

Hesperidin and SARS-CoV-2: New Light on the Healthy Functions of Citrus Fruit

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Abstract

Among the many approaches to COVID-19 prevention, the possible role of diet has so far been somewhat marginal. Nutrition is very rich in substances with a potential beneficial effect on health and some of these could have an antiviral action or in any case be important in modulating the immune system and in defending cells from the oxidative stress associated with infection. This short review draws the attention on some components of Citrus fruits and especially of the orange (*Citrus sinensis*), well known for its vitamin content, but less for the function of its flavonoids. Among the latter, hesperidin has recently attracted the attention of researchers, because it binds to the key proteins of the SARS-CoV-2 virus. Several computational methods, independently applied by different researchers, showed that hesperidin has a low binding energy both with the coronavirus "spike" protein, and with the main protease that transforms the early proteins of the virus (pp1a and ppa1b) into the complex responsible for viral replication. The affinity of hesperidin for these proteins is comparable if not superior to that of common chemical antivirals. The preventive efficacy of vitamin C, at dosage attainable by diet, against viral infections is controversial, but recent reviews suggest that this substance may be useful in case of increased stress on the immune system. Finally, the reasons that suggest undertaking appropriate research on the Citrus fruits addition in the diet, as a complementary prevention and treatment of COVID-19, are discussed.

Keywords

Citrus fruits, *Citrus sinensis*, hesperidin, COVID-19, vitamin C, SARS-CoV-2, sweet orange.

Introduction

COVID-19, being a new and largely unknown disease, has given doctors and researchers the opportunity to try new approaches and interventions. In the early stages of the pandemic, many attempts were prompted by urgency, but now our knowledge is increasing. On the prevention front, various measures have been put in place and recommendations have been issued, although not all

based on rigorous evidence. Many hopes have been placed on vaccines, but their feasibility, efficacy and safety are still very uncertain. Although clinical trials are underway to test several antivirals and other agents, an important question for the population is whether there are any nutrients and food/nutrition? patterns that can prevent viral infection or mitigate its severity. Diet seems to be a neglected or at least underestimated aspect, although it is acknowledged that it often plays an important role in the prevention of various diseases, even those of infectious nature [1-5].

Among the benefits of the Mediterranean diet for the protection from many diseases there is also the high consumption of foods rich in bioactive substances such as vitamins A, C, D, E and polyphenols. Food polyphenols constitute a large family of substances with potential beneficial effects in a large group of communicable and non-communicable diseases. These compounds support and improve the body's defences against oxidative stress and in the prevention of cardiovascular diseases, atherosclerosis and cancer. In addition, they show anti-inflammatory, antiviral and antimicrobial properties. This article investigates the Citrus fruits, common foods in the Mediterranean nutritional pattern, and their flavonoids with promising potential against COVID-19, hesperidin.

The orange is the fruit of various *Citrus* species of the *Rutaceae* family. The most known is the *Citrus sinensis*, which is also called sweet orange. Citrus fruits are rich sources of vitamins, including especially C, anthocyanins, and flavanones, with hesperidin and naringin as the most abundant components, which have various properties, including antioxidant and anti-inflammatory activities [4]. Fibers such as pectin, more present in the solid part, help to regulate intestinal functions and hinder the absorption of LDL cholesterol. There are indications that these fruits may also have beneficial effects in the prevention and treatment of virus diseases [6]. Without neglecting the best known vitamin C, here we will examine the evidence, albeit very preliminary, of a possible beneficial effect in COVID-19 of the orange and its main flavonoid, hesperidin. Hesperidin is the naturally occurring form and is the glycosylated form of hesperetin, often used for its dosability in plasma.

Contents and bioavailability

Orange (per 100 g) contains 0.2 g of fats, 0.7 g of proteins, 9.9 g of carbohydrates (soluble sugars) and provides 45 kcal of energy (CREA - Tables of food composition. <https://www.alimentinutrizione.it/tabelle-nutrizionali/008012>). The fresh sweet orange juice contains (per 100 ml) traces of fats, 0.5 g of proteins, 9.8 g total carbohydrates (soluble sugars) and provides 39 kcal of energy [7]. Other active ingredients include vitamin C (mg) 45.0 ± 10.5 , carotenoids (μg) 107, total flavanones (mg) 10.7 ± 0.4 [7]. Flavanones are a group of phenolic natural chemical compounds belonging to the class of flavonoids, based on the structure of the carbon atom skeleton of the flavone progenitor. Typical examples are the bitter and soluble compounds present in the peel of Citrus fruits as glycosides. The most important orange flavone is hesperetin, which is found in the fruit in a glycosylated form like hesperidin. The latter is present mainly in the peel and in the white part (albedo) of Citrus fruits, and the consumption of the whole fruits allows a greater introduction, for the same weight of introduced food

