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Perspectives on nano-nutraceuticals to manage pre and post COVID-19 infections

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Perspectives on nano-nutraceuticals to manage pre and post COVID-19 infections

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ABSTRACT

Optimized therapeutic bio-compounds supported by bio-acceptable nanosystems (i.e., precise nanomedicine) have ability to promote health via maintaining body structure, organ function, and controlling chronic and acute effects. Therefore, nano-nutraceuticals (designed to neutralize virus, inhibit virus bindings with receptors, and support immunity) utilization can manage COVID-19 pre/post-infection effects. To explore these approaches well, our mini-review explores optimized bio-active compounds, their ability to influence SARS-CoV-2 infection, improvement in performance supported by precise nanomedicine approach, and challenges along with prospects. Such optimized pharmacologically relevant therapeutic cargo not only affect SARS-CoV-2 but will support other organs which show functional alternation due to SARS-CoV-2 for example, neurological functions. Hence, coupling the nutraceuticals with the nano-pharmacology perspective of higher efficacy via targeted delivery action can pave a novel way for health experts to plan future research needed to manage post COVID-19 infection effect where a longer efficacy with no side-effects is a key requirement.

1. Introduction

The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)-caused global coronavirus disease 2019 (COVID-19) epidemic impacting people of all ages, youngsters, and physically healthy people [1]. The advent of COVID −19, the world's third big epidemic of respiratory illnesses, has highlighted the world's socioeconomic balance. Increasing prevalence of infectious diseases have had a huge influence on millions of people's lives. [2]. SARS-CoV-2 infections have been attributed to increased cardiac involvement in both symptomatic and asymptomatic patients, according to a growing body of research [3]. The pandemic breakout has attained worrisome proportions, stunning national healthcare systems into inaction and necessitating worldwide deployment. Several randomized clinical trials aimed at treatment, on the other hand, yet must provide practical recommendations on treatment interventions and pharmacological interventions. Several effective treatment research trials are presently underway. Others developing non-traditional drug development methodologies include faster and less expensive methods of discovering effective anti-SARS-CoV2 medicines. [4]. As far as we understand, despite a wealth of literatures focusing on the manifestations, epidemiology and spread, pathophysiology, identification, and associated symptoms of SARS-COV-2, none of the previous state-of-the-art has devoted significant efforts to nano-nutraceuticals as well as novel therapeutic strategies at the current level of the global hallmarks of COVID-19 [5].

Patients with COVID 19 experience acute respiratory distress syndrome, anemia, cardiac damage, and secondary infections. Antibiotics (such as azithromycin, cephalosporins, carbapenems, quinolones, tigecycline, and vancomycin,), antivirals (such as lopinavir, oseltamivir, remdesivir, and ritonavir), and corticosteroids (such as dexamethasone and methylprednisolone) have been widely used for the treatment of COVID 19 patients. Nevertheless, the therapeutic effectiveness of such

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therapies has to be ascertained [5–7]. SARS-CoV-2 mutations that change the antigenic phenotype of the virus have the potential to allow variations to escape natural infection or vaccine protection. Evidence suggests SARS-CoV-2 has been mutated and that this has affected immune recognition to such a degree that it urgently needs to be addressed [8].

Considering the present COVID-19 pandemic when there is lack of effective preventive and curative drugs available and the mutants of the SARS-COV-2 spreading enormously affecting a large number of populations, one of the essential weapons is the robust immune system. Immunity is the ability of an organism to protect itself against harmful organisms to sustain an individual's health [9]. Malnutrition and gluttony are both dangerous conditions that can lead to illness and obesity in the long run. Nutrition and immunity are dependent on the diverse content and quality of the food to maintain a good, effective immune system. Essential amino acids, fatty acids, minerals, probiotics, and vitamins must all be at optimal levels [10, 11]. Yet while numerous natural components have been shown to activate and regulate the immune function successfully, several of these compounds even have antiviral properties, making them more suitable for combating COVID-19 [8] (Fig. 1).

2. Manifestations and managing during or post COVID-19 conditions

The first clinical symptoms of the viral illness appear, following 4–6 days of infection. Depending on the patient's age and immunological condition, the duration from the beginning of COVID-19 symptoms to death ranges from 6 to 40 days. However, early signs of infection, on the other hand, are difficult to detect [12]. Patients with pre-existing health conditions and one over the age of 70 are much likely to experience symptoms in a relatively short period. Symptoms may include fever, dry cough, tiredness with muscular soreness, and breathlessness, as well as mild respiratory diseases such as rhinorrhea, hoarseness, and so on. Patients with milder symptoms are likely to have greater stomach discomfort and a loss of appetite Nausea, diarrhea, headache, sputum secretion, dyspnea, lymphopenia, and hemoptysis, on the other hand, are further clinical symptoms [5, 13]. COVID-19 diagnosed patients show irregular breathing counts as well as increased pro-inflammatory cytokines in their plasma, fluctuations in leukocyte counts and reduction in lymphocyte levels [14]. In severe situations, the person may develop a disease in which the pleural cavity of the lungs fills with fluid, resulting in acute respiratory distress syndrome (ARDS) and the patient may need to be hospitalized. [15]. Studying these manifestations suggests that nutritional support is essential for these patients for functional recovery. Furthermore, having a good nutritional state enables you to be more resistant to the effects of pathogenic diseases like COVID-19 infection [16].

The interest in dietary supplement components that could boost immune function and reduce inflammation to help prevent COVID-19 or manage its signs and symptoms remains strong, despite the availability of COVID-19 vaccinations and the development of pharmaceutical therapies for COVID-19 [17, 18]. The efficacy of many of these nutraceuticals has not been tested in COVID-19 patients, but studies suggest that they could enhance immune function and may help minimize symptoms of the common cold, influenza, and other respiratory tract infections, according to study. Therefore, they are viewed by some scientists as promising for COVID-19, but the level of data validating these hypotheses differs significantly from study to study [19].

