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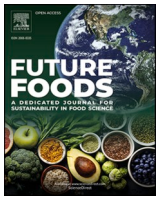

Review from host and guest approach to new frontiers nutraceuticals in the era of COVID-19

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ABSTRACT

COVID-19 continues to claim victims in the world, especially among elderly subjects and people suffering from chronic-degenerative pathologies, like cardiovascular diseases. Several vaccines and drugs have been developed to mitigate the infection spread and its deleterious consequences. However, the emergence of new variants requires the identification of solutions to deal with the challenging mutations. In this context, the investigation of phytocomplexes and related compounds used in folk medicine and culinary purposes may lead to unfold nutraceuticals endowed with antiviral, and cardioprotective properties. We have described several vegetal extracts and secondary metabolites that hit the most important viral and host targets and bind them. The connection between SARS-CoV-2 and cardiovascular diseases were also outlined, as well as phytocomplexes with potentials for their mitigation. The review provides both an entry point for new researchers in this area, and a comprehensive overview for further investigation of the natural products presented.

1. Introduction

The emergence of a novel Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) resulted in one of the greatest pandemics of human history (Fiorino et al., 2021) . This virus consists of single-strand-RNA (ssRNA) and can cause infections in several animals and human species (Iranmanesh et al., 2021) . The SARS-CoV-2 infections reported by Wordometer were 640,395,651 as at December 2nd, 2022, and the number of deaths up to 6618,579.

The virus is a member of beta-coronaviruses and spreads to all countries of the world. The World Health Organization (WHO) declared this new virus a global Pandemic in February 2020. Initially, bats were confirmed to be the primary source of the virus transmission to humans (Khoury, 2020).

Globally, over 3.7 million new cases and over 26 000 deaths were reported in the last 28 days (20 February to 19 March 2023), a decrease of 31% and 46%, respectively, compared to the previous 28 days (23 January to 19 February 2023). However, there are significant regional differences including increases in some regions. As of 19 March 2023, over 760 million confirmed cases and over 6.8 million deaths have been reported globally COVID-19 Weekly Epidemiological Update Edition 135 published 22 March 2023).

Despite the presence of a SARS-CoV-2 proofreading activity during the viral replication, WHO has been registered five major variants of SARS-CoV-2, since early 2020. Currently, Omicron BA.5 and its descendent lineages accounted for 35.3% prevalence of all shared sequences through GISAID. WHO currently has seven Omicron subvariants under monitoring due to their transmission advantage compared to other circulating variants and additional amino acid changes that are known or suspected to confer fitness advantage (WHO 2023). BQ and

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XBB subvariants, for example, present serious threats to current COVID-19 vaccines because of their advantage in evading antibodies (Wang et al., 2023).

Signs of COVID-19 include a wide range of symptoms like cold, fever, cough, diarrhea, myalgia and other signs comprising hemoptysis, headache, sputum difficulty, pneumonia with lymphocytopenia. Even though respiratory symptoms dominate the clinical presentation of COVID-19, gastrointestinal symptoms are observed in a subset of patients (Gu et al., 2020)). Early treatment of COVID-19-associated diarrhea could relieve symptoms and limit viral spread within the gastrointestinal tract (Poeta et al., 2021; Poeta et al., 2022).

Modes of transmission for SARS-CoV-2, include contact, droplet, airborne, fomite, fecal-oral, bloodborne, mother-to-child, and animal-to-human transmission. Infection with SARS-CoV-2 primarily causes respiratory illness ranging from mild disease to severe disease and death, and some people infected with the virus never develop symptoms (World Health Organization 2020).

Viral transmission mainly occurs through respiratory droplets, emitted because of coughing, sneezing, and talking of by infected people… The other way of viral transmission is represented by direct physical contact with the surface with infected droplets (Karimi et al., 2021). A study of Magurano et al., 2021 supports the hypothesis that during the hot season the increase of temperature may influence the environmental endurance of SARS-CoV-2 and reduce the probability of virus transmission. The emergence of COVID-19 forced the design of stricter requirements for new tools to prevent and cure this pandemic (Gangal et al., 2020). In addition, many studies demonstrated different mortality rates in different groups of ages. Severe COVID-19 generally occurs in people over the age of 60 (Jordan et al., 2020).

SARS-CoV-2 particles have a size of about 120 nm and their RNA (26–32 kgbase) consists of six to eleven open reading frames, converting 9680 proteins and the gene of Hemagglutinin Esterase is absent, and consists of five prime and three prime UTRs (Gao et al., 2020).

As it was already observed for many RNA viruses, Beta-coronaviruses replication involves cellular compartments such as the endoplasmic reticulum (ER), Golgi apparatus and the so-called Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC), each going through an intense remodeling induced by the viral replication. These cellular modifications imply the contribution of host cell membranes and organelles that participate to the viral replication (Cortese et al., 2020).

Some organs like lungs, kidney, liver, colon, sweat gland epithelium and dermal papillary vessels endothelia are the most likely targets of the virus because, they express ACE2 receptors. In human lungs ACE2 is expressed mainly in the alveolar epithelial type II cells and ciliated cells but the highest expression of ACE2 in the human body occurs in the brush border of the intestinal enterocytes (Qi et al., 2020).

In infected patients, SARS-CoV-2 particles were mainly detected in saliva and bronchial secretions (Iranmanesh et al., 2021).

The replication of the viral genome within the infected cells is a key stage of the SARS-CoV-2 life cycle and involves several viral and host proteins for RNA polymerization, proofreading and final capping. Thus, the studies of in vitro models of infection to investigate the fitness replication of SARS-CoV-2 and its emerging variants can be crucial for preclinical evaluation of therapeutic molecules. The inhibition of the coronavirus S protein cleavage and the mechanisms involved in the virus replication represent promising strategies to fight this viral infection. Also, the inhibition of other proteins such as TMPRSS2, RdRp, 3CLpro, ACE-2 represents a good strategy (Mamidala et al., 2022).

Scientists have devotedly braced the challenges thrown up by the Coronavirus disease (COVID-19) with the development of vaccines and other health management protocols used to curtail the ravaging effects of the virus. However, the high mutation rate of SARS-CoV-2 has been responsible for the difficulty to develop an efficient vaccine (Mehmood et al., 2021) . Several novel vaccines against COVID-19 are still undergoing studies at various stages, but in the meantime the virus continues undergoing mutations that may lead to strains resistant to the available vaccines (Hossain et al., 2022)

As of November 21, 2023, the global landscape of SARS-CoV-2 showcases a dynamic evolution with the emergence of several variants of interest (VOIs) and variants under monitoring (VUMs). These variants, characterized by distinct genetic features, present a complex scenario that demands close scrutiny.

Among the variants of interest (VOIs), XBB.1.5 stands out as a recombinant powerhouse. It is a hybrid of BA.2.10.1 and BA.2.75 sublineages, incorporating elements from BJ.1 and BM.1.1.1, with a notable breakpoint in S1. This variant, identified on October 21, 2022, has undergone multiple risk assessments, highlighting its ongoing significance in the SARS-CoV-2 landscape. Similarly, XBB.1.16, identified on January 9, 2023, represents a fusion of BA.2.10.1 and BA.2.75 sublineages, incorporating S:E180V, S:K478R, and S:F486P mutations. Its genetic complexity has prompted continuous risk assessments, underscoring its relevance in the ongoing dynamics of SARS-CoV-2.

