Chapter

Reappraisal of Dietary Phytochemicals for Coronavirus Infection: Focus on Hesperidin and Quercetin

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Abstract

Food polyphenols constitute a large family of substances with beneficial properties in a large group of communicable and non-communicable diseases. These compounds support and improve the body's defences against oxidative stress and are helpful in the prevention of pathologies related to metabolic syndrome. Furthermore, they exhibit anti-inflammatory, antiviral, and antimicrobial properties. This chapter draws attention to certain nutritional components such as hesperidin and quercetin, which are emerging as good candidates for a complementary beneficial effect in the case of diseases caused by viruses, including COVID-19. These nutraceuticals have a complex mechanism of action, which involves both cellular defence against oxidative stress and the modulation of inflammation, which although normally is a defence, repair and activation mechanism of the immune system, it can elude its controls and become a systemic and destructive pathology (cytokine storm, respiratory distress syndrome). Furthermore, recent in silico simulation tests suggest that both hesperidin and quercetin may interfere with SARS-CoV-2 by binding to cell receptors and the proteolytic enzymes involved in its replication. In addition to the inhibitory effects on the virus at cellular level, the two flavonoids can have indirect effects in respiratory infectious diseases as they prevent or improve metabolic and vascular comorbidities that can complicate the clinical course. This brief review focuses on biochemical and pharmacological mechanisms of action of polyphenols in the context of the revaluation of dietary approaches to the prevention and treatment of infectious diseases caused by viruses, with a special application to COVID-19.

Keywords: hesperidin, quercetin, citrus flavanones, functional food, nutraceuticals, respiratory virus, oxidative stress, SARS-CoV-2, COVID-19, metabolic syndrome, Nrf2

1. Introduction

In modern medicine and chiefly in the approach infectious diseases, nutrition seems to be a neglected or at least underestimated aspect, although it is recognised that it often plays an important role in the prevention of various diseases, including infectious ones [1, 2]. Flavonoids are abundant functional substances in plants with potential health benefits and are used as valuable food components or as supplements. Some of these substances may have an antiviral action or in any case be

important in modulating the immune system and defending cells from the oxidative stress associated with infection.

Flavonoids are hydroxylated polyphenolic compounds based on the structure of the 15-carbon backbone of the parent flavone (2-phenyl-1,4-benzopyrone), which consists of two phenyl rings (A and B) and a heterocyclic ring (C) (**Figure 1A**). They can be divided into various classes based on their molecular structure and according to the C-ring replacements scheme: flavones, flavonols, isoflavones, anthocyanins, flavanols and flavanones. More than 4,000 varieties of flavonoids have been identified.

In the human diet, flavonols are widespread with quercetin standing out among them (**Figure 1B**). The most represented flavanone is hesperetin (**Figure 1C**) which is found in citrus fruits in glycosylated form as hesperidin (**Figure 1D**). Flavanones lack a double bond between C2 and C3 and this makes them chiral in the C2 position. Chirality implies that the B ring is not planar like in flavonols and is twisted with respect to the A-C rings. Such a difference in molecular orientation is relevant because it can affect the way the different flavonoids interact with their biological targets and therefore their bioactive properties.

Quercetin [International Union of Pure and Applied Chemistry (IUPAC) name: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one, with a molecular weight of 302.23 g/Mol] contains five hydroxyl groups linked in position 3,5,7,3′ and 4′ to the basic flavonol skeleton. In plants and as a consequence of biotransformation by the intestinal bacterial flora, some of these hydroxyl groups are glycosylated and constitute the main derivatives of quercetin. Hesperidin (with a molecular weight 610.6 g/Mol) is a glycosylated derivative of hesperetin [IUPAC name: (2S)-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydrochromen-4-one, with a molecular weight of 302.28 g/Mol], with a 6-O-(alpha-L-rhamnopyranosyl) -beta-D-glucopyranosyl disaccharide in position 7 via a glycosidic bond.

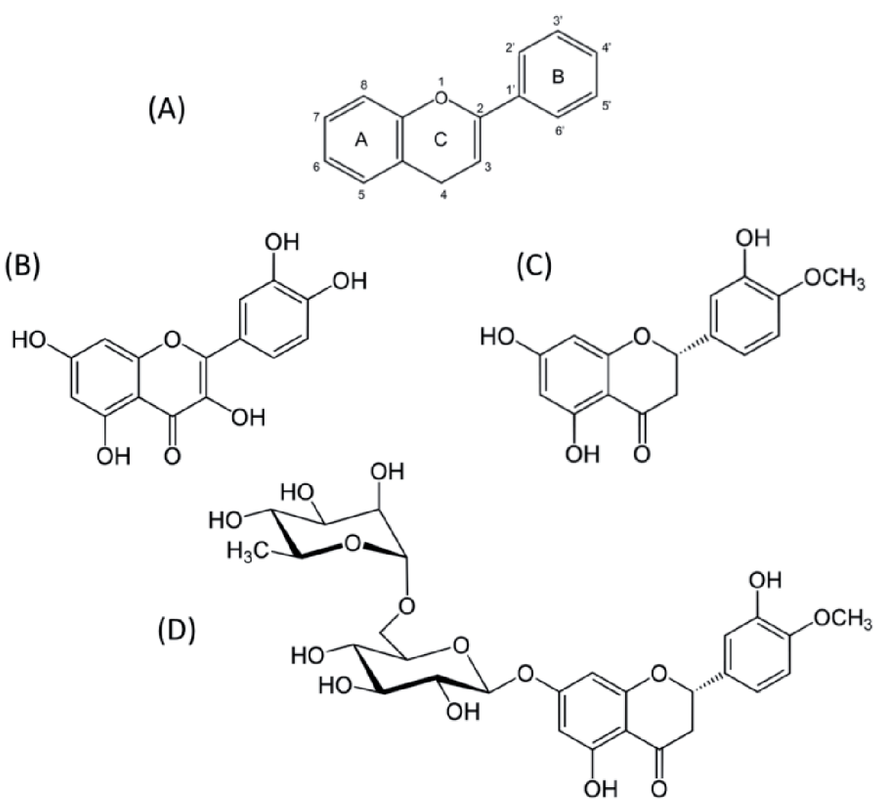

Figure 1.
Molecular structure of flavone (A), quercetin (B), hesperetin (C) and hesperidin (D).