3. Emergence of nutraceuticals in current covid scenario

With a large population of people realizing the importance of immune-enhancing supplements purchasing patterns and consumer behavior towards nutraceuticals have shifted dramatically. People are increasingly procuring healthcare items in the form of vitamin capsules, chewable pills etc. [20]. Clinicians are also prescribing various sorts of nutraceuticals such as vitamin and zinc supplements to patients who

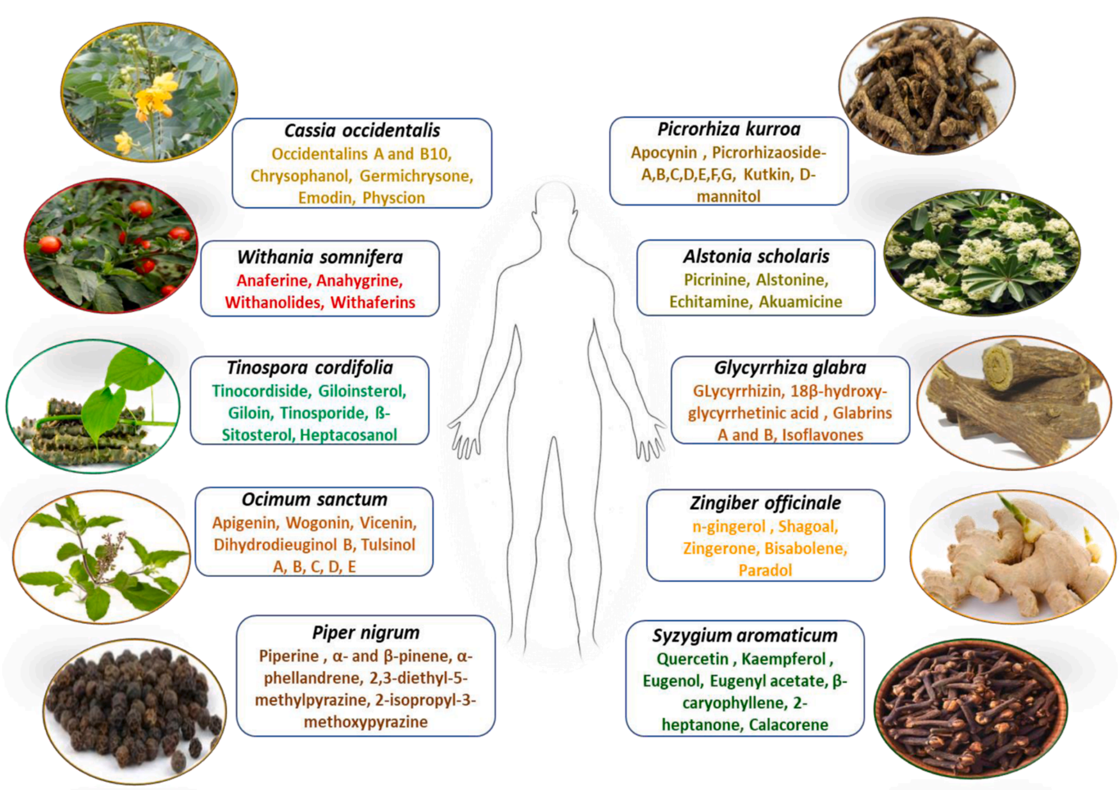

Fig. 1. Natural products and respective phytochemical constituents for COVID-19 prevention and treatment.

have been infected by the virus, in addition to preventive treatment. For each clinician, a special purpose is to assess several tests to see the patient's condition such as inflammatory indicators, insulin regulation and nutritional status, and discover any imbalances or deficiencies [21]. The addition of various nutrients and nutraceuticals during illness development may affect viral reproduction and cellular processes. Thereby realizing that every patient has their own individual requirements according to their body needs, fulfilling the adequate nutritional requirements can help in the sooner recovery process [22].

A balanced diet rich in physiologically active components is essential for obtaining health advantages that go beyond the typical nutritional impacts. The research community is questioning whether or not; can nutraceuticals or dietary supplements provide therapeutic and preventive advantages [23, 24]. The word "nutraceuticals" refers to nutrients found in food that are beneficial to an individual's health. These can be obtained from various sources and types, supplemented in diets, or used as nutritional supplements. The proportion of nutraceuticals found in natural foods is insufficient to provide health advantages and thus need to be consumed in forms of supplements in order to meet the body's nutritional requirements [25].

Naturally occurring substances or nutritional supplements with immune-stimulating and antiviral actions capable of boosting the body's immune defenses have been shown to shorten the severity and chronicity related to colds, flu and other respiratory viral infections as well as reduce the prevalence of major complications, based on clinical evidence [26]. Studies predicted that consuming an oral supplement containing lactobacillus can help to decrease the severity of an acute respiratory infection. Probiotics are effective in curing respiratory tract infections because they improve the health of the intestinal microbiota, which allows for proper element absorption in the digestive tract, which is a crucial step in sustaining a positive immune function [27, 28]. In patients with COVID-19, nutraceuticals may help activate the immune response because they boost the immunological system's efficiency and restrict the virus's viability by reducing its reproduction [20]. The plethora of nutritional supplements function in two mechanisms: either by assisting in the enhancement of developmental stages such as tissue and system development, or by assisting in the avoidance of disease onset such as pathophysiological processes activity [29].

4. Natural products as medicines for COVID-19

For severely ill (noncritical) COVID-19 patients, several researchers described an early nutritional supplement regimen. Their idea is based on the fact that nearly all patients admitted to the hospital had a severe inflammatory condition and anorexia, which resulted in a significant drop in food consumption. They administered milk proteins, minerals, and vitamins (as well as cholecalciferol, if needed) intravenously until the required dietary intake was met [30]. Dubey and colleagues described the systematic progression of the symptoms of COVID-19 in patients from the early stage of infection to the stage of criticality, along over recovery phases. Considering the phases of infection with the progression of the disease, the stage of the disease can be ranged from the asymptomatic to the fatality and post-infection stage [5]. These stages of infection can be studied for the therapeutic aspects of compounds from natural source at each phase and understand the importance of each of the compound in prevention and recovery from the disease.