EG.5, derived from XBB.1.9.2 + *S*:F456L, is another variant unraveling genetic complexity. Identified on February 17, 2023, it features various subvariants like EG.5.1, HK.3, and HV.1. Continuous risk evaluations have been conducted to understand the implications of its intricate genetic profile. BA.2.86, a variant relative to BA.2, includes the JN.1 subvariant with the S:L455S mutation. Initially documented on July 24, 2023, it has undergone an initial risk evaluation as of November 21, 2023. Turning to variants under monitoring (VUMs), DV.7, documented since January 19, 2023, exhibits noteworthy genetic alterations with CH.1.1 + *S*:N185D, S:L858I mutations. It is subject to monitoring with a risk assessment conducted on October 23, 2023. XBB*, identified on August 19, 2022, showcases an intriguing genetic composition derived from BA.2 with multiple spike mutations. Risk assessments were conducted on October 12, 2022, highlighting its uniqueness in the spectrum of SARS-CoV-2 variants (WHO, 2023).

The ongoing evolution of SARS-CoV-2 variants underscores the need for continuous monitoring and assessment. These variants, each with its distinctive genetic features, contribute to the dynamic nature of the pandemic.

2. COVID-19 pharmacotherapy: antivirals and immunomodulators overview

The current pharmacological interventions for addressing COVID-19 encompass distinct categories of drugs, each meticulously selected with specific regulatory designations: those that act directly on the virus and those that modulate the host response. Notably, Remdesivir and ritonavir-boosted nirmatrelvir have earned explicit approval from the Food and Drug Administration (FDA) for their targeted efficacy against COVID-19. In contrast, Molnupiravir and high-titer COVID-19 convalescent plasma (CCP) operate under Emergency Use Authorizations, acknowledging their critical role in mitigating the impact of the disease.

The treatment horizon extends into hospital settings for both adults and children, where Remdesivir, either as a standalone agent or in combination with immunomodulators, takes center stage.

For patients requiring conventional oxygen, the synergistic application of dexamethasone and remdesivir is recommended. In cases marked by escalating oxygen requirements and systemic inflammation, other immunomodulators, notably baricitinib, tocilizumab, abatacept, infliximab are administered.

Also, the Janus kinase (JAK) inhibitor PO tofacitinib or the interleukin-6 (IL-6) inhibitor IV sarilumab, available exclusively as a subcutaneous injection, alongside dexamethasone is emphasized.

Therefore, strengthening the search for new substances able to inhibit SARS-CoV-2 may be relevant to decrease the impact of the pandemic. Drug discovery processes may be mainly exerted in two ways: the identification of synthetic molecules able to hit guest or host targets, and the investigation of plants and related compounds used in folk medicine such as Traditional Chinese Medicine, Unani Medicine,

Ayurvedic Medicine, African traditional medicine.

In ancient times, people used to apply plants extracts and infusions as therapeutic agents for many diseases, including viral infections (Mani et al., 2020) . In these traditional systems, both foods and plants extracts had an essential role in the management of several pathologies. Traditional medicinal knowledge provided significant contributions to the development of vegetal extracts and isolated compounds endowed with several biological activities including antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory effects.

In the last years, the research on natural products has attracted increasing attention from the scientific community (Dar et al., 2017) . In this context, the research focuses on the achievement of two main objectives: the identification of food matrices, phytocomplex fractions and compound classes endowed with potential therapeutically activities and the discovery of new active compounds that may be further studied for pharmaceutical purposes (Zeka et al., 2017).

The term 'phytocomplex' refers to mixtures of organic compounds and trace elements, extracted from plants, that may be able to affect several molecular networks influencing each other. For example, *Olea europea* L. leaves extracts are rich in oleuropein, which has the capacity to reduce the vascular tone and exert several other biological activities, including antioxidant and anti- inflammatory effects, resulting in a general improvement of the health status in people suffering from atherosclerosis and hypertension (Micucci et al., 2015; Micucci et al., 2016). Other plants extracts were also shown to inhibit influenza A viruses and decrease inflammation, like in the case of Honeysuckle Extracts (Li et al., 2022; Magurano et al., 2023). For this reason, it is worthy of note that the research on substances with the ability to act both on viruses and host cells, according to a model defined as "host and guest targeting approach", is a great way of discovering new phytopharmaceutical molecules (Magurano et al., 2023). Several phytocomplexes and phytochemicals, including those obtained from *Citrus paradisi* Macfad. contain among others, limonoids and flavonoids that were shown to inhibit SARS-CoV-2 replication, reduce oxidative stress and decrease airways inflammation in SARS-CoV-2 patients (Majnooni et al., 2020). Preliminary data strongly suggest the potential of some vegetal extracts and natural compounds as effective agents against COVID-19 . In addition, several traditional herbs were administered to COVID-19 affected patients, with promising results (Liu et al., 2020; Karimi et al., 2021; Koshak et al., 2021; Soni and Paari, 2023). Some clinical trials suggest positive effects of phytocomplexes, such as taurisolo (Varnasseri et al., 2022), polyherbal formulations such as Aayudh Advance (Duru et al., 2021), Infuza & Kulzam (Chandra et al., 2022), Kabasura Kudineer (Natarajan et al., 2021), in the management of COVID-19. Notably, the traditional Unani medicine formulations Infuza and Kulzam have been used for decades, are well tolerated, and have not been associated with any safety issues. All adverse events/reactions were monitored and recorded, with detailed safety procedures submitted to the ethics committee. Similarly, in the study of Kabasura Kudineer, no adverse events were reported in both the control and study groups, indicating a high level of safety in its clinical use

The investigation of phytocomplexes may lead both to the identification and development of nutraceuticals to be used against COVID-19 and new antiviral drugs. In this sense, some Citrus limonoids were discovered to inhibit SARS-CoV-2 in vitro (Magurano et al., 2021b) . Other phytochemicals could be further studied as anti-COVID-19 agents since they can block the SARS-CoV-2 life cycle, interacting with many different viral and host proteins (Lim et al., 2021) .

The various enzymes such as transmembrane protease serine 2 (TMPRSS2), Angiotensin-converting enzyme 2 (ACE2), RNA-dependent-RNA polymerase (RdRp), 3Chymotrypsin-like protein (3CLpro), and Spike protein (S protein) are discussed, and the mechanisms of the viral infection highlighted. Studies on the effectiveness of phytocomplexes and isolated compounds with potency to mitigate the infection and the virus spread are also presented with emphasis on the target proteins and enzymes acted upon. Therefore, this review brought together current knowledge on the effectiveness of phytocomplexes and isolated compounds for the mitigation of SARS-CoV-2 effects and treatment of COVID-19, with the aim that the knowledge will favor the finding of novel and efficient treatment of the pandemic.