In fresh orange juice the content of hesperidin is about 30 mg per 100 ml and in commercial juice it

can be a little higher [8], probably because the industrial processing incorporates more peel. There are no major differences between the different varieties of oranges and between oranges and tangerines. The flavonoid content of the red orange [9] is mainly hesperidin (44 mg / 100 ml), followed at a distance by narirutin (4.8 mg / 100 ml) and dimidine (2.4 mg / 100 ml). According to a recent review [10], in 100 ml of orange juice there are 20–60 mg of hesperidin, of tangerines 8–46 mg, of lemon 4–41 mg, of grapefruit 2-17 mg. This means that we can take about 100 mg of hesperidin just in a large glass of orange juice.

Some tests have tried to assess the amount of hesperidin (or its metabolite hesperetin) in the blood of people drinking orange juice. Healthy volunteers drank orange juice in one intake (8 ml / kg) [11]. In blood and urine samples collected between 0 and 24 hours after administration, the resulting plasma concentrations of hesperetin were 2.2 ± 1.6 micromol/L, with significant variations in different subjects. Elimination half-lives ranged from 1.3 to 2.2 hours, therefore plasma concentrations reflect short-term intake and kinetics. In another experiment [12], after a night fast, five healthy volunteers drank 0.5 or 1 liter of commercial orange juice containing 444 mg/l of hesperidin, along with a polyphenol-free breakfast. The flavanone metabolites appeared in the plasma 3 hours after the ingestion of the juice, peaked between 5 and 7 hours, then returned to the baseline value at 24 hours. The peak plasma concentration of hesperetin was 0.46 ± 0.07 micromol/L and 1.28 ± 0.13 micromol/L after taking 0.5 and 1 liter, respectively. The authors concluded that, in the case of moderate or high consumption of orange juice, flavanones represent an important part of the pool of total polyphenols in plasma.

However, it would not be correct to evaluate the bioavailability of phenols only with the dosage of hesperetin. In fact, there is evidence that hesperidin and naringin are metabolized by intestinal bacteria, mainly in the proximal colon, with the formation of their aglycones hesperetin and naringenin and various other small phenols [13]. Studies have also shown that Citrus flavanones and their metabolites are able to influence the composition and activity of the microbiota and to exert beneficial effects on gastrointestinal function and health. Other bioavailability studies have calculated that if the phenolic catabolites derived from the colon are added to the glucuronide and sulphate metabolites, the polyphenols derived from orange juice are much more abundant and available than previously thought [14].

Action mechanism

To explain the possible effect of the Citrus components on COVID-19, it is useful to start by giving a brief description of the virus's infectivity and its pathology. Figure 1 presents the main steps of the viral cycle and its consequences on the cell, with the sites where the modulating action of hesperidin and vitamin C might take place, as discussed in the subsequent chapters.

In order to enter human cells, the SARS-CoV-2 binds its "spike" protein to the ACE2 receptors, and event followed by the "internalization" of the viral particle in a vesicle, whose envelope is then removed, allowing the genomic RNA to be released into the cytoplasm. The ORF1a and ORF1b RNAs are produced by the genomic RNA and then translated into pp1a and pp1ab proteins respectively. The pp1a and ppa1b proteins are then broken down by a proteolytic process, resulting in

a total of 16 non-structural proteins. Some non-structural proteins form a replication / transcription complex (RNA-dependent RNA polymerase), which uses genomic RNA (+) as a model. Eventually, subgenomic RNAs produced through transcription are translated into structural proteins that will form new viral particles. To this purpose, structural proteins are incorporated into the membrane and the nucleocapsid N protein combines with the genomic RNA of the filament (+) produced through the replication process, to become a nucleoprotein complex. The various components merge into the complete viral particle in the Golgi endoplasmic reticulum-apparatus, which is finally excreted in the extracellular region.