1 Ashwagandha (Withania somnifera)

The Ashwagandha plant is a tiny shrub native to India and North Africa with yellow blooms. The ancient Indian herb ashwagandha (*Withania somnifera*), often known as 'Indian winter cherry,' improves stamina, reduces stress and anxiety, and boosts the immune system. Several ailments are treated with extracts or powder made from the plant's root or leaves [31]. It's a convenient over-the-counter nutritional supplement with an established safety record. It's an adaptogen, which means it's thought to assist the body cope with physical and emotional stress. Compounds in it have been shown to help relax the mind, decrease edoema, lowering blood pressure, and modulate the immune function [32]. *W. somnifera* contains alkaloids (anaferine, anahygrine, cuscohygrine, isopelletierine, etc.), saponins, and steroidal lactones (withanolides and withaferins) as its active components [33].

While there have been numerous research on Ashwagandha to better understand its advantages in various diseases, the Ministry of Ayush together with All-India Institute of Ayurveda, has teamed up with a foreign university London School of Hygiene and Tropical Medicine, UK to look into its efficacy on COVID-19 patients. There are plans from Ministry of Ayush to perform a study on 'Ashwagandha' to promote recovery from COVID-19 and to provide a boost to the traditional Indian medicine system. Succeeding in the study might mark an important step forward in the development of traditional Indian medicine. As per the study protocol, a group of 1000 patients will be administered Ashwagandha (AG) pills for three months, while the other group will be given a placebo that has similarity to AG. In the double study, the both patients and the physicians will be uninformed of the group's treatment [34].

In Ayurvedic therapy, Ashwagandha is used to treat basic ailments. COX-2 inhibition and prostaglandin suppression are the mechanisms through which AG exerts its antipyretic action [35, 36]. *W. somnifera* has been shown to reduce preceding pathophysiology aspects of disease development and to protect critical organ systems. It can be studied for its effectiveness in viral fever and associated mild symptoms of COVID-19. The antiviral effects of Ashwagandha reported in various other studies are promising and should be clinically investigated in people with moderate symptoms [37].

Researchers in a community-based participatory research study evaluated the efficacy and safety of Ayurveda (AG) treatment for mild to moderate symptoms in 28 patients of COVID-19 for assessing the efficacy and safety of Ayurveda intervention in relieving symptoms [38]. SARS-CoV-2 might be treated with Ashwagandha since it inhibits both viral infections and the cytokine storms. To enhance immunity, *W. somnifera* contains a series of bioactive compounds termed withanolides. Withanolide_G, Withanolide_I, and Withanolide_M had the highest affinity for PLpro, 3CLpro, and spike proteins respectively. It may be beneficial against SARS-CoV-2 by modulating the host's Th-1/Th-2 immune system [31, 39, 40].

1 Guduchi Ghanavati (*Tinospora cordifolia*)

Tinospora cordifolia (willd.) Hook. f. and Thoms. (Guduchi) is a tropical and subtropical climbing shrub, which has a wide distribution in Southeast Asia, Africa, and Australia [41, 42]. There are a lot of polysaccharides throughout this family as well as terpenes, alkaloids and phagocytosis stimulants, anti-diabetic, antioxidant compounds among many other things. Researchers extracted and characterized molecules from diverse water and solvent fractions, including sesquiterpenes and phenylpropanoids [43].

Giloy Ghanavati is a pill made from the aqueous extracts of *T. cordifolia*. In a clinical study, the administration of Guduchi Ghanavati twice daily for 28 days in the form of two 500 mg tablets in 91 asymptomatic patients of COVID-19 showed unclear results on the safety and efficacy of the drug. The outcome of the study was based on the time between the first COVID-19 positive result and the first COVID-19 negative result, referred to as virologic clearance [44, 45].

Another study emphasizing the effectiveness and safety of Guduchi Ghanavati in the therapy of asymptomatic COVID-19 were carried in 91 patients out of which 46 asymptomatic patients considered for the study. For two weeks, all participants were given two 1000 mg pills orally twice a day. At baseline, day 3, day 7, and day 14, clinical parameters were collected. Throughout the research, patients were carefully evaluated for adverse effects and complications related. The findings indicated Guduchi Ghanavati possessing a potential function in virologic cure with no adverse effects [46]. Tinocordiside (CID_177,384), a cadinene sesquiterpene glycoside and a phytochemical isolated from *T. cordifolia* (Giloy) showed highest binding affinity as compared to built-in ligand N3 for SARS-CoV-2 M^{pro} with the binding energy of 8.10 kcal/mol [47, 48].

1 Tulsi (*Ocimum sanctum* L.)

In the basil family *Lamiaceae*, Tulsi is a fragrant plant originated in central and northern India and currently flourishes in the tropics of eastern Asia. Tulsi is a perfect illustration of Ayurveda's holistic approach to wellness, as it is a spicy, bitter herb that has potential to enter deep tissues, dry tissue secretions, and balance the kapha and vata energies [49]. A large no of phytochemicals is found in *Ocimum sanctum,* of which flavones and flavonoids are abundant in the extracts, making them a valuable source of antioxidants. As a significant class of flavonoid compounds, flavones are mainly composed of 2-phenyl-1-benzopyran-4-ones as the backbone. Apigenin, baicalein, chrysin, luteolin, scutellarin, tangeritin, wogonin, and 6-hydroxyflavone are all examples of flavones found naturally in plants and flowers [50, 51].