3. Phytocomplexes and isolated compounds targeting- SARS-COV-2 and host proteins

Plant extracts are characterized by the presence of numerous organic molecules characterized by a high degree of structural and functional heterogeneity. The study of these substances also includes phytochemical investigations which may lead to the discovery of chemotypes capable of interacting with known molecular targets. From this point of view, scientific research focused on food chemistry and nutraceuticals may have a double purpose, the identification of new chemotypes that could constitute scaffolds for the development of new pharmaceutical molecules and the development of substances with nutraceuticals applications (Lordan and Rando, 2021). In this paragraph, phytocomplexes and isolated compounds interacting with viral and human targets involved in SARS-CoV-2 infection are discussed.

3.1. Phytocomplexes and isolated compounds targeting Angiotensin-Converting enzyme 2 (ACE2)

Angiotensin-converting enzyme 2 (ACE2) was described in 2000 as a homolog of angiotensin-converting enzyme (Liu et al., 2020) . ACE2 consists of 805 amino acids, and has two domains namely, amino- and carboxy-catalytic terminal domains. The zinc metalloprotein site, which has the carboxy-catalytic domain consists of 41.8% ACE sequence (Liu et al., 2020). ACE2 encoding gene is located on the X chromosome, Xp22.2., with evidence showing its expression in the heart, kidney, lung, liver, testis, as well as gastrointestinal organs. Biological functions of this important enzyme could be split into two: peptidase dependent and peptidase independent. The peptidase-dependent function is responsible for metabolizing angiotensin I (Ang I) into angiotensin 1–9 (Ang 1–9) peptide and angiotensin II (Ang II) into angiotensin 1–7 (Ang 1–7) peptides while the peptidase-independent function is mainly responsible, among other functions, for the reception of coronavirus infection. ACE2 was identified in 2003 as a functional receptor for SARS-CoV infection and transmission (Liu et al., 2020) . The SARS-CoV Spike protein binds the tip of the subunit I of the ACE2 but not the subunit II nor the active site of the peptidase. Once SARS-CoV attaches to ACE2 and cleaves into the cell, endocytosis of transmembrane domain occurs. Comparing the spike protein sequences of SARS-CoV-2 and SARS-CoV, Liu and colleagues found similarities between 76% and 78% for the whole protein, about 73%–76% for the receptor-binding domain, and 50%–53% for the receptor-binding motif. (Liu et al., 2020) . Examination of the spike protein trimer of SARS-CoV-2 with a 3.5-Å-resolution cryo-electron microscope (cryo-EM) in prefusion conformation shows that SARS-CoV-2 spike protein has the same mechanism of triggering, similar to other viruses of the Coronaviridae family (Wrapp et al., 2020) . However, biophysical and structural evidence showed that the spike protein of SARS-CoV-2 binds to ACE2 with 10- to 20- fold higher affinity than spike protein of SARS-CoV. The high affinity index of SARS-CoV-2 spike protein for human angiotensin-converting enzyme 2 (hACE2) might facilitate the spread of the virus from human to human. Moreover, the SARS-CoV-2 spike protein and hACE2 receptor were discovered to colocalize the alveolar epithelial cells, which further confirms the results that SARS-CoV-2 virus uses the hACE2 as a receptor for cell entry (Bao et al., 2020).

Among many plants that have shown potential in SARS-CoV-2 infection prevention and treatment, garlic stands out as one phytocomplex that acts efficiently on ACE-2 protein. This substance has been used as coadjuvant in the treatment of flu and SARS-CoV-2 induced pneumonia. Garlic essential oil was extracted from commercial garlic using steam distillation, and its composition was identified by GC–MS

analysis. The phytocomplex was chemically characterized and the main detected compounds allyl disulfide, allyl trisulfide, allyl (E)−1-propenyl disulfide, allyl methyl trisulfide, and diallyl tetra sulfide showed great inhibitory activity towards ACE-2. Sulfur compounds were shown to strongly bind ACE2 amino acids. In a docking simulation study by (Thuy et al., 2020) it was observed that these molecules effectively interact with Trp 566, Pro 565, Gln 102, Ala 396, Gln 101, Gly 205, Gln 98, Glu 208, Lys 94, Asn 210, Lys 562, Ser 563 and Val 209 and the greatest interactions were noticed for amino acids containing sulfur in their structure. They found a total of 17 compounds in the garlic essential oil that inhibit ACE-2 protein to 99.4%. These molecules may be further studied for the management of pneumonia related to COVID-19. The study also highlighted the importance of the extraction and analysis methods in determining the active compounds in garlic essential oil, which are critical for its effectiveness against SARS-CoV-2. In addition, the identification of active molecules in the essential oil endowed with ACE2 inhibitory effects may also provide new chemical scaffolds for the development of novel drugs (Thuy et al., 2020) . Considering the correlation between absorbed and excreted organosulfur compound amounts and ACE-2 inhibition activity, it can be speculated that high doses of black garlic may have a significant effect on ACE-2. For instance, if a daily dosage of 20 g of black garlic results in a 12.9% elimination rate, it could be hypothesized that high doses (e.g., 40 g or 60 g) might lead to an even significant elimination percentage, potentially enhancing the ACE-2 inhibition effect. (Moreno-Ortega et al., 2023)

Several phytocomplexes extracted from Pomegranate peels were tested on SARS-CoV-2 spike proteins and ACE2. The results obtained showed that an extract at three concentrations between 0.04 and 1 mg/mL, inhibited, in a dose dependent manner, the binding of spike protein to ACE2. This effect may be due to, at least to punicalagin, ellagic acid, and gallic acid. On this target, punicalagin and ellagic acid seem to act in synergy (Tito et al., 2021).

In a separate clinical study, patients received a dietary intervention consisting of pomegranate juice (200 ml, three times daily) and sumac (1.5 gs, twice daily) alongside standard medications. The intervention led to improvements in respiratory, pain-related, gastrointestinal, and general symptoms. Overall, these observations suggest that the synergistic interplay between punicalagin and ellagic acid, among other compounds, could contribute to the observed anti-SARS-CoV-2 effects (F Forouzanfar et al., 2022). Meanwhile, in a separate study, the administration of 500 mL of natural pomegranate juice daily to hospitalized COVID-19 patients for a 14-day period, following a randomized, double-blinded, placebo-controlled design, led to significant reductions in crucial inflammatory markers and improvements in hematological parameters, reflecting improved conditions in the PJ group, thereby supporting the potential anti-inflammatory benefits of pomegranate juice consumption in COVID-19 patients. (Yousefi et al., 2023) Additionally, in a separate investigation, the administration of 50 mL of pomegranate juice per day for two weeks brought about around a 36% decrease in serum angiotensin-converting enzyme (ACE) activity among seven out of ten hypertensive patients. (Aviram and Dornfeld, 2001) These findings collectively underscore the potential of pomegranate-derived compounds in ameliorating inflammation and supporting health in COVID-19 patients. While the absence of significant side effects is noted, it remains critical to acknowledge the limitations of these studies, such as challenges in ensuring patient adherence to post-COVID-19 follow-up protocols

Ellagitannins may exert a central role in this effect as an *Alchemilla viridiflora* Rothm. methanolic extract was shown to inhibit the virus attach to host cells through several mechanisms including ACE2 inhibition (Radovi et al., 2022). The extraction process involved air-drying the aerial parts of the plant at room temperature, followed by solvent extraction using methanol. LC-MS analysis identified ellagitannins and flavonoid glycosides, primarily tiliroside, as major components. Indeed, flavonoids can play an important role in ACE2 inhibition. Indeed, tiliroside, a flavonoid, has a high affinity with ACE2 receptor (Radovi et al., 2022) . Also, geranium and lemon oils were shown to inhibit ACE2 activity due to the presence of several compounds, with citronellol and limonene endowed with the ACE2 expression downregulating activity (Senthil Kumar et al., 2020).