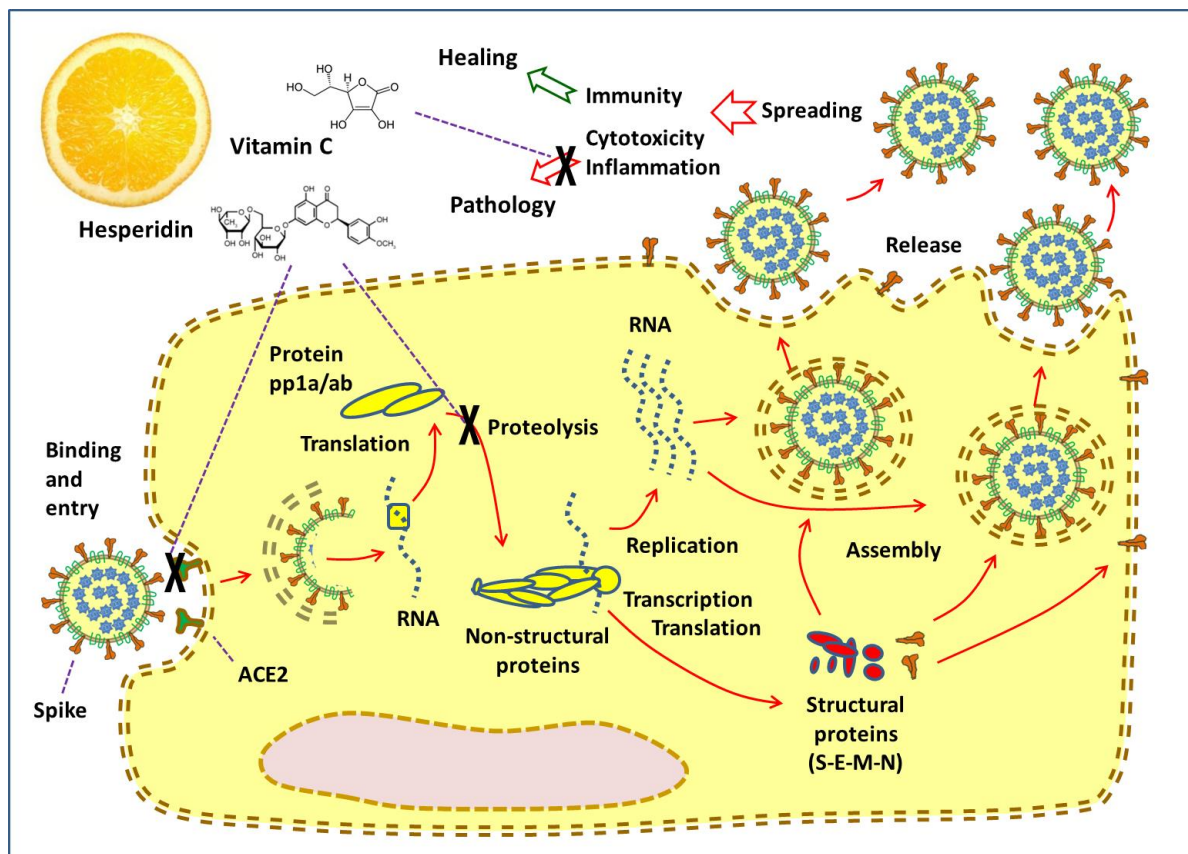


Figure 1. Summary of the cycle of the SARS-CoV-2 virus and of the possible mechanisms of the inhibition of virus-induced cellular and systemic pathology by hesperidin and vitamin C (indicated with "X").

The new copies of the virus spread into the environment and go to infect other cells in the body, in a chain expansion. When the viral load is high and the cell is invaded by many viral particles, all its protein synthesis apparatus is dedicated to viral replication, up to the cell death. The last phase can take place with the "apoptosis" mechanism (if death is slow and controlled) or following an "energetic-metabolic chaos" such as to cause the breakdown of the various cell membranes and the total loss of structural integrity. Possibly, also autoimmune phenomena are involved in the attack to the infected

cell by T-lymphocytes and antibodies [15]. In this case, both in the tissue where many cells have died (first of all in the lung), and systemically (lymph, blood, immune system, coagulation, kidney, liver), an inflammatory reaction develops, which can be clinically very serious, especially in patients with co-morbidities. Excessive and "vicious" inflammation can be mediated by a distorted activation of the cytokine network, by clotting disorders, even by a paradoxical excess of the immune reaction (autoimmunity, cytotoxic lymphocytes).