The antiviral properties of several naturally occurring flavonoids have been established in research. It has been shown that myricetin and scutellarein are potent pharmacological inhibitors of the SARS-CoV helicase, mediated through suppression of ATPase function [52] (Fig. 2). The immunomodulatory activity of alcoholic leaf extracts was demonstrated by a decrease in hepatic parasite and a skewing of the humoral response toward Th1 type at an IC50 value of 73.3 g/ml [53, 54].

Studies reported among the phytochemicals present, SARS-CoV-2 M^{pro} binding affinity was much higher for Vicenin (CID 3,084,407), Isorientin 4′-O-glucoside 2′′O-p-hydroxybenzoagte (CID 44,257,986), and Ursolic acid (CID 64,945) than the built-in ligand N3. Vicenin has the greatest binding energy of 8.97 kcal/mol, according to research. Isorientin 4′-O-glucoside 2′′-O-p-hydroxybenzoagte the second inhibitor, having a binding energy of 8.55 kcal/mol and another inhibitor Ursolic acid, having a binding energy of 8.52 kcal/mol [48]. Another *in-silico* study of flavonoids and polyphenolic acids in Tulsi suggests that they could also act as inhibitors of M^{pro}. The antiviral properties of these phytochemicals have been demonstrated in laboratory studies [55]. As a result, chlorogenic acid and luteolin-7-O-glucuronide emerge as the most promising candidates. Chlorogenic acid is mostly found in coffee beans, although it is also found in tea leaves [56]. Varshney and colleagues reported that Dihydrodieuginol B and Tulsinol A, B, C, D, E, F, G from *O. sanctum* can be utilised as possible inhibitors for papain-like Protease (PL^{pro}) and SARS COV-2 Main Protease [57] (Fig. 3).

1 AYUSH-64

To treat malaria, the Central Council for Research in Ayurvedic Sciences developed AYUSH-64, an Ayurvedic formulation and a repurposed medication for COVID-19 as suggested by the government. It is a mixture of four Ayurvedic drugs: *Alstonia scholaris* R. Br. (bark extract), *Picrorhiza kurroa* (rhizome extract), *Swertia chirayita* Buch Ham (whole plant extract), and *Caeselpinii crista* (fine powder of seed pulp). Following the mixing of the extracts, 500 mg tablets of each extract are created by combining the extracts. Scientists have discovered that AYUSH 64 is effective in treating asymptomatic, mild, and moderate COVID-19 infections both alone and in conjunction with conventional treatment, according to the ministry [58–60].

Standard of care was proven to be considerably more effective and safer when used in conjunction with AYUSH-64 (a polyherbal Ayurveda medication that has been standardized and tested for safety and efficacy). A shorter hospital stays, improved physical and emotional health and a faster clinical recovery were some of the results [61]. In asymptomatic, mild to moderate instances of COVID 19, AYUSH 64 may be beneficial. In asymptomatic, mild to moderate COVID 19 patients, the

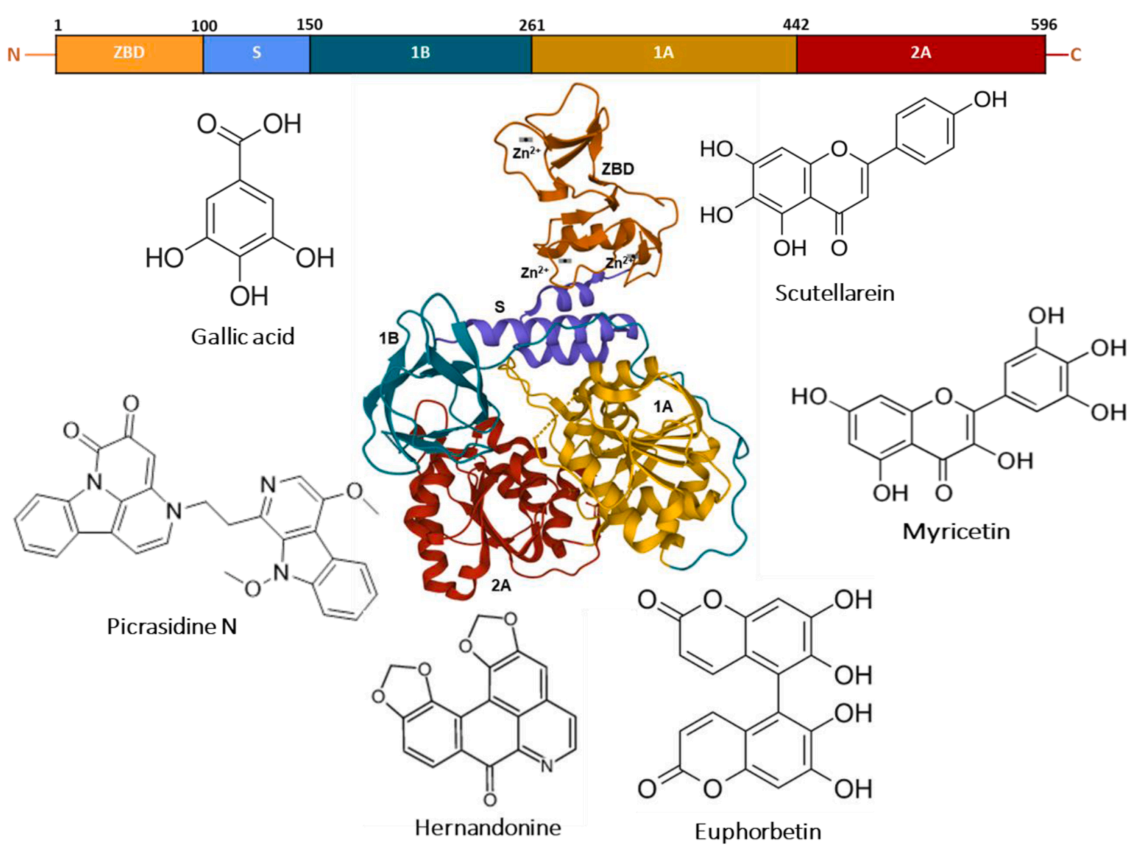

Fig. 2. Domain representation of SARS-CoV-2 *nsp13* and the structural ribbon representation of the SARS-CoV-2 helicase with potential inhibitors.