The structure–activity studies show that the antioxidant and anti-free radical properties of flavonoids are due to the ketone group, the double bond between the 2 and 3 carbons, the 3′, 4′-catechol and the 3-hydroxyl moiety in the flavonoid skeleton (the latter two are present in quercetin but not in hesperidin) [3]. The C2-C3 double bond extends the π conjugation to the carbonyl group in the C ring, so the radical elimination capacity of unsaturated flavonoids is greater than saturated structures, such as flavanones [4]. The antiradical capacity of flavonols in aqueous solvents is mainly exerted by the mechanism of electron transfer with sequential proton loss, associated with the C3 hydroxyl group, or of electron-proton transfer in the catechol component. Therefore, the type of substitution of the B ring is also considered as a determinant of the antiradical potency of flavonoids [4].

Many of the biological effects of flavonoids appear to be related to their ability to modulate receptors, enzymes, cell signalling cascades, rather than to a direct antioxidant effect. In fact, the maximum concentrations of flavonoids that can be reached in the blood with very high intakes (~ 2 μmol/L) are much lower than the concentrations of other antioxidants, such as ascorbic acid (~50 μmol/L) uric acid (200–400 μmol/L) and glutathione (700–1500 μmol/L). The functional interaction between flavonoids and enzymes or receptors occurs through hydrogen bonds and hydrophobic interactions with key amino acids of targeted proteins. For example, an inhibition of the activity of the enzyme xanthine oxidase by quercetin is exerted thanks to hydroxyl groups of C5 and C4 [5], and the anti-inflammatory activity depends not only on the number of free hydroxyl groups, but also on the methyl group [6]. Here the binding capacity of quercetin and hesperidin to some important proteins of the SARS-CoV-2 virus will be described in more detail.

In fresh orange juice the hesperidin content represents about 30 mg per 100 ml [7], but it is found in greater quantities in the white part of the peel [8]. Quercetin is widely present in the plant kingdom [9, 10] with an average daily consumption of 25–50 milligrams [11], up to about 250 mg per day in "high-consumers" of fruit and vegetables [12].

Both hesperidin and quercetin have long been known for their antioxidant, anti-inflammatory and anti-lipemic properties. This review will focus on their effects in viral infections, with special prominence on the recently exploded COVID-19 pandemic and its SARS-CoV-2 responsible virus. With the outbreak of COVID-19 and the scientific world's focus on the search for preventive, antiviral and immunomodulatory substances, other particularly interesting characteristics of dietary phytochemicals have emerged. Many studies have highlighted the importance of the intracellular redox state as a new target for natural or synthetic drugs aimed at blocking both viral replication and excess inflammation [13, 14]. It has therefore been suggested that early flavonoid treatment may be a way to restore redox balance, prevent cell damage and the resulting inflammatory storm that causes lung damage with respiratory dysfunction [15–18].

Although there is still no clinical evidence of efficacy for COVID-19, the two flavonoids are emerging as some of the most capable substances of specifically inhibiting binding to cellular receptors of the SARS-CoV-2 virus and its replication [8, 14, 19–21]. A recent randomised study, which appeared in as a preprint version, suggests that quercetin, administered together with vitamin C, could help health care workers in the prevention of SARS-CoV-2 infection [22].

Here we will examine the known mechanisms of action of hesperidin and quercetin, taking SARS-CoV-2 as a paradigm, and without neglecting to mention the important properties of these natural substances for health care in general. Following a logical order, the various passages of the disease will be dealt with starting from cellular infection to clinical consequences, specifying the points where these flavonoids could act.

2. Effects at cellular level

Tests on laboratory animals have shown the ability of flavonoids to inhibit infection by various viruses such as herpes simplex-1, parainfluenza and respiratory syncytial virus [23, 24], poliomyelitis-1 [25], rhinovirus [26, 27], hepatitis C [28], rotavirus [29], influenza [30–36], SARS-coronavirus-1 [37]. Here we will examine recent evidence regarding the SARS-CoV-2 virus in more detail.

Coronaviruses are a group of single-stranded RNA viruses with a corona-like morphology, mainly causing enteric and respiratory diseases of varying extents. Once the first mucosal barriers and possible intervention of the immune system have been overcome, the viruses enter the cell via specific receptors, the nucleic acid is then expressed causing various intracellular changes, including replication into multiple copies and various types of damage to the host cell. In each of these steps it is possible to imagine the action of compounds that tend to block entry or slow down replication and its pathological consequences (**Figure 2**).

2.1 Receptor binding and entry

The internalisation of SARS-CoV-2 in human cells is mediated by the binding of the virus' spike glycoprotein (S) to its receptor on cell membranes, which is the angiotensin converting enzyme 2 (ACE2) [38, 39]. ACE2 is expressed in many tissues including the lung, liver, heart, colon, oesophagus, intestine, kidney, and even the brain, which is consistent with the variety of cell types that can be infected, and the variety of symptoms reported in COVID-19 patients [40–45]. The S protein has two subunits, the first of which contains a receptor binding domain (RBD), which is responsible for binding to ACE2. Binding and entry are also favoured by the presence of a polybasic cleavage site between the two subunits of the spike and by proteolytic enzymes attached to the receptor, of which trans membrane serine protease-2 (TMPRSS2) is particularly important.

The discovery that the hesperidin molecule has a chemical–physical structure suitable for binding to the spike of the SARS-CoV-2 virus (* 1 in **Figure 2**) has recently aroused scientific interest [14, 46–51]. Wu et al. [46] used in silico

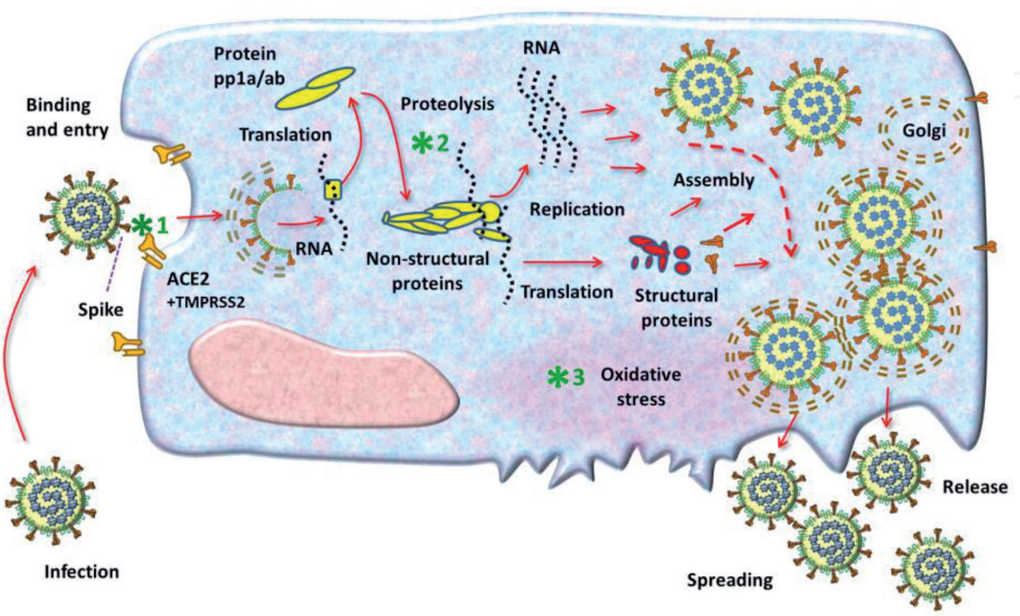

Figure 2.
Intracellular cycle of the SARS-CoV-2 virus. Green asterisks and numbers indicate the points of the flavonoid actions described in the text.