3.2. *Phytocomplexes and isolated compounds targeting Transmembrane protease serine 2 (TMPRSS2)*

TMPRSS2 is a protein found on host cells that enables viral infection, spread and pathogenesis of viral disease through the fusion with ACE2. TMPRSS2 comprises of in reverse: a C-terminal serine protease domain, a scavenger receptor cysteine-rich (SRCR) domain, a stem region made of LDLRA (LDL receptor class A) domain, a type II transmembrane domain, an N-terminal intracellular domain. However, the contributions of these domains to the functions of the TMPRSS2 in organisms have not been fully understood till date. Studies with mutants of TMRPSS2 suggest the involvement of the LDLRA domain in enzymatic activity by contributing to the activation of related Type II transmembrane serine proteases (TTSPs), matriptase and matriptase2 (Wettstein et al., 2022). The exact role of the SRCR domain in TMPRSS2 is still very unclear, but generally believed to be involved in interactions with the cell surface or extracellular molecules (Wettstein et al., 2022). For instance, analysis of TTSP in TMPRSS2 mutants suggested that SRCR domain has a yet to be fully appreciated role in proteolytic activities. SRCR domain is made up of a catalytic triad consisting of histidine (H296), aspartate (D345) and serine (S441), and preferentially cleaves substrates with a monobasic arginine (R) or lysine (K) residue at the P1 position (Wettstein et al., 2022) . TMPRSS2 trascripts were found in the epithelia of the respiratory tract such as nasal, tracheal, alveolar and bronchial tissues. (Wettstein et al., 2022) .

Several phytocomplexes and isolated compounds have been found to inhibit the TMPRSS2 expression in host cells, thereby contribute to prevent SARS-CoV-2 entry and infection. Some of these phytocomplexes have been used for centuries in folk medicines and have recently been studied in vitro and in vivo. *Glycyrrhiza* species for example is an herbal plant frequently used for COVID-19 treatment. GB-1 is a polyherbal formulation of Traditional Chinese Medicine, consisting of *Glycyrrhiza uralensis* Fisch. ex DC. roots and *Camellia sinensis* (L.) Kuntze var. assamica leaves where the phytocomplexes were obtained through decoctions of raw materials. GB-1 was shown, in vitro, to decrease TMPRSS2 protein expression in HepG2 cells, in a concentration dependent manner. This effect may be due to at least in part, the presence of the aflavin-3-gallate (Wu et al., 2020b). A similar formulation was shown to reduce TMPRSS2 protein expression also in vivo, in lungs and kidneys of mice (Wu et al., 2020a) . Also, the aqueous extract of *Glycyrrhiza glabra* L. roots containing glycyrrhizin was reported to exhibit inhibitory activities against SARS-CoV-2 infected Vero E6 cells. The extract exhibited anti-viral activity at a concentration of 2 mg/ml., without any toxic effects. Glycyrrhizin, a triterpenoid glycoside in pure form shows a significant degree of antiviral effects, with an EC_{50} of 0.44 mg/ml. This compound has also shown to significantly reduce the SARS-CoV-2 RNA levels (van de Sand et al., 2021) . Based on the provided data, the EC50 for Glycyrrhizin's antiviral effects is 0.5336×10^{-3} μmol/L. Considering an average human body weight of 70 kg, the calculated hypothetical dose for a 70 kg individual would be approximately 0.0314 mg/kg. (Lan et al., 2021) In a separate clinical trial, the administration of 300 mg/die of licorice extract (equivalent to 60 mg of glycyrrhizin) to COVID-19 patients reduced the time to recovery and ameliorated prognosis. No significant new or worsening side effects were more frequently observed in the intervention group compared to the control group. The study reported no significant differences in renal and liver functions or other organ function parameters between the groups. Only mild nausea and vomiting were noted in two patients during the initial days of licorice extract use. The incidence of other adverse events was generally similar between the intervention and

placebo groups, with no adverse events leading to the discontinuation of the study drug. (Gomaa et al., 2022)

Also Glycyrrhizic acid, a compound derived from licorice root, has gained attention in recent medical research for its potential antiviral properties, including its ability to inhibit the replication of several viruses in vitro. In the context of COVID-19 treatment with comorbid liver injury, glycyrrhizic acid has shown promise. A study published in PubMed suggests that the effective dosage of glycyrrhizic acid preparation (GAP) for this condition is generally 150 mg of diammonium glycyrrhizate (DG) administered three times a day, along with 150 mg of magnesium isoglycyrrhizate (MIG) injection once a day or 100 mg per day. These dosages have been recommended based on the findings of the study, but further research is needed to validate their effectiveness and explore individualized treatment approaches. While several studies have reported some adverse reactions such as rash, nausea, vomiting, diarrhea, and abnormal liver function, the overall adverse reactions caused by the use of GAP in the treatment of COVID-19 are few and generally mild. It is noted that the impact of combining antiviral drugs cannot yet be excluded and some studies have suggested that GAPs may cause adverse reactions such as sodium retention and hypertension. It is important to note that while glycyrrhizic acid has shown potential against SARS-CoV-2, more studies are required to fully understand its mechanism of action and its role in the development of antiviral drugs. (Asl and Hosseinzadeh, 2008; Liu et al., 2022) .

Water extracts of *Prunus mahaleb* L. fruit, obtained through an extraction process involving homogenization and ultrasound-assisted water extraction (UAE) - containing gallic acid, catechin, chlorogenic acid, epicatechin, caffeic acid, chicoric acid, coumaric acid, ferulic acid and rutin, strongly reduce the expression of the TMPRSS2 gene in H1299 lung adenocarcinoma cells (Orlando et al., 2021) . Extracts from *Withania somnifera* (L.) Dunal leaves and stems induce, in T.Tn cells, the TMPRSS2 expression downregulation at transcriptional and translational levels. The authors found that the isolated compounds withanone, withaferin-A, withoxy, withanolide-A, withanolide-B, withanoside-IV and withanoside-V were able to determine this effect at nontoxic concentrations, with withanone showing the highest potency. In addition, in silico studies suggest that withanolides may directly inhibit TMPRSS2 (Dhanjal et al., 2021).

In a recent clinical trial evaluating the efficacy of Withania somnifera in mild and moderate COVID-19 cases, participants were administered two 250 mg tablets of Ashwagandha roots water extract and two 500 mg capsules of dried rhizome, twice a day for a duration of 15 days. This dosage regimen was found to effectively reduce the duration of clinical recovery and improve viral clearance. Regarding safety outcomes, the study reported no adverse events (AE) in any of the participants in either of the study groups. Additionally, liver and kidney function tests remained within normal limits for all participants on day 15, and no study participants withdrew or dropped out due to adverse events. However, it is important to note that this dosage is based on the specific study mentioned and further research is necessary to establish the optimal dosage of Withania somnifera for the treatment of COVID-19. (Singh et al., 2023)

Also, a water extract from *Scutellaria barbata* D.Don, prepared from the whole plant using Taiwanese GMP methods and guidelines, where 2.5 g of powder was boiled with 10 mL ddH2O for 10 min, followed by centrifugation and filtration, was analyzed using LC/MS and was found to contain apigenin, naringenin, scutellarin, baicalein, luteolin, and wogonin, and to prevent SARS-CoV-2 infection through TMPRSS2 inhibition (Huang et al., 2021) .

