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A Review of the Potential Roles of Antioxidant and Anti-Inflammatory Pharmacological Approaches for the Management of Mild-to-Moderate Symptomatic COVID-19

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In the past 2 years, the coronavirus disease 2019 (COVID-19) pandemic has driven investigational studies and controlled clinical trials on antiviral treatments and vaccines that have undergone regulatory approval. Now that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants may become endemic over time, there remains a need to identify drugs that treat the symptoms of COVID-19 and prevent progression toward severe cases, hospitalization, and death. Understanding the molecular mechanisms of SARS-CoV-2 infection is extremely important for the development of effective therapies against COVID-19. This review outlines the key pathways involved in the host response to SARS-CoV-2 infection and discusses the potential role of antioxidant and anti-inflammatory pharmacological approaches for the management of early mild-to-moderate COVID-19, using the examples of combined indomethacin, low-dose aspirin, omeprazole, hesperidin, quercetin, and vitamin C. The pharmacological targets of these substances are described here for their possible synergism in counteracting SARS-CoV-2 replication and progression of the infection from the upper respiratory airways to the blood, avoiding vascular complications and cytokine and bradykinin storms.

Keywords: Anti-Inflammatory Agents, Non-Steroidal • COVID-19 • Flavonoids • Hesperidin • Indomethacin • Quercetin

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Background

The severe acute respiratory syndrome, caused by SARS-CoV-2, leads to a wide spectrum of multi-organ pathologies, known as coronavirus disease 2019 (COVID-19). While there is obviously a great deal of pharmacological research going on, no specific definitive drugs are currently available for treating low-to-moderate-risk COVID-19. Patients admitted to hospitals in the most advanced countries receive intensive care, but the problem of lack of specific care mainly concerns the care provided in the early stages of the disease and therefore home care.

The Italian Ministry of Health and the Italian Medicines Agency (AIFA) have issued guidelines for the home management of patients with COVID-19, which follow the most up-to-date acquisitions of evidence-based medicine (https://www.aifa.gov.it/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-della-malattia-covid19). Low-risk patients are defined there by the absence of increased risk factors (eg, neoplastic pathologies or immunosuppression) and on the basis of the following characteristics: a) flu-like symptoms (eg, rhinitis, cough without breathing difficulties, myalgia, headache); b) absence of dyspnea and tachypnea (documenting, whenever possible, the presence of an SpO_2 >92%); c) fever ≤38°C or >38°C, for less than 72 h; d) gastro-enteric symptoms (in the absence of dehydration and/or multiple diarrheal discharges); e) asthenia, ageusia/dysgeusia/anosmia. In such patients, lacking a widely approved therapeutic strategy and pending evidence-based guidance, the health authorities suggest a "watchful waiting" or "monitoring" of clinical evolution and the use of symptomatic drugs, such as paracetamol or non-steroidal anti-inflammatory agents (NSAIDs), unless there are specific contraindications. However, lack of treatment in the first 72 h or limiting it to symptomatic medications could be risky in many patients, whose disease is destined to progress to more severe forms [1-4]. Indeed, many patients have a significant increase in D-dimer levels, an indicator of thrombosis, which correlates with a worse prognosis [5,6]. It is now well known that the virus, on entering the blood stream, can bind itself to platelet receptors, leading to hyper-aggregation and micro-thrombi [7]. Some patients develop a condition of severe pneumonia, with reduced oxygen saturation often associated with systemic inflammation, activation of intravascular coagulation, thrombosis, and multiple-organ failure [8].

Actually, some therapies have already been approved for early treatment of COVID-19 in "high risk patients", namely, Remdesivir, Molnupiravir, Paxlovid (Nirmatrelvir and Ritonavir) [9-11], and monoclonal antibodies (Bamlanivimab and Etesevimab, Casirivimab and Imdevimab, and, recently, Bebtelovimab) [12-14]. Among these drugs, only Molnupiravir and Paxlovid can be administered at home, while Remdesivir and monoclonal antibodies have to be administered in a hospital setting. In particular, among the monoclonal antibodies, only Bebtelovimab is specific for the Omicron variant, and Casirivimab is also partially active on this variant. However, according to the aforementioned guidelines and recent updates (https://www.salute.gov.it/portale/nuovocoronavirus/dettaglioComunicatiNuovoCoronavirus.jsp?lingua=italiano&id=5858), home therapies with monoclonal antibodies or with antivirals are indicated only for subjects with COVID-19 of recent onset, who present risk factors for the development of severe forms of the disease.