simulation techniques to screen 1066 natural substances with a potential antiviral effect, plus 78 antiviral drugs already known in the literature. Of all of them, hesperidin was the most suitable for binding to the SARS-CoV-2 spike, wedging into the shallow middle sulcus of the RBD, where some hydrophobic amino acids, including Tyr436, Try440, Leu442, Phe443, Phe476, Try475, Try481 and Tyr49 form a hydrophobic pocket to contain the compound.

Various authors have confirmed the affinity of hesperidin for the RBD fragment of the spike protein and its ability to hinder the binding with ACE2 or to make the interaction unstable (**Figure 3**) [52, 53]. The anchoring of hesperidin is stabilised by two hydrogen bonds (shown with green lines in **Figure 3**) with the amino acids Phe457 and Glu455 on the spike protein. According to other in silico screening studies, hesperidin also has an affinity for TMPRSS2 protease, which is involved in the functioning of the receptor when the vesicle is internalised with the virus [54, 55].

Molecular dynamics simulations and energy landscape studies revealed that other flavonoids such as fisetin, quercetin and kaempferol bind to the ACE2-spike complex with favourable free energy [56]. Another group reported studies showing that quercetin has a high affinity for viral spikes, blocking the sites of interaction with cellular receptors [19]. According to other authors who followed a gene expression approach [57], quercetin is identifiable as one of the highest scoring natural substances, altering the expression of numerous human genes that encode SARS-CoV-2 protein targets, including ACE2.

2.2 Proteolysis and assembly

A second theoretical site of flavonoid action is the main protease that allows the processing of the first proteins transferred from the viral genome (point *2 in **Figure 1**).

After interacting with membrane receptors and their associated proteases, the viral particle is internalised by means of a vesicle formed by the same membrane, the shell of which is then removed, allowing the release of the genomic RNA into the cytoplasm. The coding sequences of the genomic RNA are translated into pp1a

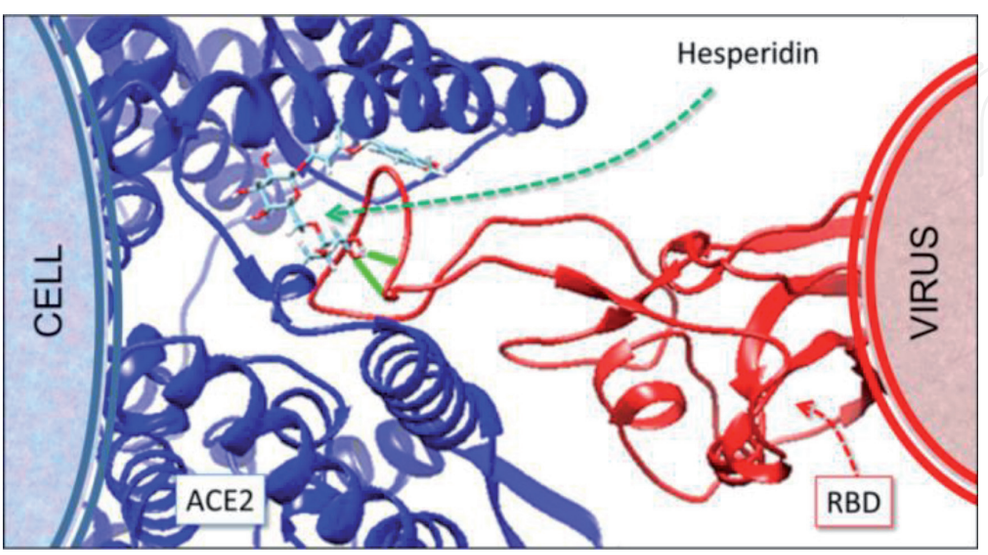

Figure 3.
Binding of the ACE2 protein with the spike in the presence of hesperidin. The RBD fragment of the spike protein (331–524) is shown in red, and the hesperidin molecule in the stick model and human ACE2 is shown in blue. Figure created using a diagram component from the cited work [52] with authorisation from Creative Commons.

and pp1ab proteins, which are then broken down by a proteolytic process for a total of 16 non-structural proteins. The main enzyme that carries out this transformation is called 3-chymotrypsin-like protease (3Clpro) or major protease (Mpro) by various authors and is in fact the target of many chemical antiviral drugs.

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

A strong affinity of hesperidin to Mpro has been discovered by various authors [46, 47, 50] in the screening of thousands of potential molecules using molecular docking techniques. Hesperidin binds with hydrogen bonds to various amino acids, mainly Thr24, Thr25, Thr45, His4, Ser46, Cys145 [50]. An important precedent exists when the authors investigated natural compounds capable of inhibiting Mpro of the SARS virus [37], using cell-based proteolytic cleavage assays. Out of seven phenolic compounds tested, hesperetin inhibited proteolytic activity efficiently with an IC50 of 8.3 μmol/L. Since the coronavirus main protease structure and active site conformation are preserved despite sequence variations [51], it is conceivable that the inhibitory effect of hesperidin, previously observed in the SARS virus, could also be exploited in SARS-CoV-2. Furthermore, hesperidin binds to structural protein 16 (nsp16) of the coronavirus, which is a methyltransferase dependent on S-adenosyl methionine [58]. This protein plays an important role in viral replication and prevents recognition by the innate immune system.