3.3. Phytocomplexes and isolated compounds targeting RNA-Dependent-RNA polymerase (RdRp)

Coronaviridae viruses possess a single-stranded, positive-sense RNA genome that relies on RNA-dependent RNA polymerase (RdRp) for replication and transcription (Singh et al., 2023). This genome can be categorized as either positive- or negative-sense ssRNA, based on whether it aligns with the sense of mRNA or its antisense. Positive-sense RNA can directly translate viral proteins, while negative-sense RNA requires initial transcription to mRNA before it can be used as a template for positive-sense RNA synthesis. The RdRp, encapsulated within the virus, orchestrates these complex processes (Zhu et al., 2020)."

The RdRp enzyme is characterized by its unique structural domains: palm-like, finger-like, and thumb-like, observable in both closed and right-handed forms. SARS-CoV-2 shares significant structural resemblance with its predecessors, SARS-CoV and MERS-CoV, particularly in the polyproteins encoded by open reading frames 1a and 1b. These polyproteins are processed into 16 nonstructural proteins (NSPs) by virus-specific proteases. NSP12 forms the RdRp complex, aided by cofactors NSP7 and NSP8 (Zhu et al., 2020). The exact mechanisms of these processes remain not fully understood.

Even though the transcription of SARS-CoV-2 is still very unclear, it is hypothesized that the RdRp jumps to the gRNA template from transcription-regulatory sequences and generates the negative-sense RNA intermediate. The protein structure of SARS-CoV-2 NSP12 has been analyzed by electron cryomicroscopy, and found to have a right-handed polymerase structure similar to SARS-CoV (Singh et al., 2023). RdRp is an important enzyme involved in the life cycle of viruses and it is essential for coronavirus replication and transcriptional activities through complexing with cofactors (Shawky et al., 2020). It is also important for catalyzing and replicating RNA templates. Therefore, slowing down or completely stopping SARS-CoV-2 replication could be achieved by employing molecules with capacity to block the RdRp's ability to complex RNA (Gao et al., 2020)

The rapid repurposing of drugs has highlighted remdecibir as a promising anti-COVID-19 candidate, though its efficacy against rapidly mutating virus strains remains a concern (Wang et al., 2020). In contrast, phytocomplexes and isolated compounds offer a multitarget approach. For instance, Houttuynia cordata Thunb., used in Traditional Chinese Medicine, has shown potential in inhibiting SARS-CoV-2′s RdRp (Yuan et al., 2022). Azadirachta indica A.Juss., prepared from neem bark powder macerated in methanol, demonstrates comparable activity (Sarkar et al., 2022).Additionally, Lantana camara L., with its flowers and leaves extracted by sonication in ethanol, reveals similar properties (Darwish et al., 2022). These studies collectively indicate that phytocomplexes can directly inhibit the viral RdRp enzyme and potentially affect its transcription epigenetically.

Clinical trials seem to confirm these preclinical data: in a related study, a 28-day regimen of 50 mg neem capsules, taken twice daily, reduced the risk of COVID-19 infection compared to a placebo group, highlighting its potential as a preventive measure. In terms of safety, among the 190 participants, 8 (4.2%) developed treatment-emergent adverse events (TEAEs), with 5 (5.3%) in the intervention group. However, no significant changes were observed in vitals, hematology, biochemistry, or ECGs in either group, indicating a favorable safety profile of the neem capsule regimen (Nesari et al., 2021). various polyphenols and natural compounds, such as hesperidin (Mosquera-Yuqui et al., 2022), glycyrrhizin (Rehman et al., 2021), and quercetin (Metwaly et al., 2022; Souid et al., 2022), as potential RdRp inhibitors. Furthermore, anthocyanins and other phytochemicals, including EGCG and theaflavin (Singh et al., 2021), have shown strong binding affinities to RdRp, suggesting their potential in inhibiting the enzyme's activities. High molecular weight compounds like michellamine B and curcumin (Kumar et al., 2022; Murali et al., 2022) have also demonstrated favorable binding energies to RdRp, implying their role in modifying the enzyme's effects. Moreover, in vitro experiments with compounds like 1, 2,3,4,6-O-pentagalloy-beta-d-glucose have confirmed their inhibitory impact on RdRp (Jin et al., 2022; Allam et al., 2022). Additionally, secondary metabolites like secoiridoids from Centaurium spicatum (Kar et al., 2022) and amarogentin from Swertia chirata (Kar et al., 2022) have exhibited potential RdRp inhibitory effects.

Essential oils and related phytochemicals, such as chamazulene and

eugenol, have also been screened for their ability to bind to RdRp (da Silva et al., 2020), indicating their potential as RdRp inhibitors. Collectively, these findings underscore the diverse potential of natural compounds in targeting RdRp, offering new avenues for therapeutic interventions against SARS-CoV-2.

3.4. Phytocomplexes and isolated compounds targeting 3Chymotrypsin-like protein (3CLpro)

3Chymotrypsin-like protein (3CLpro), also known as main protease (Mpro), a fundamental enzyme in processing reaction of oligopeptides of SARS-CoV-2 that enables the proper functioning of the viral structural proteins (Negri et al., 2021) . 3CLpro appears to be the most important protease of the virus because it cleaves 11 sites out ~~of~~ atthe 16 sites of the N- and C-terminals of the virus polypeptide chain to produce each functional proteins, a single-stranded RNA-binding protein, a helicase, an endoribonuclease, an exoribonuclease, a 2′-O-ribose methyltransferase, and an RNA-dependent RNA polymerase (Montone et al., 2021). With more cleavage sites, 3CLpro should be the perfect non-structural protein site for the development of anti-SARS-CoV-2 drugs.

An oral 3CLpro nitrile warhead peptidomimetic inhibitor (PF-07,321,332) was developed by Pfizer pharmaceuticals and used in combination with ritonavir in Phase 2 and 3 clinical trials (NCT04960202 and NCT05011513) for SARS-CoV-2 treatment (Báez-Santos et al., 2015) . However, it is important to note that PF-07, 321,332 is an optimized version of the peptidomimetic inhibitor PF-00, 835,231 developed for SARS-CoV 3CLpro (Báez-Santos et al., 2015) . There is a great similarity between the sequence of SARS-CoV-2 3CLpro and SARS-CoV 3CLpro (96%), with only 12 points of mutation (Montone et al., 2021), which provides the basis to use SARS-CoV 3CLpro peptidomimetic inhibitors as scaffolds for the design of SARS-CoV-2 antiviral drugs. Therefore, phytocomplexes and isolated compounds previously used for SARS-CoV infection may also represent an excellent starting point for the identification of tools able to mitigate the current SARS-CoV-2 effects.