Paracetamol is an analgesic and antipyretic drug widely used in Italy to reduce fever and pains due to viral diseases. Although this drug is considered very safe, there are 2 aspects that may cast doubt on its usefulness in the case of COVID-19. The first is that it has a strong analgesic and antipyretic power, but has little anti-inflammatory effect. Therefore, intervention aimed solely at lowering the body temperature does not seem useful, or at least is not of primary importance. The second reason that would argue against the use of paracetamol is the fact that it is metabolized also by consumption of glutathione and could worsen oxidative stress [15-17]. This type of biochemical change may lower antiviral protection [18] or worsen the course of the disease, particularly in patients with liver dysfunction [19-21].

Moreover, with regard to the choice of the most suitable anti-inflammatory drugs, among the dozens available at the moment there is no criterion based on randomized studies, although a preliminary network pharmacology and molecular docking study seems to preferentially suggest indomethacin or rofecoxib as candidates for having a better impact, not only on the symptoms but also on the course of the disease [22]. Even regarding the most widely used drugs worldwide, such as ivermectin and hydroxychloroquine, there are diverging opinions and the meta-analyses are not conclusive [23-27].

In our previous study [6] we have shown that prompt treatment with different drugs featuring synergistic action mechanisms, which included anti-inflammatory drugs, acetyl salicylic acid with antiplatelet dosage, omeprazole, and a food supplement recently made available in Italy, comprising hesperidin, quercetin and vitamin C, produced a clear reduction of hospitalizations, symptom duration, and other important outcomes in patients with mild-to-moderate COVID-19.

Our retrospective study [6] confirmed the importance of early treatment by comparing therapy outcomes in 2 cohorts of patients (treated within 72 h vs later), but its aim was not to compare the efficacy of one treatment versus another. However, the study, despite being observational and retrospective, showed that this combination of drugs, used within the first 72 h from the beginning of symptoms, produced

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no hospitalizations, important reduction of symptom duration, and best outcomes of the disease. The aim of the current paper is, therefore, to more comprehensively review the pharmacological bases of drugs and food supplements which could counteract the main known pathophysiological alterations in this disease. This study could provide the rationale for endorsing a clinical trial comparing this multitherapy approach and other drugs that can be used in the initial phase of COVID-19 disease.

The COVID-19 pandemic has driven investigational studies and controlled clinical trials on antiviral treatments and vaccines that have undergone regulatory approval. However, there remains a need to identify pharmacological approaches to treat symptomatic COVID-19. This review outlines the key pathways involved in host response to SARS-CoV-2 infection and discusses the potential role of antioxidant and anti-inflammatory pharmacological approaches for the management of mild-to-moderate symptomatic COVID-19, such as combined indomethacin, low-dose aspirin, omeprazole, hesperidin, quercetin, and vitamin C. From the complex syndrome of COVID-19, we will consider only the aspects that seem most important as targets for pharmacological regulation as expressed in our multitherapy approach hypothesis.

Characteristics of COVID-19 in Its Earliest Stages

The pharmacological rationale for certain remedies can only be based on the pathophysiology of the disease itself, which we briefly summarize below in its essential stages, and on the well-known action mechanisms of the drugs already widely used for other indications.

When the virus meets the infected person's mucous membranes, it remains there for a few (3-4) days in a paucisymptomatic phase. If not intercepted by specific IgA, the SARS-CoV-2 virus enters the cells through the binding of the spike glycoproteins (S) to the angiotensin-converting enzyme-2 (ACE2) receptor [28,29], with the involvement of the cellular serine proteases transmembrane serine protease 2 (TMPRSS2) and/or the cathepsin system. The ACE2 receptor, which also has a fundamental enzymatic function in blood pressure homeostasis, is expressed in the lungs and many other tissues of the body, which explains the involvement of many organs and the systemic nature of the disease when the virus spreads [30-35]. Furthermore, the cysteine protease cathepsin L plays a role in the preparation of the spike protein of the virus and the internalization of the virus in the host cells [36].