Quercetin has also been shown to inhibit the Mpro of the SARS-CoV [59], MERS-CoV [60] and SARS-CoV-2 [61] coronaviruses. The binding points of quercetin and hesperetin on SARS-CoV-2 Mpro are partially different [19]: the first in fact binds to Glu288, Asp289 and Glu290, while the second to Glu290, Asp289, Lys5. Furthermore, hesperetin, naringenin and kaempferol bind to the regulatory site Leu286, which quercetin does not do. All this suggests that the different molecules do not overlap as a pharmacological activity on the Mpro, but can synergise.

An even more recent study [62] confirms the affinity of quercetin to Mpro using the measurement of the enzymatic activity. Evidence of its inhibitory effect was obtained with a fairly low dose of quercetin (7.7 μmol/L). **Figure 4** shows the molecular complex formed by quercetin bound in the cavity that constitutes the active site of Mpro (in blue), in the most favourable position to inhibit the protein enzymatic activity in order to block the replication of the coronavirus.

Da Silva et al. [63] have expanded the search for molecules interacting with Mpro to a series of flavonoid glycosides using a molecular docking approach. The interactions and binding affinity with the protease by quercetin and even more by its glycosidic derivatives quercetin-3-O-rutinoside (rutin), quercetin-3-O-glucuronide, quercetin-3′- O-sulphate, quercetin-7-O-glucuronide, quercetin-7-O-sulfate were thus predicted. It should be noted that the absorbed flavonoids normally undergo extensive metabolism in the epithelial cells of the small intestine and in the liver. Metabolites conjugated with the methyl, glucuronate and sulphate groups are the predominant forms present in plasma [64–66]. Quercetin has also been indicated as one of the substances capable of binding and thus inhibiting RNA-dependent RNA polymerase, an essential enzyme in the replication of viral RNA in the host cell [63].

Russo et al. [20] further confirmed the ability of known flavonoids (e.g. quercetin, baicalin, luteolin, hesperetin, gallocatechin gallate, epigallocatechin gallate)

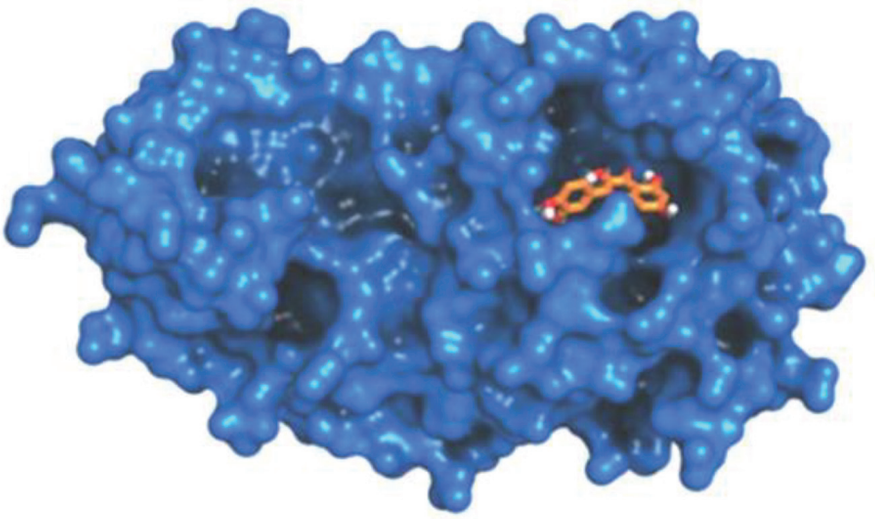

Figure 4.
Representation of the quercetin molecule (in orange) within the active site of the Mpro of the SARS-CoV-2 virus. Developed by Bruno Rizzuti on the basis of the study of which he is co-author [62]. Reproduction authorised by the author.

to inhibit the key proteins involved in the infectious cycle of SARS-CoV-2. They suggested that flavonoids and their derivatives, due to their pleiotropic activities and lack of systemic toxicity, may represent target compounds to be tested in future clinical trials to enrich the arsenal of drugs against coronavirus infections.

2.3 Oxidative stress

Oxidative stress is an important cell pathology mechanism which is involved in many diseases, including those caused by viruses. Viral respiratory infections are generally associated with the production of cytokines, inflammation, cell death and other pathophysiological processes, which could be linked to increased production of reactive oxygen species (ROS), redox imbalance and oxidative stress.

Many lines of evidence suggest that viral infections are accompanied by signs of increased production of ROS, presence of oxidation products in blood plasma and urine, and reduced antioxidant capacity [67]. This pathological and pathogenic phenomenon has been observed in the infection of viruses such as hepatitis B [68], hepatitis C [69], influenza [70] and SARS-CoV-2 [71]. In the latter, ROS could also determine an unfavourable evolution in elderly subjects with low antioxidant capacity [72, 73], perhaps because the intracellular redox environment alters the presentation of antigens [74] and the expression of ACE2 [75, 76]. In fact, the severity and mortality risk of SARS-CoV-2 or COVID-19 have been associated with age [73].

Studies have shown that the ability of viral envelope glycoproteins to fuse to the surface of a cell membrane depends on the disulphide-thiol balance of the cell, even if the binding of coronaviruses to cell receptors seems rather insensitive to these parameters [77]. It seems possible that the oxidation of thiols to disulphides, under an oxidative stress mechanism, increases the affinity of spike proteins for the ACE2 receptor and, therefore, increases the severity of COVID-19 [75]. In this regard, reduced glutathione (GSH) may also have direct anti-SARS-CoV-2 potential: in fact, a computational study indicates that the binding of the spike protein to ACE2 is at its highest when the ACE2-sulfur groups are in the form of disulphides and are altered when they are fully reduced to thiols: therefore a pro-oxidant environment with low levels of GSH would favour the cellular entry of viruses [75, 78].

In the course of viral diseases, analgesic and antipyretic drugs are widely used, and of these one of the most common is paracetamol (acetaminophen). However, the fact that this drug depletes glutathione reserves and can worsen oxidative stress is not always taken into account [78, 79]. This type of biochemical modifications can decrease the antiviral defences [80] or complicate the course especially in patients with abnormal liver tests or liver failure [81, 82].

As described in the Introduction, flavonoids have a molecular structure capable of participating in redox reactions and free radical scavenging, which are involved in the biochemical phenomena described here and in the cellular pathology resulting from viral infection (point * 3 in **Figure 2**). Hesperidin contributes significantly to antioxidant defence systems and has been reported to act as an effective agent against superoxide and hydroxyl radicals [83], while hesperetin inhibits the production of nitric oxide by lipopolysaccharide (LPS)-stimulated microglial cells [84].

