficial action of the flavonoid on the nutritional status of the patient and the subsequent effect on the investigated clinical parameters.

Nutraceutical supplementation should be avoided in the treatment of patients with severe illnesses such as COVID-19 and patients should be correctly informed about the proper nutritional status to address the pathogenetic course of SARS-CoV2 infection, particularly during early symptoms.

To my knowledge, no sound association between COVID-19 prevalence and flavonoid-rich food intake has been reported. Furthermore, although the literature is endowed with numerous papers dealing with the beneficial effects of flavonoids (e.g., hesperidin), studies on toxicity are usually restricted to very few reports and sometimes only one [7].

The paroxysmal attitude to rapidly plan a highly successful therapy against COVID-19 is crowding the scientific community with proposals from natural and complementary medicine, sometimes with even potential competing interests. Any proposal is settled to enhance the weapons against the pandemic but the misleading consideration that a food-derived phytochemical may be considered a pharmaceutical drug raises controversial issues and may hamper the ethical movement to correctly address COVID-19 in early home therapy.

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