Based on this concise description, substances with a possible beneficial effect in coronavirus infection may act in the various stages: (a) preventing the binding of the virus to the receptors or inhibiting the function of the receptor itself, when it sets in motion the internalization process, (b) inhibiting viral replication by blocking for example RNA polymerase, proteases or new particle assembly, (c) helping the cell to resist viral attack, i.e. stopping the cytotoxicity process, (d) blocking the spread of the virus in the body, (e) modulating the inflammation when, starting as an innate defensive mechanism, it becomes offensive and cytotoxic.

The prototype of the substances that act on steps (a) and (d) are specific antibodies, produced by active or passive immunization (plasma, purified IgG), even if in the case of coronaviruses this mechanism finds an obstacle in the risk of augmentation of the viral action by the same antibodies ("antibody-dependent-enhancement") [16] or autoimmune phenomena [15]. Step (b) is the target of most antiviral drugs. Since the cytotoxicity process (step "c") involves oxygen-derived free radicals in many cell damage mechanisms, this pathologic process could be slowed down, if not blocked, by natural antioxidants. Finally, the modulation of the inflammatory disorders (e) can be tackled with a wide variety of steroidal and non-steroidal anti-inflammatory drugs, or with new "biological" drugs such as antagonists of cytokines or TNF.

Hesperidin and the virus

Returning to hesperidin, this substance has multiple antimicrobial, anti-cancer, antihypertensive and anti-ulcer medicinal properties [17-22]. Human studies have long shown the safety and good tolerability of hesperidin up to very high doses [10]. The discovery that the molecule has a chemical-physical structure suitable for binding to key proteins in the functioning of the SARS-CoV-2 virus has recently aroused scientific interest. At least six searches yielded concordant results [23-28].

The researchers started from the detailed knowledge of the virus protein structure to try to verify which molecules, natural or artificial, are capable of binding with a low binding energy (the lower the energy required, the stronger and more specific the binding is). This technique is called "*in silico*", as it is performed through the computer (with reference to the silicon of the chips). The *in silico* study is currently applied to simulate drug behaviour and accelerate the detection rate, screening many drugs and reducing the need for expensive laboratory work and limiting efficacy clinical trials to the best candidates.

Wu and collaborators [23] have tested SARS-CoV-2 proteins, whose chemical-physical structure is known, with 1066 natural substances with potential antiviral effect, plus 78 antiviral drugs already

known in the literature. Of all, hesperidin was the most suitable to bind to the "spike". By superimposing the ACE2 - RBD complex on the hesperidin - RBD complex, a clear overlap of hesperidin with the ACE2 interface is observed, which suggests that hesperidin may disrupt the interaction of ACE2 with RBD.

A second theoretical site of low energy binding of hesperidin with SARS-CoV-2 is the main protease that allows the processing of the first proteins transferred from the viral genome - pp1a and pp1ab - into functional proteins in the host cell [23]. This enzyme is called "3CLpro" or "Mpro" by the various authors and is the target of many chemical antiviral drugs. This specific binding has also been confirmed by other authors: in a screening of 1500 potential molecules capable of binding to 3CLpro, hesperidin is the second most efficient for binding to chain A with a free energy of -10.1 Kcal mol⁻¹ [24]. Lopinavir (-8.0) and Ritonavir (-7.9) are given as reference drugs, and they show less binding capacity. The binding to chain B occurs with -8.3 Kcal mol⁻¹, while Lopinavir (-6.8) and Ritonavir (-6.9) have lower binding capacity.

Another detailed molecular docking study of the interaction between hesperidin and Mpro was recently published [27]. In a screening of 33 natural and already known antiviral molecules, the authors found that the lower binding energy (indicating maximum affinity) is characteristic of rutin (-9.55 kcal / mol), followed by ritonavir (-9.52 kcal / mol), emetine (-9.07 kcal / mol), hesperidin (-9.02 kcal / mol), and indinavir (8.84 kcal / mol). Hesperidin binds with various amino acids, among which particularly are the hydrogen bonds with THR24, THR25, THR45, HIS4, SER46, CYS145. Further evidence came from the work by Joshi et al. [28], who identified hesperidin among several natural molecules that strongly binds to SARS-CoV-2 main protease and interestingly also to the viral receptor angiotensin-converting enzyme 2 (ACE-2).