Quercetin also acts as a free radical scavenger, donating two electrons to oxidised species which are reduced. When this occurs with the transfer of one electron at a time, a semiquinonic intermediate molecule is formed. This antioxidant activity of quercetin is exploited in synergy with vitamin C, thanks to the ability of ascorbate to recycle the flavonol molecule, protecting it from oxidation and recycling its oxidised quinonic form after the scavenger action on free radicals [85]. In addition to ascorbic acid, glutathione is also important for maintaining quercetin in its reduced and therefore functional form and preventing the risk that quercetin quinone, in turn, may oxidise the thiol groups of proteins [86, 87].

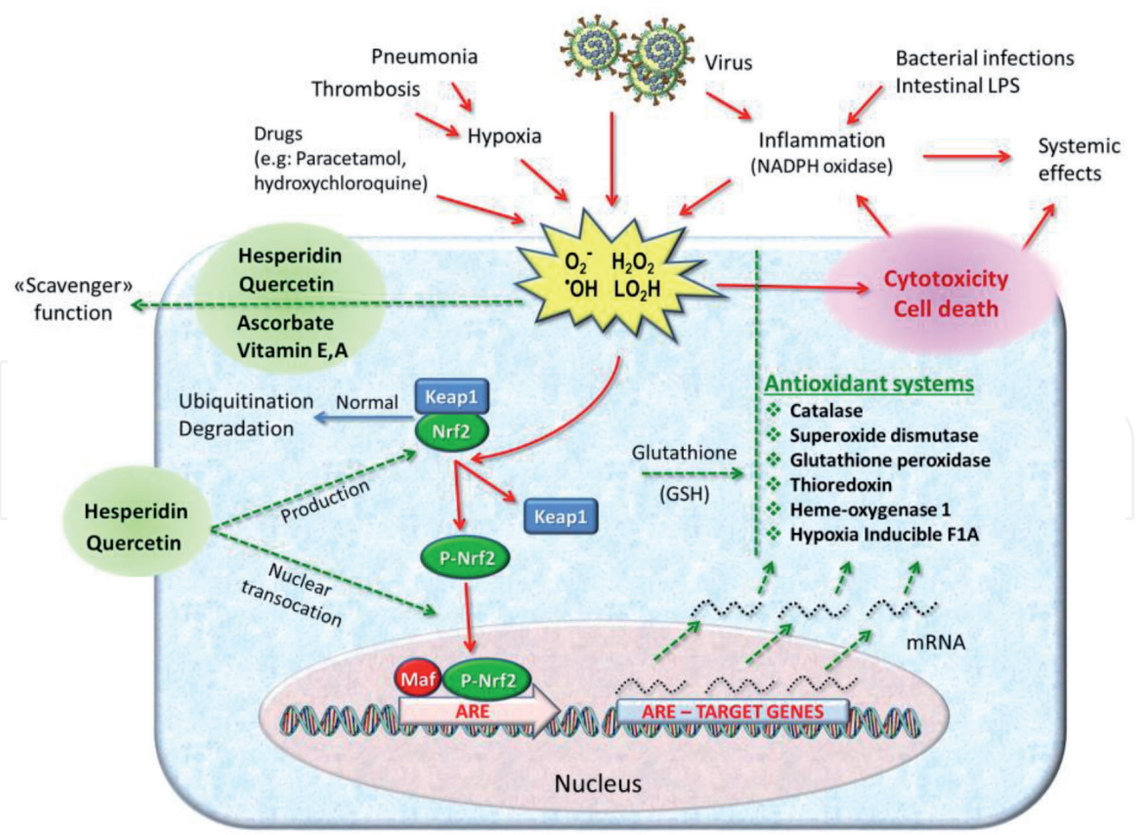

Figure 5.
Oxidative stress induced by several pathogenic factors (top part) and cellular defensive effects of flavonoids, functioning as direct free radicals scavengers in synergy with ascorbate and other liposoluble vitamins (A, E) and as stimulants of the Nrf2/ARE pathway. O2-: Superoxide anion; H2O2: hydrogen peroxide; °OH: hydroxyl radical; LO2H: Lipid hydroperoxide; LPS: lipopolysaccharide; Keap1: Kelch-like ECH-associated protein 1; Nrf2: nuclear factor erythroid 2–related factor 2; Maf: musculoaponeurotic fibrosarcoma element; ARE: antioxidant response element.

Various in vitro and in vivo studies have shown that the antioxidant activity of hesperidin and quercetin is not limited to their scavenger activity, but actually increases cellular defences against oxidative stress through the signalling path Nrf2/ARE [88–95] (**Figure 5**).

The nuclear factor erythroid 2–related factor 2 (Nrf2) is of primary importance because it regulates gene expression through a promoter sequence known as the antioxidant response element (ARE). Normally Nrf2 is attached to another protein called Kelch-like ECH-associated protein 1 (Keap1) and is rapidly degraded through the ubiquitination and proteasome system, without performing any functions. On the other hand, in the presence of ROS, Nrf2 detaches from Keap1, is phosphorylated and translocates to the nucleus, where it combines with a small musculoaponeurotic fibrosarcoma (Maf) protein to form a dimer and binds to the antioxidant response element upstream of the promoter. This ARE + Nrf2 dimer then initiates the messenger RNA transcription of a series of target genes such as those encoding antioxidant enzymes ("Antioxidant systems" in **Figure 5**).

The ability of hesperidin to fight damage from toxic oxygen radicals and stimulate the expression of Nrf2 has been reported by various authors in other experimental models namely in hepatocarcinogenesis [96], hepatotoxicity [97], neuroinflammation and neurodegeneration [91, 98–102]. The protective effects of quercetin in neurodegenerative disorders and cerebrovascular diseases, demonstrated both in in vitro and in vivo studies are also largely linked to its ability to stimulate the defences against oxidative stress [103].

3. Organ failure and systemic pathology

Once they have reproduced in the cells of the entry tissues and overcome the first barriers of innate defences, the viruses spread to target organs and cause various types of clinical consequences in different individuals. It is known that the severity of COVID-19 as well as other viral respiratory infections is related to many different parameters (age, gender, nutritional status, comorbidities, etc.) and that people with pre-existing conditions such as diabetes, hypertension, and lung, heart and kidney diseases (all diseases in which ROS play a pathogenetic role) are at increased risk of developing severe effects. In serious cases, endothelial dysfunction, coagulopathy and pulmonary thrombosis cause hypoxia, mitochondrial chain abnormalities, mitochondrial dysfunction, oxidative stress, DNA damage [104, 105]. Another mechanism that links systemic inflammation syndrome and oxidative stress is hyperferritinemia, which often characterises COVID-19 [106, 107].