After internalization, the coding sequences of the viral RNA are translated into a polyprotein, 1ab, which then undergoes a proteolytic process to form a series of non-structural proteins and, eventually, a replication complex. The main enzyme that performs this proteolytic transformation is the 3-chymotrypsin-like protease (3Clpro), or main protease (Mpro), which is the major target of antiviral drugs. Once viruses have entered the cells and started the replication process, they multiply exponentially, causing cell, tissue, and organ damage, which, together with the body's inflammatory reactions, generates a broad range of local and systemic symptoms.

Since SARS-CoV-2 initially infects the upper respiratory tract, mucosal immunity and secretory IgA appear to be crucial in the local immune response and in preventing the spread of the virus into the host organism. However, time is needed for the immune response to develop and the mucous membranes and salivary glands need to be preserved as much as possible from virus damage. The oral cavity is an important reservoir of SARS-CoV-2, and saliva is involved in viral transmission [37,38]. Available data indicate that the oral cavity is an active site of infection [39]. A growing body of evidence suggests that patients with COVID-19 experience various oral health problems such as dry mouth, blisters on mucous membranes, rashes, necrosis of the lips, and loss of taste and smell [40]. Furthermore, interactions between oral, pulmonary, and intestinal microbes appear to occur dynamically, so a dysbiotic oral microbial community could influence respiratory and gastrointestinal diseases [39].

Viral infections also cause an increase of reactive oxygen species (ROS) production, which is revealed by a decrease in the antioxidant capacity of biological fluids and an increased presence in the serum of derivatives from the oxidation of lipids and proteins [41]. Oxidative stress has been reported in hepatitis B [42], hepatitis C [43], influenza [44], and SARS-CoV-2 [16,45,46] infections. The phenomenon is particularly worrying when it occurs in elderly people, who already have a reduced antioxidant capacity [47,48], which could reduce the efficiency of the immune system [49] and modify the expression of the membrane receptors [50,51]. Indeed, severity and risk of mortality from COVID-19 have been associated with age [48]. This mechanism could be involved in the receptor interaction because the oxidation of SH residues of proteins can increase the affinity of the spike protein for ACE2 and thus facilitate infection [50]. A clinical study has confirmed the existence of oxidative stress, reporting that subjects with COVID-19 at an early stage had lower plasma free thiol concentrations than in healthy subjects [52]. A decrease of glutathione would lead to a decrease of antioxidant defenses and favor the entry of viruses into the cells [15,50]. The use of antioxidant therapies based on natural substances, supplements, and vitamins has also been proposed in an extensive review by Fratta Pasini et al [53].

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As the virus spreads through the body, with its cytotoxic effects, a systemic reaction develops, which is responsible for most clinical symptoms. Excess immune and inflammatory reactions can lead to a cytokine storm, multiple-organ failure, coagulation disorders, and eventually to autoimmune phenomena [54-57]. Inflammation seems to be involved in viral replication in cytomegalovirus (HCMV) infection: PGE2 stimulates the activity of the major immediate early promoter that controls the synthesis of viral regulatory proteins, which are essential for HCMV replication [58,59]. IL1beta and PGE2 significantly increase the expression of ACE2 and TMPRSS2 in gingival fibroblasts, thus facilitating virus entry [60]. Histamine released by mast cells, by increasing IL-1 production, can also amplify the inflammatory process in lung infected with SARS-CoV-2 [61]. The dual role of inflammation, both defensive and facilitating infection [62], makes the choice of anti-inflammatory drug type a particularly delicate one, possibly explaining the discrepancies in results in different patients and at different stages of the disease.