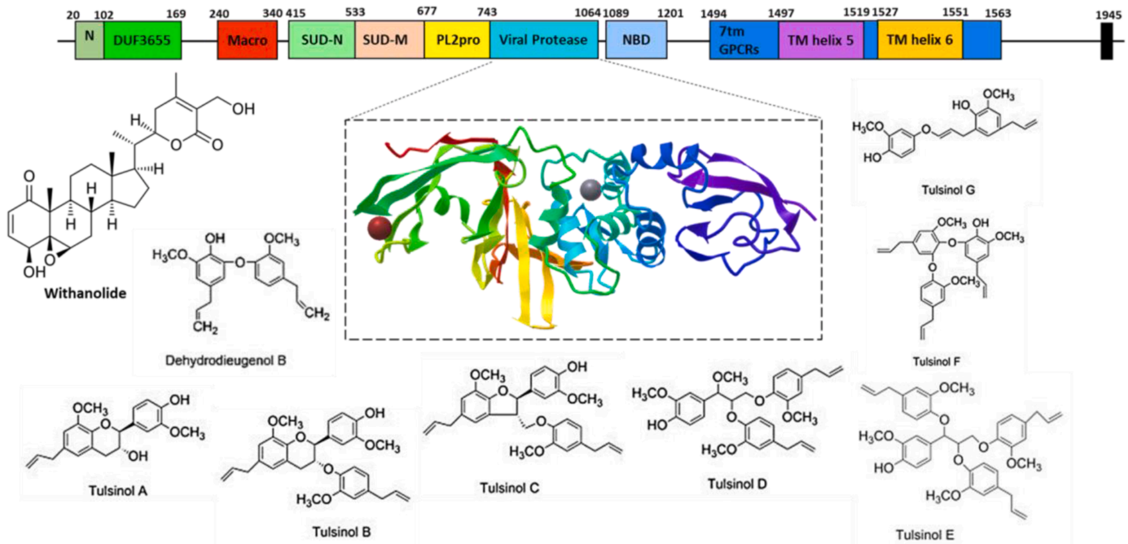

Fig. 3. Overview of the SARS-CoV2 *nsp3* structural and genomic organization along with possible inhibitors of SARS-CoV-2 papain-like protease (PLpro).

study found indications of early clinical recovery with considerable improvements in COVID-19 symptoms and inflammatory marker levels. AYUSH 64 was well tolerated, with no notable side effects observed and no evidence of disease progression from asymptomatic and mild COVID-19 patients to severe instances. Repurposing the medication for COVID 19 might provide a viable approach and a quick method for eradicating the virus and creating an anti-COVID-19 treatment in the country [62].

It was shown that 35 of the 36 Phyto-constituents in AYUSH-64 had a high binding affinity against the COVID 19 virus in the *in-silico* research. Even when used to treat influenza-like diseases, it has shown extremely encouraging outcomes. As a result of the findings, AYUSH-64, an authorized and safe medication for treating joint pain, fever, and influenza-like disorders, is a strong candidate for repurposing against COVID-19. The anti-protease activities of AYUSH-64 against COVID-19 might thus be verified by future experimental and clinical investigations [63].

In preliminary research, a one-week AYUSH 64 intervention facilitated individuals to recover from influenza-like illness (ILI) symptoms while using acetaminophen and antihistamines less frequently. Hematology and biochemical markers were unaffected by the treatment. During the research, no significant side effects were observed. In ILI, AYUSH 64 in combination with standard therapy is safe and effective, and it might be utilized in other viral infections with pyrexia as a supplement to normal care for a quicker recovery and better result [58, 64, 65].

1 Mulethi (Glycyrrhiza glabra)

Glycyrrhiza glabra, herbaceous perennial licorice, has been used for thousands of years as a flavouring ingredient in meals and medical treatments. Since ancient times, licorice root has been commonly used to cure coughs all throughout the world [66]. Pharmacological activity has been reported for several active components including glycyrrhizic acid (also known as glycyrrhizin, GLR), 18β-hydroxy-glycyrrhetinic acid (the main Gl metabolite), glabrins A and B, isoflavones, and others. In the stomach, gut microbiota rapidly breaks down glycyrrhizin into 18β-glycyrrhetinic acid, a bioactive compound found in large quantities in the therapeutic licorice root [67]. SARS-associated coronavirus (FFM-1 and FFM-2) were shown to be efficiently suppressed by GLR in Vero cells in a research study carried out by Cinatl, J., et.al, 2003. When tested for cytotoxicity, the medication had an EC50 of 300 mg/ml, but was non-cytotoxic to the host cells. Not only did GLR decrease viral multiplication, it also prevented viruses from adhering to and entering cell membranes. A drug-induced increase in nitrous oxide synthase was noted at the time, suggesting nitrous oxide might be responsible for the suppression of viral multiplication at that time [68, 69].

It was shown that glycyrrhizin, the licorice root's major active component, might protect against chronic hepatitis B and C. The point to remember is that in clinical trials, the pharmacokinetic studies showed that the substance was safe, well-tolerated and nontoxic [70]. Inhibition of 11-beta-hydroxysteroid dehydrogenase (11HSDH), results in increased cortisol levels, correlating the anti-inflammatory and mineralocorticoid properties. Glycyrrhizin's strong antiviral and anti-inflammatory characteristics make it an ideal option for future clinical trials in the treatment of COVID-19 [71, 72].