These mechanisms are involved in the extensive systemic lesions observed during severe complications associated with influenza. It has therefore been suggested that agents with antioxidant properties could be drugs of choice for the treatment of patients with such severe complications [108]. N-acetylcysteine, which supports glutathione and thus the main antioxidant defence systems [109], was used with good results in influenza syndromes [110] and acute respiratory distress syndrome (ARDS) [111], and it was suggested as a potential therapeutic agent for COVID-19 [112–114].

Figure 6 summarises the main critical points of the SARS-CoV-2 virus in the whole body and the possible interventions of the two flavonoids considered here, based on the knowledge acquired so far in other types of systemic and metabolic disorders.

Experimental evidence showed that treatment with hesperidin safeguards the aged rat's heart by increasing the levels of the Nrf2 factor and the activity of enzymatic antioxidants [115]. The same group showed a protective effect of hesperetin

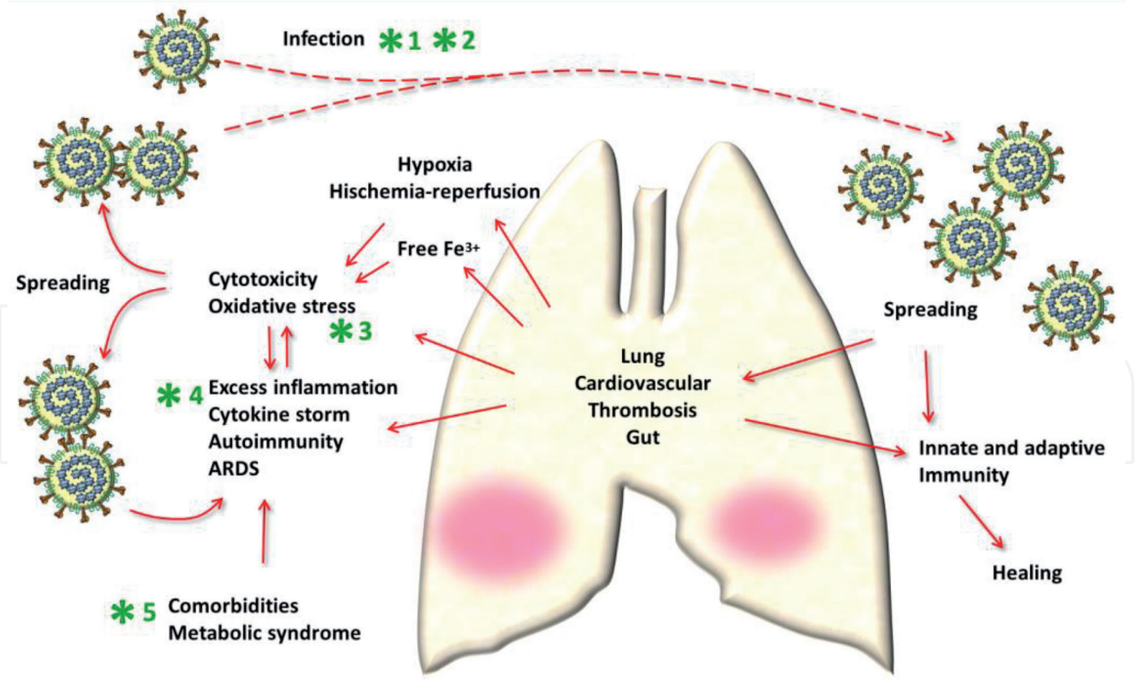

Figure 6.
*Diagram of the major systemic effects of COVID-19. The asterisks show the possible operation points of the flavonoids, as discussed in chapter 2 (*1, *2, *3) and in this chapter (*3, *4 and *5).*

on experimental heart failure in the rat [116]. The authors conclude that it is conceivable that hesperetin could be a potential therapeutic candidate that enhances Nrf2 signalling and thereby improves cardiac remodelling. Results from another study show the beneficial effects of citrus flavanones in the liver of aged rats, where nirangerin and hesperidin prevented the age-related decrease in catalase, superoxide dismutase and glutathione reductase [117].

The mechanism of ischemia–reperfusion liver injury was studied in a murine model by measuring oxidative stress indicators, serum enzymes and inflammation indices [118]. Hesperidin (100–400 mg/kg) significantly improved liver ischemia–reperfusion injury measured by serum alanine aminotransferase levels, reduced malondialdehyde content, but it increased superoxide dismutase, catalase, glutathione peroxidase levels. Furthermore, hesperidin significantly alleviated the expression levels of TNF-α, IL 6 and IL-1β. Hesperidin (100 mg/kg) protects rats from liver damage and dyslipidaemia caused by cadmium chloride [119].

The antioxidant effect of quercetin was studied in a two-week, randomised, crossover-controlled intervention trial [120]. Fourteen individuals ingested 2 capsules (total 1 g/d) of quercetin or a placebo. Blood samples were collected before, after 2 weeks of supplementation and after a period of strenuous exercise. Quercetin significantly reduced erythrocyte lipid peroxidation levels and susceptibility to haemolysis induced by free radicals, while no differences were found in antioxidant enzyme activities and glutathione homeostasis between the two groups. After a single period of intense exercise, quercetin supplementation improved redox status as assessed by the reduced glutathione/oxidised glutathione ratio and by thiobarbituric acid reactive substances levels in both erythrocytes and plasma.

3.1 Excess inflammation

During the spread of the virus in the tissues (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 comorbidities. Excessive and "vicious" inflammation can be mediated by a distorted activation of the cytokine network, by coagulation disorders, even by a paradoxical excess of the immune reaction (autoimmunity, cytotoxic lymphocytes) [121]. Oxidative stress and excess inflammation are linked, as shown in **Figure 6** (points *3 e *4). Autoimmune phenomena are also likely to be involved in the attack on the cell infected with SARS-CoV-2, which could have implications both in the clinical course of the disease [122, 123] and in the safety of vaccines [124].

The two flavonoids which are reviewed here have a remarkable ability to modulate local and systemic inflammatory responses, through various mechanisms. Hesperidin showed antioxidant activity in rats after an intense training programme and, at the same time, alleviated cytokine secretion by stimulated macrophages [125, 126]. Furthermore, the administration of hesperetin has been shown to significantly reduce the levels of myeloperoxidase, malondialdehyde (a marker of lipid peroxidation) and inflammation in experimental models of colitis [127] and hepatic trauma [128]. A study on macrophage cells in culture induced by bacterial endotoxin (LPS) clearly highlighted the main molecular effects of hesperetin capable of modulating inflammation [129].