A particularly important aspect of circulatory pathophysiology concerns the renin-angiotensin system (RAS), which is responsible for controlling blood pressure and hydro-electrolyte balances, as well as certain inflammatory and coagulation mechanisms. The relationship among the virus, the immune system, and the renin-angiotensin system is a very complex one. Physiologically, ACE2 plays a role in regulating these 3 systems that could potentially be involved in the pathogenesis of COVID-19: the renin-angiotensin system, promoting cardiovascular instability; the coagulation system, leading to thromboembolism; and the kinin-kallikrein system, resulting in acute inflammatory pulmonary edema [63-68]. Angiotensin II-mediated activation of ATR1 receptors can, in turn, reinforce prolonged inflammation in the lungs [69]. Furthermore, the physiological clearance of bradykinin by ACE2 is missing and bradykinin-mediated inflammation likely precipitates respiratory and circulatory complications [70] until vicious cycles are established in the form of a so-called “bradykinin storm” [71-73].

Prescribed Drugs and Food Supplements

Based on the above, it appears that a rational approach to COVID-19 must be based on the use of various synergistic remedies, in order to best “cover” the greatest number of pathophysiological, immunological, and biochemical disorders involved in the disease: blocking or delaying virus replication, regulating inflammatory reactions, reducing the risk of thromboembolic complications, and limiting the potentially harmful oxidative stress. It is not the purpose of this paper to systematically review all the pharmacological proposals made to date for the treatment of COVID-19, so we will focus on the substances we used in a recent cohort study [6]. The suggested drugs and food supplements, supposedly endowed with the above-mentioned features, are the following: a) Indomethacin as a NSAID with additional antiviral activity; b) aspirin at low doses, to prevent platelet aggregation; c) omeprazole as a gastric protector; and d) hesperidin, quercetin, and vitamin C with antioxidant, anti-inflammatory, and possible antiviral activity. Below, we briefly describe the pharmacological properties of the substances used in relation to their potential and/or supposed effects on COVID-19 disease progression.

Indomethacin as a Promising NSAID

While inflammation is normally seen as a defensive phenomenon, in COVID-19 it is likely to play a pathogenic role even in the early stages, helping the virus in its replication rather than fighting it. Therefore, intervening with anti-inflammatory agents in the early stages could be a very reasonable therapeutic option.

The importance of early treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of patients with COVID-19 has been suggested by several authors [74-76]. Although no conclusive evidence is available for or against the use of NSAIDs, observational studies suggest that the use of selective COX-2 inhibitors, together with other drugs, can reduce the frequency of hospitalization, although it does not reduce the duration of symptoms [3]. In particular, indomethacin is an old and inexpensive anti-inflammatory drug used for headache and arthritis [77,78], and it can combat cough [79,80], which is a major cause of the spread of infection.

Moreover, this drug also has other interesting properties. A recent network pharmacology approach identified 3 target proteins associated with the renin-angiotensin system imbalance caused by SARS-CoV-2 (MAPK8, MAPK10, and BAD) and showed that indomethacin can reduce excessive inflammation by inactivating target proteins [22]. It has also been hypothesized that indomethacin can counteract the proinflammatory effects of bradykinin, thus reducing the COVID-19-induced symptoms induced by bradykinin network activation, such as dry cough and musculoskeletal pains [80]. It has also been shown that indomethacin together with resveratrol can improve the disease [81]. Indomethacin also reduces the levels of interleukin-6 and tumor necrosis factor alpha, which, by increasing during the disease, lead to some of its detrimental consequences [82].

The particular interest of indomethacin, among the multiple NSAIDs available, is related to the fact that this drug has direct antiviral properties against several viruses, including cytomegalovirus, herpes virus 6, and hepatitis B virus [59,83,84], SARS-COV-1 [85], and, recently, SARS-CoV-2, without cytotoxic

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effects [86,87]. According to Amici [88], in a vesicular stomatitis infection model, indomethacin activated PKR (double-stranded RNA-dependent protein kinase), resulting in the phosphorylation of eIF2α and, in turn, interrupting the translation of the viral protein and inhibiting viral replication.