The therapeutic effect of Licorice extracts and *Boswellia serrate* gum as a supplementary medication in conjunction with traditional therapy in Egyptian patients with COVID-19 has been investigated in a non-randomized, clinical research study of 70 individuals to determine the severity and recovery period [73]. Licorice extract and *Boswellia Serrata* gum have pharmacological properties which could support the therapeutic approach for COVID-19. Their antiviral, anti-inflammatory, anti-lung damage, anti-bacteria, antithrombic development, and immunostimulatory properties are all well-known and extensively utilized [74, 75]. Another research in the phase 2/3 of the study proposed to study the immunity to COVID-19 with different treatment methods. Omeg-3, affects human health through a variety of processes, including antioxidant and immunity-boosting properties. Furthermore, Omega-3 has an antiviral impact on the Flu virus by reducing replication of the virus [76].

5. Other floras and dietary supplements as anti-virals against COVID-19

Researchers found that flavonoids bind to functional regions on the SARS-CoV-2 S protein, an essential glycoprotein for viral attachment and adsorption, according to research findings. By blocking the 3a ion channel of SARS-CoV-2 and HCoV-OC43, Emodin, an anthraquinone derivative extracted from *Rheum tanguticum* (Polygonaceae) roots can prevent the interaction with the SARS coronavirus spike protein [77–80].

Since SARS-CoV-2, unlike SARS-CoV, infects cells through the host receptor ACE-2, medicinal herbs that target ACE-2 can play a potential role in preventing and treating SARS-CoV-2 infection [5]. Several edible medicinal herbs, such as *Cassia occidentalis* [81], *Cynara scolymus* [82], and *Punica granatum* [83] have exhibited ACE inhibitory properties, and the same could be investigated for ACE2 inhibition.

Rudravanti, or *Cressa cretica* (Linn), a member of the Convolvulaceae family, has antitussive and broncho dilatory properties, as well as mast cell stabilizing properties and has traditionally been used to treat cough and other respiratory issues [84, 85]. Its aerial portions include oxidative characteristics regulated by β-sitosterol, *β*-sitosterol glucoside, kaempferol, noctacosanol-1, quercetin, rutin, 6-hydroxy-3,4-dimethyl coumarin, and 6-methoxy-7,8-methylene dioxycoumarin [86]. In an *in-silico* study, 3, 5-Dicaffeoylquinic acid from *Cressa cretica* was reported to have the greatest binding energy compared to Remdesivir and may block M^{pro} protein, which is necessary to cleave the mRNA and assemble viruses. 3,5-Dicaffeoylquinic acid reported the highest affinity for COVID-19 major protease (M^{pro}) of SARS-CoV-2, indicating that it might be a promising emerging research molecule (Fig. 4). As a result, active compounds of *Cressa cretica* become helpful in combating the novel corona virus and warrant immediate study consideration since they indicate a strong association with major protease (M^{pro}), suggesting antiviral activity [87].

The rhizome of *Zingiber officinale*, Ginger (Ardraka) has been used to cure colds and bronchitis by exhibiting antiviral action against respiratory syncytial virus [88]. A component of ginger called n-gingerol inhibits Th2-mediated immune responses as well as airway inflammation, while 6-gingerol was found to be effective in suppressing eosinophilia and TNF-α, IL-1β, and IL-12 production [89]. Research reports suggested that ginger and cedrat include chemicals that have a neutralizing impact on SARS-CoV-2 by blocking the spike glycoprotein in the virus and the enzyme ACE-2 in the host, both of which are critical for SARS-CoV-2 cell penetration [90].

Piper nigrum (Black pepper) and *Piper longum* (Pippali) are antioxidant, anti-inflammatory, and anti-bacterial herbs used to treat bronchial illnesses and tuberculosis (TB) [91]. Piperine is found in abundance in *P. nigrum* and *P. longum*. Pipericide, piperine, piperlonguminine, piplartine, and aristo lactams are among the alkaloids and amides found in *P. longum. P. Nigrum* inhibits allergic inflammation by inhibiting Th2/Th17 responses and mast cell activation, as well as regulating the balance of cytokines produced by Th1, Th2, Th17, and Treg cells, as well as inhibiting GATA3, IL-4, IL-6, IL-1, RORt, IL-17A, TNF-expression and increasing IL-10 and INF-secretions [92, 93]. According to the research findings, piperine is reported as a promising natural chemical for targeting nucleocapsid (NC) of SARS-CoV2 and perhaps inhibiting RNA packaging in the protein. As a result, consuming black pepper or piperine can aid in virus management. Specific laboratory and clinical investigations, however, are needed to back up the conclusions of the study [94, 95].

Syzygium (S.) aromaticum, or clove belongs to the traditional spice family that is rich in numerous phytochemicals such as hydrocarbons, monoterpenes, phenolic compounds, sesquiterpenes, and others that are used to preserve food and have a variety of pharmacological actions [96]. Clove oil has high concentrations of eugenol, eugenyl acetate, and *β*-caryophyllene, three important phytochemicals. Eugenol has been found to have analgesic, antioxidant, anticancer, antiseptic, antidepressant, antispasmodic, anti-inflammatory, antiviral, antifungal, and antibacterial properties against a variety of pathogens [97]. Cloves' traditional medical use as a treatment for respiratory ailments, as well as its experimentally proven antiviral activity, as well as its anti-inflammatory, immunostimulatory, and antithrombotic properties, portrays the potential importance of cloves and their phytochemical constituents in the fight against the COVID-19 disease. In immunosuppressed hospitalized patients, clove essential oil (CEO) has demonstrated strong antibacterial activity against infections suggesting its value in the prevention of subsequent bacterial infections in COVID-19 patients [98, 99]. Phytoconstituents derived from cloves have been suggested in computational studies as potent anti-COVID-19 drugs. Kaempferol is one of phytoconstituents which was shown to bind the substrate binding pocket of the main protease of SARS-CoV-2 with high