A research published in "preprint" by Indonesian authors has examined a wide range of active ingredients of the plants *Curcuma sp.*, *Citrus sp.* (orange), *Caesalpinia sappan* and *Alpinia galanga* with evidence of molecular docking towards the main protease of the virus, the Spike protein, and the ACE2 receptor [26]. For the three proteins, hesperidin was the most efficient binding molecule, with docking points of -13.51, -9.61 and -9.50 respectively to the SARS-CoV-2 protease, to the glycoprotein-RBD Spike and to the ACE2 receptor. Hesperidin performs a better interaction with the SARS-CoV-2 protease than Lopinavir, a reference drug used today in the clinical trials for Covid-19. These authors have observed that, in addition to hesperidin, other orange flavonoids less represented quantitatively like tangeretin, naringenin and nobiletin also have a low binding energy (comparable to the reference ligands, Lopinavir and Nafamostat) to the three essential proteins, suggesting that these interactions could also contribute to the inhibitory effect against virus infection. According to another "molecular docking" research [25], out of 26 natural phenolic compounds that are candidates for antiviral action, hesperidin was the one with the highest binding capacity to the crystallized form of the main protease of SARS-CoV-2. It interacts with hydrogen bridges with different amino acids. The link is much more effective than that with the reference drug Nelfinavir (with scores of -178.59 and -147.38 respectively).

There is an important precedent when the authors studied natural compounds capable of inhibiting 3CLpro of the SARS virus [29], using cell-based proteolytic cleavage assays. Out of seven phenolic compounds tested, hemodyne and hesperetin inhibited proteolytic activity in a dose-dependent manner, with IC₅₀ of 366 micromol/L and 8.3 micromol/L respectively. This research offers a demonstration that theoretical models are efficient in predicting real biochemical activity and provides a rough indication of the concentration of the substance capable of showing some effect. It is suggestive that this inhibitory effect occurs with concentrations of hesperidin of the same order of magnitude as those achievable in plasma with a large oral supplement of orange juice. Since coronavirus main protease structural backbone and active site conformation are conserved despite sequence variations [28], it is conceivable that the inhibitory effect of hesperidin previously observed in SARS virus can be exploited also in SARS-Cov-2.

Other potentially useful effects

Citrus fruits and their respective juices, starting from orange juice, could have positive effects in the course of COVID-19 with additional mechanisms, possibly inhibiting its virulence. As mentioned above, this disease can present, in the more advanced stages, phenomena of hyperactivation of inflammatory reactions and coagulation, with a pathology involving the pulmonary vessels, and not only. Furthermore, COVID-19 is known to affect elderly people with other chronic cardiovascular, metabolic and respiratory diseases, especially if in a severe form. Consequently, any lifestyle-related intervention, including dietary interventions, that help to maintain the health of the cardiovascular and respiratory systems during the whole life may make the person infected with SARS-CoV-2 less susceptible to its more severe complications.

A randomized, single-blind, placebo-controlled, cross-over study in subjects with increased cardiovascular risk (aged 27 to 56 years) tested the administration of 500 ml of blood orange juice / day (or 500 ml of placebo / day) for periods of 7 days [30]. Endothelial function, measured as flow-mediated dilation, improved greatly and was normalized (5.7% compared to 7.9%; $P < 0.005$) after 1 week of consuming red orange juice. The concentrations of C-reactive protein, IL-6 and TNF-alpha also decreased significantly ($P < 0.001$).

A review [31] describes numerous antioxidant and anti-inflammatory effects of hesperidin using cellular and animal models, although clinical trials are few. A randomized controlled crossover study [32] of 24 healthy and overweight men (age 50-65 years) investigated the effects of orange and hesperidin on the vascular system. During three 4-week periods, the volunteers consumed 500 ml of orange juice, 500 ml of control drink plus hesperidin (CDH) or 500 ml of control drink plus placebo (CDP) every day. After 4 weeks of consuming orange juice or CDH, the diastolic blood pressure had significantly decreased compared to CDP consumption ($P = 0.02$). Both orange juice and CDH ingestion improved postprandial microvascular endothelial reactivity compared to CDP ($P < 0.05$) measured at the peak of plasma concentration of hesperetin. The authors conclude that in healthy middle-aged men in moderate overweight, regular consumption of orange juice reduces diastolic pressure and increases endothelium-dependent microvascular reactivity. The study suggests that this

beneficial effect is due to hesperidin.