Molecular docking studies have suggested that indomethacin is a potential main protease antagonist of SARS-COV-2 [74] and is able to downregulate genes of interest for virus fusion (ACE2 and TMPRSS2), as well as other genes involved in the same pathways [89]. Direct evidence for the antiviral efficacy of indomethacin, but not of aspirin, against SARS-CoV-2 was provided in cellular models and in vivo in an infected canine model [90], suggesting that the effect is independent of anti-inflammatory action. A very recent review has shown, with system biology-based modeling, that the action of indomethacin against SARS-CoV-2 depends on the fact that prostaglandin synthetase is related to the action of some structural proteins, so that the inhibition of the former blocks the function of the latter, which are involved in the replication of viral RNA [91].

Finally, another peculiar aspect of the action of indomethacin is that it reduces bradykinin, which is linked to RAS imbalance and is responsible for important symptoms such as generalized pain, myalgia, and dry cough [80]. The specific involvement of bradykinin metabolism in the disease also depends on the fact that the enzyme ACE2 is involved in the degradation of bradykinin [92,93], and the acute phases of the inflammatory process in COVID-19 has been also defined as "bradykinin storm" [71-73,94]. Some studies have also shown that indomethacin has a favorable immunomodulatory role in the treatment of COVID-19 [86,95,96].

Low-Dose Aspirin

Low-dose aspirin has been widely used as an antithrombotic agent. Its use in SARS-CoV-2 infection could help reduce or dampen platelet hyper-aggregation, which may be caused by the binding of the virus spike to platelet ACE2 receptors, and it could be used to prevent thrombosis during the early phase of COVID-19 [97,98].

According to Rizk et al [99], aspirin would be indicated for early-stage COVID-19 because it interrupts a vicious cycle between platelet aggregation caused by the virus spike, activation and degranulation of neutrophils, coagulation, and immune-thrombosis. Others have also proposed a solid treatment option with aspirin – in addition to indomethacin, diclofenac, and celecoxib – to deactivate the inflammasome and modulate the overproduction of proinflammatory cytokines [76].

A Gastric Protector with Possible Antiviral Action: Omeprazole

The use of a gastric protector could be considered to prevent possible gastrointestinal damage due to NSAIDs [100,101]. Among these, omeprazole was chosen because, in addition to its known ability to protect against gastro-duodenal lesions caused by NSAIDs, it was proposed as a molecule capable of inhibiting the Mpro of SARS-CoV-2 by binding to its C-terminal domain [102].

Another interesting work that could support the rationale for the use of omeprazole in COVID-19 concerns the inhibition of SARS-CoV-2 internalization through ACE2 [103]. In contrast to this evidence, in renal cells omeprazole increased the expression of ACE2, but not TMPRSS2 [104]. How much the different effects of omeprazole on different cells are involved in the clinical and pharmacological treatment of COVID-19 should be the subject of further studies.

Flavonoids and Vitamin C

Taking into account the importance of oxidative stress in the dynamics of viral diseases and in particular in SARS-CoV-2 infection [105], it is proposed to include in the therapeutic scheme a food supplement based on flavonoids and vitamin C. These substances are endowed with antioxidant power and could also play a regulatory role in thrombotic mechanisms [45,48,106-108].

Hesperidin is the glycosidic flavonoid most common in citrus fruits and exerts its action by enhancing cellular antioxidant defenses through the ERK/Nrf2 pathway [109]. In addition, hesperidin has a mild anti-inflammatory action by suppressing the production of cytokines by inhibiting the activation of the NF-κB signaling cascade [110]. Hesperidin can reduce replication of the influenza virus [111,112] and the SARS virus [113]. Several lines of research have allowed us to repurpose hesperidin as a suitable candidate for blocking the interaction of SARS-CoV-2 with ACE2 receptors [114-118] or for inhibiting its replication [119-121]. Through its anti-inflammatory activity, hesperidin inhibits the secretion of proinflammatory cytokines such as INF-gamma and IL-2, thus reducing the possibility of a cytokine storm [110,122-125]. The high safety of hesperidin after oral intake has been declared by FASEB (Federation of American Societies of Experimental Biology), at the request of the FDA [110], and has been confirmed by animal [125,126] and clinical [127] toxicity studies.