Angelica keiskei (Miq.) Koidz. has been used for a long time for medicinal purposes in Traditional Chinese Medicine, underwent a detailed extraction and fractionation process for its bioactive components. The dried leaves were extracted with 95% ethanol, and the crude extract was then partitioned into hexane, ethyl acetate, and water layers. Following this, a series of chromatographic separations over silica gel, Sephadex LH-20, and RP-C18 columns, along with preparative-HPLC, were employed to isolate specific compounds. This approach led to the identification of some chalcones in its leaves, such as xanthoangelol and xanthoangelol B, which showed strong potency in inhibiting SARS-CoV 3CLpro (Park et al., 2016) . Some water extracts of *Camellia sinensis* (L.) Kuntze were effective in inhibiting SARS-CoV-2, at least in part, decreasing 3CLpro activity. The latter effect seems due to the presence of 3-isotheaflavin-3- gallate, theaflavin-3,3-digallate, and tannic acid (Takeda et al., 2021; Qi et al., 2022) . *Houttuynia cordata* Thunb is a traditional Chinese plant used in folk medicine for the treatment of respiratory diseases. Recent studies demonstrate that some components isolated from its leaves, such as alkaloids, polyphenols and flavonoids inhibited SARS-CoV-2 replication, probably through the blocking of 3CLPro or RdRp (Bahadur Gurung et al., 2021; Yuan et al., 2022) . Extracts from *Anemarrhena asphodeloides* Bunge rizhoma, *Astragalus membranaceus* Moench roots, *Pueraria lobata* (Willd.) Ohwi roots, *Forsythia suspensa* (Thunb.) Vahl fruits were shown to inhibit Mpro (Pattaro-Júnior et al., 2022) . The antiviral activity against SARS-CoV-2 of a *Cenostigma pluviosum* var. peltophoroides extract seems due to, at least in part, the ability of its hydrolyzable tannins to inhibit Mpro (Li et al., 2021). According to these results, Li and colleagues, demonstrated that tannic acid, punicalagin, and pentagalloyl glucose and their metabolites such as urolithins and pyrogallol strongly inhibit Mpro (Chakraborty et al., 2022) . Other molecules, such as withaferin A and withanone isolated from *Withania somnifera* (L.) Dunal inhibit Mpro (Y. Xiong et al., 2021) . Also, flavonoids and phenolic acids may have a role in 3CLpro inhibition. Indeed, a recent study demonstrates that the 3CLpro inhibitory effect of a *Ginkgo biloba* L. leaves extract, prepared using ultrasonic-assisted extraction from dried and powdered leaves with 60% ethanol, is mainly due to bioflavones and ginkgolic acids (Y. Xiong et al., 2021) . According to these data, dihydromyricetin, isodihydromyricetin and myricetin inhibited SARS-CoV-2 3CLpro, with high potencies (Mouffouk et al., 2021) . In this context, flavonols were shown to possess significant binding stability compared to the standard drug darunavir, suggesting the importance of the flavonols' skeleton for the inhibitory activity. The sugar moiety linked with a glycosidic bond at C3 seems to favor flavonols affinity to this enzyme (Caruso et al., 2020).

Paulownia tomentosa Steud belongs to the family of Paulowniaceae is a source of many active secondary metabolites and it shows a relevant virucidal and antiviral activity in Vero E6 cells. These activities can be directly correlated with the interaction with the 3CLpro, as suggested by SPR studies (Magurano et al., 2023). Another class of compounds endowed with the 3CLpro inhibition is represented by terpens. Indeed, the triterpenes, celastrol, pristimerin, tingenone and iguesterin isolated from *Tripterygium regelii* Sprague & Takeda strongly inhibited this enzyme (Ryu et al., 2010; Yoshimoto, 2021) . The inhibitory activity was observed also for betulinic, ursolic, and maslinic acids (Li et al., 2020) .

3.5. Phytochemical and isolated compounds targeting Spike protein (S protein)

The SARS-CoV-2 spike protein, a trimeric glycoprotein expressed by ORF2 in the viral genome, and structurally depicted as three protomers fused together to form a trimer (PDB ID: 7JJJ) with different domain organizations. Spike protein of SARS-CoV-2 is organized into receptor binding domain, S1 unit, and S2 unit. The S1 and S2 sites provide a point of ~~fussion~~ fusion between the protease furin and the trimeric glycoprotein structure. The S1 unit also cleaves to the ACE2 receptor while the S2 unit mediates fusion of the viral and cellular membranes (Shang et al., 2020) .

Using LALIGN software, Shang et al., compared the primary sequence alignments of SARS CoV-2 spike protein and those of six other human coronaviruses and found similarities between them (Bestle et al., 2020) .

A cryo electron microscopy study revealed six dynamic ways by which the virus enters into the host cells. The six steps according [(Bharathi et al., 2022)and (Basnet et al., 2022)] are:

step 1: Opening of the receptor binding domain (RBD);
step 2: Binds to the ACE2 protein of the host cell to form a complex;
step 3: Build up of the complex;
step 4: Built up the complex ~~the~~ that binds to three more ACE2 proteins of the host cell;
step 5: The resultant complex cleaves to furin; and
step 6: The furin complex cleaves at the S1/S2 sites interface, TMPRSS2 cleaves at the S2′ site, while the spike protein's S2 domain is primed for viral entry into the host cell.

Bioactive compounds from many medicinal plants were shown to bind on SARS-CoV-2 spike proteins inhibiting the virus from fusing to the ACE2. Through this mechanism, the phyto-compounds may prevent or treat the COVID-19. Among the various compounds that show effectiveness on binding to spike proteins of SARS-CoV-2, Cholestan-3-ol, 2-methylene-, (3 beta, 5 alpha), caffeic acid hexoxide, and phloretin from different varieties of seaweed appeared to be effective because they bind the spike proteins of the Omicron variant of SARS-CoV-2. Cholestan-3-ol, 2-methylene-, (3 beta, 5 alpha) from the seaweed variety, *Corallina officinalis* L. acted against the LEU452 and ALA484 residues of the omicron B.1.1.529 spike protein, while caffeic acid hexoxide, and phloretin from *Sargassum wightii* Greville ex J.Agardh seaweeds inhibited ACE-2 spike protein-binding residues of the Omicron variant,

specifically at ASN417, SER496, TYR501, and HIS505 interfaces according to the study conducted by (Basnet et al., 2022; Kataria et al., 2022) .

Olive contains some bioactive compounds that inhibit spike glycoprotein and main protein of SARS-CoV-2. For example, hydroxytyrosol rich aqueous olive pulp extract HIDROX was elucidated to deactivate the activities of SARS-CoV-2 in an in vitro process. Therefore, HIDROX could be used to control the spread of COVID-19, however, it has been suggested that HIDROX may change the molecular weight of the spike protein of SARS-CoV-2 (Qi et al., 2022).