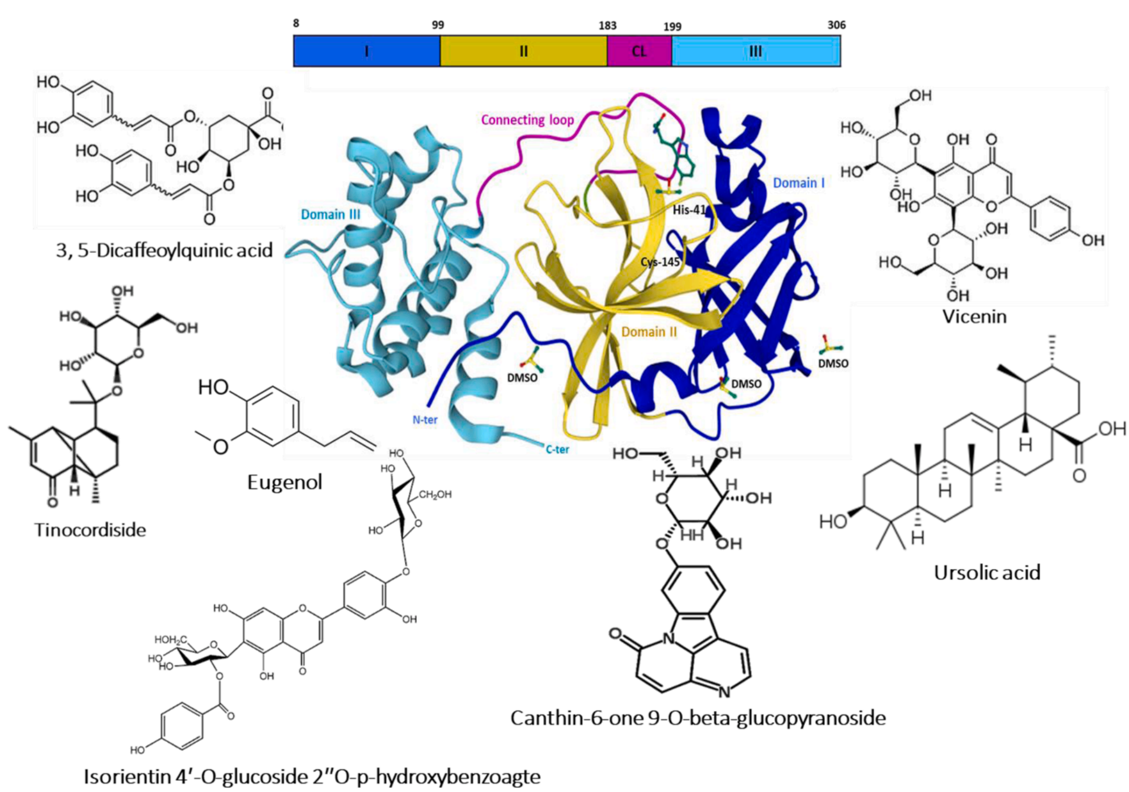

Fig. 4. Structural representation of SARS-CoV-2 M^{pro} monomer *nsp5* composed of: N-terminal domain I (blue), domain II (golden yellow), and C-terminal domain III (light blue) along with possible phytochemical inhibitors. Substrate recognition site in (green and red) and catalytic dyad residues, His41 and Cys145 are highlighted and labeled.

affinity *in-silico*, interacting with active site residues such as Cys145 and His41 through hydrophobic interactions and hydrogen bonding, suggesting that natural compounds such as clove flavonoids could act as SARS-CoV-2 novel inhibitors [100–102].

6. Vitamins

The true capacity of vitamins and herbal supplements is still unknown. Still, numerous studies are being conducted to see if these agents can be used as possible treatments and/or as additions to the current therapeutic approaches, which vary around the world because there is no curative therapy at this time. Furthermore, vitamins and herbal supplements, depending on the composition, might be reasonably priced and easily obtained [103].

Recent research has emphasized the importance of nutritional supplements, which, provided in higher-than-recommended daily dosages, might help COVID-19 patients reduce viral load and hospitalization [104]. Vitamins are necessary dietary components due to their antioxidant and immunomodulatory capabilities [105]. Several of them promote immunological cell development and differentiation by regulation of gene expression in immune cells. Vitamins C and E are good strong sources of antioxidants fight free radical damage [106].

Vitamin B1 has been shown to have an anti-inflammatory impact on macrophages and to inhibit oxidative stress-induced NF-kappa B activation [107]. Thiamine insufficiency impacts immunity through various pathogenic mechanisms such as inflammatory processes, oxidative stress, and metabolic abnormalities, which leads to the generation of abnormal antibodies. Thiamine has been shown to have an important role in eliminating the SARS-CoV-2 virus by inducing humoral and cell-mediated immunity. As a result, adequate thiamine levels aid in the development of immunity against SARS-CoV-2 patients [108, 109].

According to the literature reports, vitamin D deficiency might result in respiratory tract infection. As a result, the role of vitamin D has been extensively researched in the treatment for severe respiratory tract infections [110], and supplementing vitamin D can be used to boost humoral immune response and glutathione synthesis, and to help prevent and cure COVID-19 [111]. Xu et al. studied that calcitriol (vitamin D agonist) protects against acute lung damage by regulating the expression of ACE2 in lung tissue, which is one of the pathogenic mechanisms in COVID-19 [112].

Vitamin E, a fat-soluble antioxidant that protects membrane-bound polyunsaturated fatty acids (PUFAs) from oxidation, regulates the generation of reactive oxygen and nitrogen species, and modulates signal transmission [113]. Because of its high metabolic activity and poly unsaturated fatty acids (PUFA) content, vitamin E in immune cells of COVID-19 patients protects them against oxidative damage and age-associated dysregulation of the immune system [114]. Vitamin E's scavenging properties make its antioxidant therapy potential useful in preventing oxidative damage associated with SARS-CoV-2 development [115].