Quercetin is a carbohydrate-free flavonoid that is most abundant in vegetables and fruits and is the most-studied phytochemical when it comes to assessing the biological effects

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of flavonoids [128,129]. Quercetin also acts as a free radical scavenger, donating 2 electrons to oxidized species which are reduced. Colunga Biancatelli et al argued that this antioxidant activity of quercetin could be exploited in the treatment of COVID-19 in synergy with vitamin C [130]. In fact, vitamin C has the ability to protect the flavonol molecule, recycling its oxidized quinonic form after the scavenger action on free radicals. As its action mechanisms, quercetin directly inhibits the coronavirus major protease [131,132] and the inflammasome NLR family pyrin domain containing 3 (NLRP3) in macrophages [133]. Interestingly, a molecular docking study showed that hesperidin and quercetin interact with the SARS-CoV-2 enzyme Mpro on different amino acids of its activation site, suggesting that they have synergistic antiviral actions [134].

A prospective randomized controlled open-label study suggested quercetin supplementation at an early stage of COVID-19. The results of this study have shown a reduction in the frequency and duration of hospitalizations, the need for non-invasive oxygen therapy, progression to intensive care units, and the number of deaths [135]. A further study has shown that quercetin, in the bioavailable form of phytosome, resulted in a greater likelihood of early benign disease resolution in subjects with COVID-19 [136].

It is also interesting that, in mouse models, quercetin has a protective effect against gastric [137] and intestinal epithelial injury [138] induced by high doses of indomethacin, suggesting that in our proposed multitherapy, quercetin may have a further protective effect, besides omeprazole.

The Combined Therapy

The main aim of a therapy in the early stage of the disease is to prevent spread of the virus and to reduce the risk of excessively pathological reactions. A reduction of morbidity and mortality for COVID-19 has been described with a prompt intervention based on the use of different associations of drugs, as compared with no treatment [2] or delayed treatment [6].

In theory, the ideal therapy should include drugs that block the virus on the mucous membranes, preventing it from entering the bloodstream and spreading to vital organs for long enough to allow the affected person to form enough antibodies, particularly mucosal secretory IgA, to control and render the virus harmless. The first humoral responses to SARS-CoV-2 are dominated by IgA antibodies, which appear to have greater neutralizing power than IgG. After natural infection, secretory and neutralizing IgA are found in the saliva for a longer time, at least 2-3 months after the symptoms [139], but immune responses to vaccination do not develop an adequate mucosal IgA response [140]. Furthermore, it is known that the dimeric form of IgA, which is found in response to the virus in all mucosal secretions, in both the respiratory and intestinal tracts, is more potent against SARS-CoV-2 than both the monomeric form of IgG and monomeric IgA [141,142]. Furthermore, it is possible that mucosal immunity could be exploited for beneficial diagnostic, therapeutic, or prophylactic purposes [143].

To this end, drugs with antiviral action should be used at the first symptoms of the disease, which, by interfering with the virus binding to the host's cellular ACE2 receptors, prevent further invasion of the blood stream and vital organs, thus giving the infected person time to form sufficient neutralizing levels of secretory IgA. Nutraceutical compounds, such as flavonoids, which dissolve slowly in the oral cavity, could be of considerable importance in protecting the mucous membranes of the salivary glands and tonsils, which are the primary lymphatic organs involved in defending against infection [144-146]. The defense could be direct, by preventing the virus binding to abundant receptors in the oral mucosa, but also indirect, because flavonoids could protect the mucosal epithelial cells [147] and periodontal tissue [148-151] from oxidative stress and thus promote phagocytosis and secretory IgA formation (epithelial function).