A *Tinospora cordifolia* (Wild.) Miers methanolic extract was shown to inhibit the interaction between hACE2 and S1-RBD, likely due to the presence of cordifolioxide A, palmitoxide G, amritoside B, cordifolide A, and palmitoside F (Shang et al., 2020). A Tinospora cordifolia based formulation was shown to contribute positively to covid 19 patient outcomes. (Kataria et al., 2022). An Alchemilla viridiflora Rothm. methanolic extract, obtained by solvent extracting air-dried, powdered plant material, demonstrated the ability to inhibit the binding of the S protein to the ACE2 receptor (Surui et al., 2022). likely due to the presence of ellagitannins such as tellimagrandin I and brevifolin carboxylic acid. Indeed, a pomegranate extracts rich in ellagitannins inhibited the interaction between S-glycoprotein and ACE2 (Moreno-Ortega et al., 2023; Surui et al., 2021). It is worthy of note that urolithin A, a metabolite of ellagitannins produced by colon bacteria, inhibits the binding of SARS-CoV-2 to ACE2 receptor (Surui et al., 2021) .

We summarize all the viral and host targets of these Phytocomplexes and isolated compounds in Fig. 1.

4. Phytocomplexes and isolated compounds endowed with both anti-SARS-CoV2 properties and cardiovascular protective activities

Pomegranate juice was shown to exert several biological activities resulting in the protection of cardiovascular system from oxidative stress and inflammation leading to atherosclerosis and to an increased risk of thrombosis in COVID-19 patients. Indeed, this substance reduced inflammatory markers in rats with high fat diet – induced atherosclerosis (Surui et al., 2022) . Other molecular mechanisms are associated with pomegranate juice's ability to reduce diastolic and systolic blood pressure and to decrease inflammatory and oxidative stress markers in healthy, metabolic syndrome, ischemic heart disease and polycystic ovarian syndrome affected subjects (Utomo et al., 2020; Goswami et al., 2020; Díaz-Rubio et al., 2015; Kojadinovic et al., 2017).

Pomegranate's ability to reduce parameters related to oxidative stress and inflammation makes this fruit a possible nutraceutical to be administered to patients suffering from cardiovascular disease, in which these parameters are more altered in case of SARS-CoV 2 (Razani et al., 2017) .

Many preparations based on *Glycyrrhiza glabra* L. may have a role in decreasing oxidative stress and inflammatory markers in COVID-19 patients. A licorice roots extract may reduce the expression of several inflammatory proteins such as COX-2, inducible nitric oxide synthase, TNF-α, IL-6, IL-1β, IL-12 in COVID-19 patients (Esmaeilinezhad et al., 2020; F. Forouzanfar et al., 2022; Jain et al., 2022; Liao et al., 2020; Abraham and Florentine, 2021; Bode and Dong, 2015; Fu et al., 2013).

Several compounds were found to act as antinflammatory agents. In

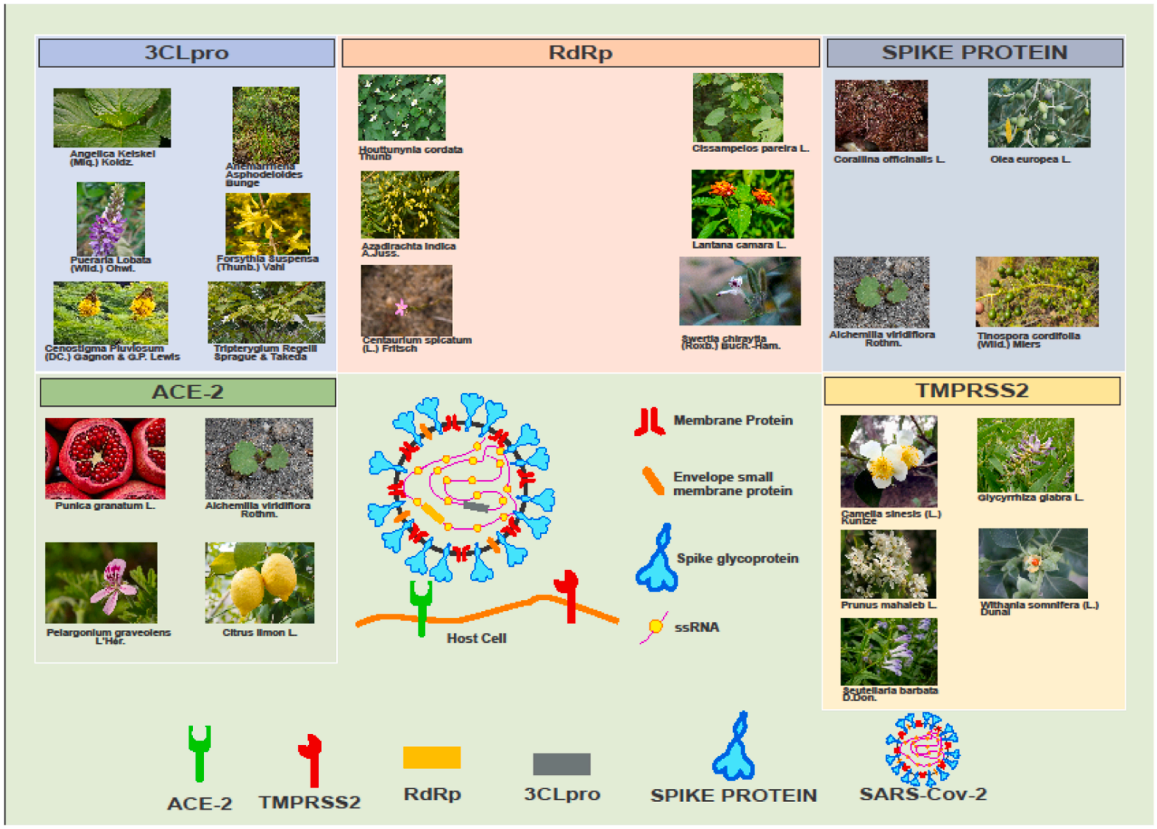

Fig. 1. Phytocomplexes and isolated compounds targeting TMPRSS2, ACE-2, Spike protein, RdRp, 3CLpro and PLpro.

particular, glycyrrhizin decreased inflammatory cell counts, TNF-α, IL-1α, IL-6, myeloperoxidase activity, and NF-kB activity in mice treated with LPS (Lee et al., 2019) . In addition, the compound exerts an antithrombotic effect, due to its inhibitory effect on thrombin (Mendes-Silva et al., 2003) . Also, glabridin possess antinflammatory properties as it decreased, in endothelial cells, ICAM-1, VCAM-1, and E-selectin LPS-induced expression (Kang et al., 2006). This compound also affects macrophages functions as it decreases the release of superoxide through the inhibition of NADPH oxidase (Rosenblat et al., 2002; Rosenblat et al., 1999) . Furthermore, its ability to increase paraoxanase (Yehuda et al., 2016) may be relevant in patients with severe COVID-19, where these enzymes are reduced (Begue et al., 2021) . Also, clinical data suggest the administration of licorice may reduce oxidative stress (Carmeli et al., 2008)Accordingly, Rizvi and colleagues observed that a *Glycyrrhiza glabra* L. extract, prepared by dissolving dry root powder in water, followed by centrifugation and filtration, to produce a 100% aqueous extract, decreased oxidative stress and inflammation in SARS-CoV-2 infected hamsters (Rizvi et al., 2022). In line with these results, the administration of a licorice syrup to hospitalized COVID-19 patients resulted in an improvement of O2 saturation and inflammatory markers. However, it's important to note that in the licorice group, ten patients had to discontinue the syrup, with six discontinuations due to taste intolerance and four due to hyperglycemia. Apart from these instances, there were no other adverse events related to licorice syrup reported in the patients (Soleiman-Meigooni et al., 2022).