A dietary medical history study determined the total dietary intake of 10054 Finnish men and women in the previous year [33]. Intakes of flavonoids in food have been estimated and compared with the incidence of diseases considered by different national public health registers. People with higher hesperetin intakes had lower incidence of cerebrovascular disease (RR 0.80; CI 0.64-0.99; P = 0.008) and bronchial asthma (RR 0.64; CI 0.46-0.88 ; P = 0.03).

In mouse studies, protective effects of hesperetin were observed in lipopolysaccharide-induced neuroinflammation (LPS), neuronal oxidative stress and memory impairment [34]. While treatment with LPS resulted in microglial activation and astrogliosis and increased the expression of inflammatory mediators such as TNF- α and IL-1 β , concurrent treatment with hesperetin (50 mg / kg body weight) significantly reduced the expression of inflammatory cytokines and has attenuated the generation of reactive oxygen species induced by LPS. In addition, hesperetin improved synaptic integrity, cognition and memory processes. In a recent review, it was noted that the nutraceutical, antioxidant and anti-inflammatory properties of hesperidin could be useful also in the prevention and treatment of many disorders of the central nervous system [35].

Gene expression analysis has shown that hesperidin modulates the expression of genes involved in atherogenesis, inflammation, cell adhesion and cytoskeletal organization [36]. Physiologically relevant concentrations of flavanone reduce the adhesion of monocytes to endothelial cells stimulated by TNF- α , influencing the expression of related genes and so offering a potential explanation of its vasculoprotective effects. A daily dose of 292 mg of hesperidin, corresponding to 500 ml of orange, was sufficient to achieve the described effects.

Vitamin C

This article focuses more on hesperidin for its newly suggested anti- SARS-CoV-2 properties, but the importance of vitamin C, perhaps the best known component of the fruit, cannot be overlooked. A complementary therapeutic effect of intravenous high doses of vitamin C has been reported [37, 38] and clinical trials are ongoing, but the role of dietary interventions is much more difficult to assess and any suggestion at present is just speculative or, at best, a working hypothesis [39].

There are conflicting data on the effect of vitamin C to prevent the common cold and other respiratory diseases. However, while many studies on the efficacy of vitamin C megadoses in preventing respiratory diseases are inconclusive or negative, meta-analyses suggest a consistent and statistically significant benefit of vitamin C for preventing the common cold in people exposed to short periods of stress, intense exercise or in a cold environment [40, 41]. Coronaviruses are among the viruses that cause the common cold, a disease that has never had an effective cure or vaccine. Considering that SARS-CoV-2 is a coronavirus and taking into account the low cost and high safety of natural foods rich in vitamin C, it has been suggested that it might be useful to evaluate whether to increase the daily intake of these foods during the COVID-19 pandemic [39, 42].

Vitamin C, in addition to participating in the synthesis of collagen in the connective tissue, has a

strong antioxidant effect, able to reduce the effects of free radicals, together with other vitamins, enzymes and minerals (zinc, selenium). Vitamin C is believed to prevent oxidation of LDL and to protect human vascular smooth muscle cells from apoptosis [9]. The properties of various *Citrus* fruits include anticancer, anti-inflammatory and cardiovascular protection activities [9, 43]. Studies on animals infected with the flu virus have shown that vitamin C boosts the immune system and reduces the inflammatory state of the lung [44, 45]. We suggest that a potentially beneficial effect of low-medium doses of vitamin C in the first stages of COVID-19 infection could be due to the protection of cells from free radical damage during the out-of-control inflammatory phenomena (see Figure 1).

The effect of orange juice on inflammation and oxidative stress induced by a high-fat meal was studied [46] in three groups of 10 normal and healthy subjects, invited to drink water, or 300 kcal of glucose, or juice orange in combination with a high-fat meal of 900 kcal. On In the blood samples obtained before and 1, 3 and 5 hours after the consumption of the meal and of the different drinks, some indexes of inflammation were determined. The high-fat meal increased the expression of NADPH oxidase, toll-like receptors and metalloproteinase-9 in mononuclear cells and plasma. These changes, indicative of oxidative stress, were significantly reduced by the intake of orange juice. Other authors [47, 48] have also described antioxidant effects in healthy volunteers after taking orange juice and whole fruits rich in vitamin C.