Based on these considerations and our results, the main substances used in this study appear to have synergistic antiviral actions when administered early at the onset of symptoms (**Figure 1**, steps no. 1-2) [74,81,87,120,152-155]. In addition, hesperidin, quercetin, and vitamin C counter oxidative stress, namely the SARS-COV-2 cytotoxic effects (**Figure 1**, step no. 3) [45,46,115,130,156-160], and the action of phagocytes activated NADPH oxidase (**Figure 1**, step no. 4) [161,162]. Finally, the known anti-inflammatory properties of indomethacin and aspirin may help prevent complications associated with excessive inflammatory and immune reactions (**Figure 1**, step no. 5).

Figure 1 also shows a "bifurcation" point (asterisk at step no. 6), which is very important in determining the evolution of the disease – whether the patient is heading toward recovery or is likely to have clinically serious complications.

A multi-drug approach is also crucial to limit the possibility of developing strains resistant to a single drug that may have shown great efficacy in early applications. The same strategy led to the victory against HIV [163]. Our approach involves the use of indomethacin and 2 flavonoids that act both on the spike protein/ACE2 receptor binding and on the major protease that is a key step in viral replication.

Perspectives

The evidence presented in this review could help design suitable clinical trials for the therapy of early stages of COVID-19.

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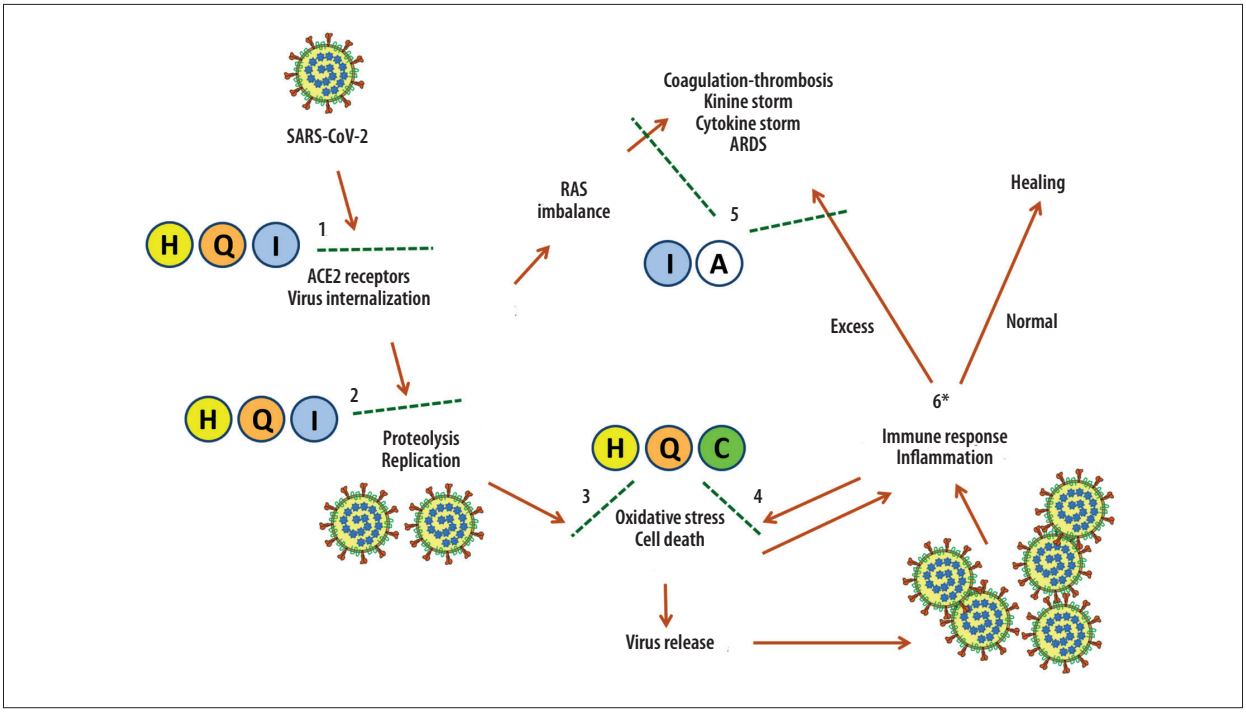

Figure 1. Schematic representation of the main cellular (**1-2-3**) and systemic (**4-5-6**) biological events following SARS-CoV-2 infection and synergistic effects of the substances described in this study. H – Hesperidin, Q – Quercetin, I – Indomethacin, C – Vitamin C, A – Low-dose aspirin. ACE2 – Angiotensin-Converting Enzyme-2; RAS – Renin-Angiotensin System. Bibliographic references of the indicated effects are given in the text. The figure was created with PowerPoint software (Microsoft Office 2019).