One of the most frequently used experimental models is LPS-induced pneumonia in mice, which somewhat mimics ARDS. Three separate studies have shown that hesperidin (in doses between 10 and 200 mg/kg) significantly reduces the accumulation of fluid in the lung and proinflammatory cytokines [130–132]. The protective and anti-inflammatory effect of hesperidin or hesperetin was also demonstrated in rats with acute lung injury induced by mechanical ventilation [133] and lung infection with the H1N1 influenza virus [36]. Finally, hesperidin has anti-inflammatory and antioxidant effects in chronic obstructive pulmonary disease (COPD) caused by smoking, reducing the levels of IL-6, IL-8 and malondialdehyde [134].

Quercetin is a powerful antioxidant but also acts as an enzymatic inhibitor in a series of mechanisms involved with inflammation [135]. In LPS-stimulated macrophages, quercetin treatment inhibited NF-kB activation and proinflammatory cytokines [136]. A randomised, parallel-group, controlled polycentric study showed the efficacy of a dietary supplement based on quercetin (150 mg), perilla dry extract (80 mg) and vitamin D3 (5 μg) in preventing allergic rhinitis flare-ups in children [137, 138].

The antiallergic property of quercetin has been explored in the laboratory setting by studying the secretory response of activated mast cells in both human and animal models [139–143], and by evaluating the release of histamine from human basophils [144, 145]. This flavonol inhibits several protein tyrosine and serine/threonine kinases involved in signal transduction in inflammatory cells [26, 103, 139, 146–148]. These inhibitory properties on the release of histamine could also be interesting for COVID-19, given that the pulmonary mast cells are involved in the phenomenon of worsening the pulmonary picture in the event of a "cytokine storm" [149].

A meta-analysis of seven randomised trials sought to quantify the effect of quercetin on inflammatory mechanisms in vivo by measuring plasma C-reactive protein (CRP) concentrations. Meta-analysis showed a significant reduction in circulating CRP levels following supplementation with quercetin, especially at doses of 500 mg /day or more and in patients with CRP <3 mg/l [150].

3.2 Comorbidities

Since COVID-19 is a multi-organ disease and has more serious clinical consequences in patients with pulmonary, intestinal, hepatic and cardiovascular comorbidities, it is conceivable that its clinical course may profit from the multiple beneficial

effects of hesperidin and quercetin in systemic pathologies of this type (point * 5 in **Figure 6**). Epidemiological studies have reported an inverse relationship between citrus flavonoid intake and the risk of cardiovascular disease [151, 152]. From a careful review of the literature [153], the use of natural antioxidant polyphenols seems to be an excellent approach as they have strong antioxidant and anti-inflammatory properties.

A constellation of risk factors for cardiovascular disease is called metabolic syndrome (MetS), whose determining factors are, in order of importance: weight, genetics, ageing and lifestyle [154]. The criteria for defining MetS are based on the presence of 3 out of 5 factors, including obesity, elevated triglycerides, reduced HDL-C, elevated blood pressure and elevated fasting glucose [155]. It has been shown that individuals with these characteristics are also commonly prone to a chronic, low-grade inflammatory states. Oxidative stress phenomena are also involved in MetS, probably due to the disturbance of the nutrient metabolism at the mitochondrial level [154].

In this context, it is interesting to note that good results have been obtained in clinical studies with the integration of orange juice, polyphenols and particularly with both hesperidin and quercetin, with antioxidant and antihypertensive effects, and by regulating glucose metabolism and lipid profiles. A recent experimental study showed that hesperidin (15 or 30 mg/kg) improved biochemical alterations and cardiac dysfunction in a high-fat diet-induced MetS model in rats [156].

Soy isoflavones, citrus products, hesperidin and quercetin improved lipid metabolism [157]. Rizza et al. [158] performed a randomised, placebo-controlled study to investigate whether oral administration of hesperidin (500 mg once daily for 3 weeks) improves endothelial function in individuals with MetS. As a measure of efficacy, they measured the difference in flow-mediated dilation of the brachial artery between subjects receiving placebo or hesperidin. In the clinical study, hesperidin treatment increased flow-mediated dilation and decreased the circulating inflammatory biomarkers (highly sensitive C-reactive protein, serum amyloid A protein, soluble E-selectin). The authors concluded that hesperidin recovers endothelial dysfunction and reduces circulating markers of inflammation. Such vasculoprotective actions may explain the beneficial cardiovascular effects of citrus fruit consumption.

A double-blind study documented the beneficial effects of hesperidin supplementation (500 mg/day) on blood pressure and inflammatory markers in type 2 diabetes [159]. The mechanisms by which hesperidin could contribute to blood pressure control are associated with improvements in endothelial function, oxidative stress and inflammation [160]. In a study with a parallel group design, 49 patients with MetS received either 500 mg of hesperidin or a placebo, twice daily for 12 weeks [155]. Hesperidin led to a significant decrease in serum levels of glucose, insulin, triglycerides, total cholesterol, low density lipoprotein cholesterol, TNF-α and high sensitive-CRP. The data on the antihypertensive effect of hesperidin is more uncertain but recently Valls et al. published a study on healthy volunteers in which they actually showed an antihypertensive effect of orange juice enriched with hesperidin [152].

A systematic review has highlighted the potential antidiabetic action of citrus flavonoids and their molecular mechanisms based on in vitro and in vivo studies [161]. The research identified 38 articles, mostly on experimental animals, which reported that citrus flavonoids regulate glycaemic control biomarkers, lipid profiles, kidney function, liver enzymes and antioxidant enzymes, and modulated signalling pathways related to glucose uptake and insulin sensitivity that are involved in the pathogenesis of diabetes and its related complications. Citrus flavonoids, therefore, are promising antidiabetic candidates, while their antidiabetic effects have yet to be verified in upcoming human studies.

Quercetin supplementation also may have positive effects among patients with MetS and related disorders [162]. A meta-analysis identified 9 studies on this topic, which showed overall that quercetin supplementation did not affect fasting plasma glucose or insulin resistance. However, in the subgroup analysis, quercetin supplementation slightly but significantly reduced fasting glucose in studies lasting 8 weeks and using quercetin in doses equal to or > 500 mg/day. Better effects were found in individuals <45 years of age. Regarding lipid levels, a meta-analysis of 9 clinical studies [163] found a significant reduction in LDL in overweight and obese human subjects who took doses ≥250 mg/day of quercetin for rather extended periods, reaching a total dose of ≥14,000 mg; however, HDL cholesterol, triglyceride and total cholesterol levels remained unchanged ($p > 0.05$).