The beneficial effects of Citrus fruits can depend on the synergistic effects of their compounds. Therefore, the contribution of natural compounds through a balanced diet together with an adequate amount of fruits could provide protection against oxidative damage in different conditions and can be more effective than the integration of a single antioxidant.

Conclusions and perspectives

The scientific literature on the healthy properties of fruit and vegetables [49-51] and especially of Citrus fruits [9, 52], is vast and beyond the scope of this article, which has focused on the remarkable and surprising interaction between hesperidin and the key proteins of the SARS-CoV-2 virus. Since these methods are now the "gold standard" for screening new drugs and their targets, we feel hopeful about the beneficial effects of hesperidin COVID-19 as well, even if there is still no clinical evidence of therapeutic efficacy. The binding of hesperidin to the central part of the spike and to the main protease is much stronger than that of conventional antivirals, and it can be expected that this molecule may soon be tested in randomized trials of patients with COVID-19 or subjects exposed to contagion, as it is the case for quercetin (<https://clinicaltrials.gov/ct2/show/NCT04377789>) or for a mix of quercetin, green tea, cinnamon and liquorice [53].

The systematic review that studied the relationship between fruit, vegetables and pathologies [52] in the American population, for Citrus fruits found a non-linear relationship with the more overall indicator, total mortality, with nadir for an average consumption between 50 and 100 g / day, with a tendency of the dose-response curve to apparently cancel the benefits around 250 g / day. This might happen because of sweetened juices, as the consumption of sugary drinks in the USA was associated with an increase in global mortality [54]. Even if the latter data refer to a different

population, a habitual consumption of Citrus fruit close to 100 g / day would seem optimal, preferring whole fruits, which are associated with a maximum intake also of hesperidin, in addition to dietary fiber and other nutrients, in comparison with juices or centrifuged drinks.

The recently accumulated evidence supports the hypothesis that hesperidin supplementation may be useful as complementary treatment during COVID-disease, as recently suggested by others [55]. It remains to be seen whether regular Citrus consumption, or an increase in consumption, may be advisable among the preventive dietary measures for COVID-19. A dose of Citrus fruits or vitamin C-based supplements, higher than that of a typical diet of the Italian population, does not seem suitable for long-term prevention. However, in periods of intense stress (that may be considered similar to the exposure to pathogenic microorganisms during the epidemic peak or during an other infectious disease, possible benefits from therapeutic doses of vitamin C are expected [41]. It was suggested that the prevention of infection requires dietary intakes of vitamin C (i.e. 100-200 mg / day) [56], which provide adequate plasma levels to optimize cell and tissue levels, while the treatment of established infections requires significantly higher doses high (grams) of vitamin to compensate for the increased inflammatory response and metabolic demand [57]. If you rely on food, these doses may be reached with a temporary large consumption of juices, taking care to crush well also the albedo, which is the part richest in hesperidin. In our opinion, it is certainly suggestive to think that inside a tasty fruit, given to us by Nature for thousands of years, there may be a molecule potentially useful to fight a virus of the 21st century!

For the strong and consistent computational evidence of the interaction with viral proteins, it is easy to imagine that hesperidin will become part of the candidate drugs for a therapeutic effect, but in the meantime it is conceivable that a preventative protection can be obtained with food doses. The aforementioned article [29], which shows the ability of micromolar doses of hesperidin to inhibit the enzymatic activity of the main SARS coronavirus protease is indicative of the fact that this pharmacological activity can also be achieved in the plasma of subjects taking medium-high daily quantities of citrus fruits. The potential benefits of citrus fruits in COVID-19 (at least in the early stages of the disease or in its prevention during the epidemic) derive from the properties here described and their large availability as part of Mediterranean diet, especially during the winter season. This aspect is also important, due to the known difficulty in changing eating habits, even when there are strong scientific evidence of the healthiness / harmfulness of certain foods.

Finally, what we report above could suggest nutritional intervention studies or with hesperidin-based supplements, as it has already been proposed for vitamin C [58], or at least it could be planned an epidemiological research based on the investigation of the eating habits of subjects affected by COVID-19 in various stages of severity, from asymptomatic positives to people recovered after going through critical phases. Given the wide range of available cases and the relative ease and low cost of such studies, such a search could identify potentially important factors associated with good or bad prognosis of the disease, also to prepare for possible "new waves" of this or similar epidemic respiratory viruses.

Competing interests

The author has no competing interests.

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