Several isolated compounds acting as cardioprotective agents, such as quercetin (Farzaei et al., 2019) and curcumin (Cox et al., 2022) were shown to reduce inflammatory and oxidative stress markers in patients with COVID-19 (Shohan et al., 2022; Di Pierro et al., 2021; Asadirad et al., 2022; Hassaniazad et al., 2021).

4.1. Clinical perspective

In light of the accumulating evidence from recent clinical studies, these natural compounds hold promise as adjunct therapies in the management of COVID-19. Their diverse mechanisms of action and potential clinical benefits, ranging from ACE-2 inhibition to improved symptomatology and viral clearance, highlight the multifaceted roles they can play in combating the pandemic. Nevertheless, it is imperative to emphasize the need for further investigations to refine dosing regimens, establish safety profiles, and elucidate the precise mechanisms underpinning their therapeutic effects. The integration of these compounds into comprehensive treatment strategies could pave the way for more effective and holistic approaches to mitigating the impact of COVID-19.

These findings collectively underscore the therapeutic potential of these natural compounds in the context of COVID-19 management, shedding light on their specific benefits, dosing regimens, and timeframes for intervention. Further exploration of these compounds is essential to optimize their clinical utility and advance our understanding of their roles in combating the ongoing pandemic.

4.2. Future prospects

The current review of nutraceuticals in the context of COVID-19 has highlighted several promising compounds with potential therapeutic effects. As the pandemic evolves and the virus mutates, the quest for effective treatments becomes more urgent. The future prospects in this field are multi-dimensional and include several key areas:

Advanced Clinical Trials: There is a need for more robust, large-scale clinical trials to validate the efficacy of these compounds. Future studies should focus on diverse populations and include long-term follow-up to assess the sustainability of the therapeutic effects and any long-term side effects.

Mechanism of Action: Further research is required to fully elucidate the mechanisms through which these nutraceuticals exert their effects. Understanding the molecular pathways involved can aid in the development of more targeted therapies and combination treatments.

Safety Profiling: Comprehensive safety profiling of these compounds is essential. This includes studying potential interactions with standard COVID-19 treatments and other medications, as well as understanding the impact on various organ systems.

Dosage Optimization: Determining the optimal dosages for maximum efficacy with minimal side effects remains a challenge. Future studies should focus on dosage refinement to establish standardized treatment protocols.

Personalized Medicine: Exploring personalized treatment approaches based on individual genetic makeup, comorbidities, and other factors could enhance the efficacy and safety of nutraceuticals in treating COVID-19.

Combination Therapies: Investigating the synergistic effects of nutraceuticals in combination with other treatments, including vaccines and antiviral drugs, could provide more comprehensive care options.

Global Accessibility and Affordability: Ensuring the global availability and affordability of these treatments is crucial, especially in low-resource settings. This involves scaling up production and addressing regulatory and logistical challenges.

Public Health Integration: Integrating these nutraceuticals into broader public health strategies, including preventive measures and early treatment protocols, could play a significant role in managing the pandemic.

Compound	Clinical Effects	Specific Benefit	Dosage	Duration	Reference
Black Garlic	ACE-2 Inhibition (Speculated)	Potential ACE-2 modulation	40–60 g daily	N/A	[Moreno-Ortega et al., 2023]
Pomegranate-Derived	Symptom Improvement	Respiratory, Pain, GIsymptom relief	200 ml 3x daily	Varies	[F Forouzanfar et al., Mediators Inflamm., 2022; Yousefi et al., 2023]
Glycyrrhizic Acid	Recovery Enhancement	Reduced time to recovery, improved prognosis	150 mg/die	N/A	[Gomaa et al., 2022]
Withania somnifera	Recovery Acceleration	Shortened clinical recovery, enhanced viral clearance	2 tablets 2x daily + 2 capsules 2x daily	15 days	[Singh et al., 2023]
Azadirachta indica	Preventive Efficacy	Lowered risk of COVID-19 infection	50 mg 2x daily	28 days	[Nesari et al., 2021]
Tinospora cordifolia	Positive Patient Outcomes	Positive contribution to COVID-19 outcomes	N/A	N/A	[Kataria et al., 2022]

The potential of nutraceuticals in managing COVID-19 is promising. However, their integration into clinical practice requires further research to overcome current limitations and maximize their therapeutic potential. The ongoing and future studies in this field will pave the way for more effective, safe, and accessible treatments for COVID-19 (Paudel et al., 2022)

5. Conclusions

SARS-CoV-2 still represents a global health issue, as it undergoes mutations that require the identification of new compounds endowed with antiviral activities.

Medicinal and edible plants represent a great source of polar and non-polar compounds, generally acting on several molecular networks, in addition to provide antimicrobial activities against many pathogenic bacteria, fungi and virus including coronavirus, such as SARS-CoV-2.

Several compounds inhibiting many viral proteins act in a dual mode which we named host and guest targeting paradigm (Magurano et al., 2021a).

In this review, we have described some phytocomplexes and isolated compounds that have the capacity to act based on the above paradigm. For example, an extract from *Citrus paradisi* Macfad. (Magurano et al., 2023) was able to exert both an antiviral activity in Vero E6 cells and cytoprotective and antioxidant effects in A549 cells. In the context, it was possible to identify nomilin, a limonoid to have a wide spectrum activity against SARS-CoV-2 and the host cells. We also outlined the connection between SARS-CoV-2 and cardiovascular diseases and highlighted the phytocomplexes with potentials for their mitigation.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Ethical statement

Hereby, I, Dr Fabio Magurano, consciously assure that for the manuscript "From host and guest approach to new frontiers nutraceuticals in the era of COVID-19″ the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed. Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

The violation of the Ethical Statement rules may result in severe consequences.

I agree with the above statements and declare that this submission follows the policies of Solid State Ionics as outlined in the Guide for Authors and in the Ethical Statement.

CRediT authorship contribution statement

Matteo Micucci: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Silvia Gioacchini:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Melissa Baggieri:** Visualization, Methodology, Data curation. **Raoul Fioravanti:** Investigation, Formal analysis, Data curation. **Paola Bucci:** Methodology, Formal analysis, Data curation. **Roberto Giuseppetti:** Methodology, Investigation, Formal analysis. **Srwa S. Saleem:** Methodology, Funding acquisition, Formal analysis. **Sazan Q. Maulud:** Methodology, Investigation, Formal analysis. **Fuad O. Abdullah:** Methodology, Investigation, Formal analysis. **Badr Q. Ismael:** Methodology, Investigation, Formal analysis. **Jivan Q. Ahmed:** Methodology, Investigation, Data curation. **Emilio D'Ugo:** Methodology, Investigation, Formal analysis. **Antonella Marchi:** Methodology, Investigation, Formal analysis. **Udodinma Jude Okeke:** Methodology, Investigation, Formal analysis, Conceptualization. **Fabio Magurano:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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