The supplementation of nutrition with quercetin on blood pressure and endothelial function among patients with MetS was investigated with a meta-analysis [164]. The authors found a significant reduction in systolic blood pressure but not diastolic pressure.

Finally, the health of the intestine cannot be neglected, which is an organ where viral infections tend to be found, and it is also fundamental because the release of endotoxins (LPS) due to an increased mucosa permeability or intestinal dysmicrobism could enhance systemic inflammatory reactions. It has been argued that the interaction between the lung and gut could lead to a vicious cycle of lung and intestinal inflammation which may be a potential factor leading to the death of patients with COVID-19 [165]. Citrus flavanones may have an impact on the intestinal microbiome, exerting beneficial effects on the intestinal barrier function and gastrointestinal inflammation [166]. In intervention studies on volunteers, orange juice positively modulated the composition and metabolic activity of the microbiota, increasing the population of Bifidobacterium spp. and Lactobacillus spp. [167] or of Lactobacillus spp., Akkermansia spp. and Ruminococcus spp. according to other authors [168], suggesting that orange juice showed a prebiotic effect, modulating the intestinal microbiota by improving blood sugar and the lipid profile. In a recent review [169], it was highlighted how the beneficial effects of hesperidin on cardiovascular risk factors can be partly attributed to the modulation of the intestinal microbiota. Based on the current evidence, some of the contradictory effects of hesperidin in human studies are in part due to the interindividual variability of hesperidin in its bioavailability. Quercetin also has a profound influence on the intestinal microbiome, which in turn modulates its bioavailability [170].

In conclusion, the results indicate that supplementation with hesperidin or quercetin may have mild antihypertensive effects, improve metabolic lipid abnormalities and inflammatory status in patients with MetS. All these beneficial effects can only be reflected in a more favourable clinical course when viral infectious diseases cause systemic disorders involving oxidative stress and inflammation.

4. Conclusions

The scientific literature is filled with works that support the beneficial effects of citrus flavonoids and quercetin on viral respiratory diseases, including COVID-19, and there are several possible mechanisms by which this effect is carried out (**Figure** 7).

Inhibition of cellular infection can occur through the intercalation of these molecules between viruses and receptors and by inhibition of intracellular replication. This phenomenon could have a protective role especially in the oral cavity and in the gastrointestinal system, where the concentrations of the active ingredients are undoubtedly higher than in the blood after intestinal absorption and diffusion

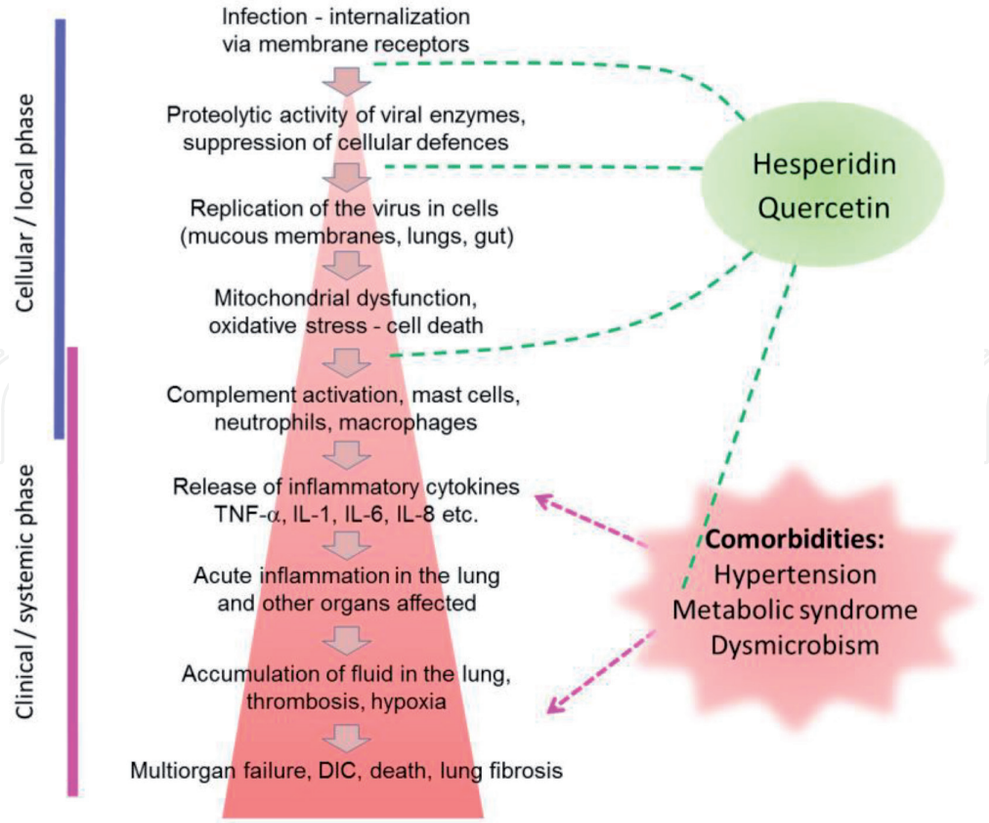

Figure 7.
Summary of the possible actions of flavonoids hesperidin and quercetin to prevent the progression of SARS-CoV-2 virus infection and its major clinical consequences.

in the body. Furthermore, the two flavonoids are able to prevent cell damage due to the virus by enhancing the antioxidant defences through the Nrf2 system and by the direct scavenger action.

The close relationship between cell damage/death and inflammation means that a positive effect can be expected in mitigating the systemic consequences of an inflammation that has eluded controls. Finally, hesperidin and quercetin can exert an indirect beneficial effect, favouring carbohydrate and lipid metabolism, improving general health conditions and thus preventing comorbidities that are contributory causes of the most serious complications. All the experimental models cited here would make it plausible for an increase in the consumption of flavonoid-rich foods, or flavonoid supplementation during periods of increased commitment of the body defences, to help the immune system in the fight against virus infections. It is therefore desirable that further suitable clinical studies are conducted to investigate the potential of these natural substances and to define effective dosages.

Acknowledgements

The article processing charges were borne by Vanda Omeopatici s.r.l. (Frascati, Roma). The sponsor had no role in the conception, writing or revision of the manuscript.

Conflict of interest

The author is scientific consultant from Vanda Omeopatici s.r.l. (Frascati, Roma), a company that produces food supplements.

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