Any antiviral will need to be administered as soon as possible at the onset of symptoms, because once the virus has entered the bloodstream in significant quantities, it will rapidly initiate platelet micro-thrombosis, with subsequent worsening, respiratory failure, and, in some cases, the triggering of an excessive immune response and cytokine storm. Therefore, to verify the efficacy of multi-drug approaches, it will not suffice to examine the efficacy of the individual components, but it will be necessary to carry out comparative studies between different formulations applied to patients at comparable stages of disease and baseline characteristics. To do this, it would be useful to carry out studies in which the basic combination therapy could be modified by the addition of a new component or the subtraction of any of the existing ones. A model of this approach was followed by Ravichandran et al [164], who formed 2 groups given the same multitherapy and differing only in that one was given paracetamol and the other indomethacin. Ideally, this type of comparative, or "non-inferiority", research between different treatment models could be carried out in randomized trials, although the organizational difficulties would be considerable and double blinding seems objectively difficult to achieve.

Another aspect is the pharmacological convenience of combating a viral disease with a wide range of active ingredients targeting various mechanisms of virus infectivity and possibly acting synergistically. Recently, Suter et al showed that early anti-inflammatory treatment of outpatients with mild-to-moderate COVID-19 could reduce the risk of hospitalization and related costs by 90%, although it did not achieve a faster recovery from symptoms [3], probably due to the lack of an antiviral and antioxidant component, or the use of NSAIDs with suboptimal antiviral defense capabilities.

It would certainly be useful to carry out robust prospective randomized studies to confirm the results of our preliminary research, carried out with a retrospective observational design [6]. The importance of identifying drug combinations for multiple targets, addressing different stages of COVID-19 and different pathophysiological changes, has also been emphasized by others [165]. This approach envisages that, from an experimental point of view, multicenter studies can be initiated on large numbers of patients treated with different combinations of drugs and supplements, but following a common protocol of recruitment, data collection, and analysis, to compare the different options in the field by means of multivariate analysis. In such a complex viral disease, which is likely to be progressive, and in the absence of an effective and decisive drug, there are obviously several therapeutic proposals, which mostly consist of various drug combinations. It is essential that the results of the various approaches can be compared, so that the most suitable choices for each stage of the disease can be progressively specified and clarified on the basis of hard evidence.

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The critical point of disease progress described in **Figure 1** (step no. 6) is influenced by the subject's general state of health, and hence by age and the possible presence of unfavorable genetic factors, comorbidities, or metabolic disorders, such as diabetes, hypertension, or dyslipidemia. Therefore, these potentially confounding factors should be controlled in the protocol of any comparative multicenter study of different treatment approaches. Equally important will be to take note of the delay of initiation of therapy compared to the onset of symptoms, as this factor seems crucial in determining outcome [2-4,6].

Our model of treatment does not present a "magic formula", but a working hypothesis based on common and proven safe drugs, although obviously the specific contraindications of each of the substances mentioned here must be taken into account. Moreover, it should be stressed that we present a basic scheme and deliberately do not deal with clinical complications and hospital treatment, which require additional drugs.

Conclusions

While waiting for a resolving drug, the complexity of the dynamic alterations of the COVID-19 disease, particularly the double role (defensive and offensive) of the immunological and inflammatory mechanisms, requires a multitherapy approach that affects the different targets. Indomethacin, aspirin, hesperidin, quercetin, vitamin C, and omeprazole are presented as a set of safe and inexpensive substances with synergistic effects on the early stages of infection, viral replication, cytotoxicity, oxidative stress, and excess inflammation. This approach could be compared, through controlled clinical trials, with other combinations of potentially useful drugs.

Declaration of Figures' Authenticity

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