When vitamin K hepatic factor is deficient, coagulation factors take precedence over hepatocellular ones [116]. Vitamin K's various and unique roles in blood coagulation, elastin breakdown, immunomodulatory, and vascular patient treatment, along with its low human exposure, make it an appealing treatment to use prophylactically as a supplement or clinically to enhance COVID-19 clinical outcomes [117]. MGP, a vitamin K-dependent protein, inhibits soft tissue mineralization and elastic fiber breakdown. To preserve the pulmonary extracellular matrix from breakdown caused by inflammation, the lungs of SARS-CoV-2 patients produce more Matrix Gla protein (MGP), which increases the use of vitamin K from extrahepatic vitamin K reserves [118, 119].

7. Minerals

Numerous research studies have shown that a low intake of essential minerals in the meal has a significant role in preventing and reducing cardiovascular-related illnesses, which could also be implicated in the advancement of corona infections [120]. Some results from early COVID-19 research suggest that the presence and absence of minerals in the body are crucial in controlling the production of angiotensin-converting enzyme-2 (ACE2) in strengthening the immune system. The SARS-CoV-2 major targets for entrance into the respiratory system are ACE-2 receptors, which have a negative impact on this system [121]. Many nutraceuticals and dietary supplements are currently in the phase of COVID-19 clinical trial in different phases (Table 1).

Certain ailments (e.g., liver cirrhosis or inflammatory bowel disease), age, and lifestyle-related variables (e.g., vegan/vegetarian diet) can induce Zinc (Zn) deficiency, which is associated with higher vulnerability to infections caused by bacterial, viral, and fungal pathogens. Under certain instances, administering a Zn supplement in sufficient therapeutic levels has the ability to either restore or stimulate immune cell activity that has been diminished. When used with conventional antiviral treatment, it may synergise [122]. COVID-19 patients were found to have substantially lower zinc levels than healthy people, which was linked to a more than 5-fold higher risk of problems. It's crucial to differentiate between underlying zinc deficit and a deficiency developed during SARS-CoV-2 infection since supplementing techniques would differ, and acute deficiency during viral infection will necessitate active monitoring and treatments [123, 124].

Copper (Cu) insufficiency has now been linked to alterations in inflammatory processes as well as an increased risk of complications. It can arise because of prolonged TNF-induced pneumonitis, and copper dosing has been shown to alleviate these inflammatory responses in rats [125]. Cu is essential in the proper functioning of B cells, T helper cells, macrophages, and natural killer (NK) cells, which are engaged in cell-mediated immunity, confront virulent microorganisms, and generate antibodies against these pathogens [126]. According to research, Cu's exposure to coronavirus 229E damages the viral genome and irreversible influences virion morphology [127]. Furthermore, Cu processing can destroy pathogenic viruses such as poliovirus, bronchitis virus, and human immunodeficiency virus type 1 (HIV-1) as well as enhance immunity. Due to the obvious sensitivity of viral illness to Cu, copper supplementation could be a superior therapeutic option for COVID-19 patients [104].

Selenium (Se) insufficiency appears to be frequent in COVID-19, as evidenced by research conducted in South Korea, which revealed a significant prevalence of selenium deficit specific blood selenium measurements. Selenium insufficiency was linked to increased mortality in COVID-19 patients during one of the first studies of its sort [128]. Nutritional insufficiency is still quite prevalent in hospitalized patients, and selenium deficiency can be quite common in the severe type of COVID-19. Improper selenium consumption affects a huge percentage of the worldwide population in various nations, and it may have a significant influence on COVID-19 infection and consequences [129, 130]. The SARS-CoV-2 virus must locate a suitable ACE2 receptor to binding-to infect the host cell. Following binding, the virus is carried into the host cell through endocytosis, where it multiplies [131]. Selenium and selenoproteins have an indirect effect on viral activity by aiding in numerous defense mechanisms. Selenium promotes the structural integrity and integrity of the respiratory epithelial barrier, which reduces virus penetration into respiratory cells [132].

Calcium channel blockers (CCBs), drugs for lowering blood pressure have recently, have been used to suppress the reproduction of numerous new viruses, such as the Ebola virus, the Marburg virus, the Junín virus, and the severe fever with thrombocytopenia syndrome virus (SFTSV) [133]. The CCB therapy has been linked to lower CFR in SFTS patients. CCBs inhibit SARS-CoV-2 replication following entry. Even though the specific suppression method is unknown, it's probable that CCBs limit viral multiplication by blocking virus-induced intracellular calcium influx and impairing calcium-dependent cellular processes [134]. In this approach, as contrasted to antiviral medicines that target virus

Table 1
List of dietary supplements in clinical trials of COVID-19 (Source: clinicaltrials.gov).

Food supplements	Identifier	Study
Honey	NCT04323345	Efficacy of Natural Honey Treatment in Patients with Novel Coronavirus
Starch	NCT04342689	The Role of Resistant Starch in COVID-19 Infection
Methylene Blue	NCT04370288	Clinical Application of Methylene Blue for Treatment of Covid-19 Patients (Covid-19)
Vitamin A	NCT04920760	Vitamin A Supplementation in Children with Moderate to Severe COVID-19
	NCT04877509	Micronutrient Status Involved in Immunity in Elderly Patients With COVID-19 (Micro Cov Aging)
	NCT04900415	Olfactory and Neurosensory Rehabilitation in COVID-19-related Olfactory Dysfunction
Vitamin B	NCT04828538	Vitamin D, Omega-3, and Combination Vitamins B, C and Zinc Supplementation for the Treatment and Prevention of COVID-19
	NCT04407572	Evaluation of the Relationship Between Zinc Vitamin D and b12 Levels in the Covid-19 Positive Pregnant Women
	NCT04751604	Improvement of the Nutritional Status Regarding Nicotinamide (Vitamin B3) and the Disease Course of COVID-19 (COVit-2)
Vitamin C	NCT04264533	Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia
	NCT04323514	Use of Ascorbic Acid in Patients with COVID 19
	NCT04344184	Safety Study of Early Infusion of Vitamin C for Treatment of Novel Coronavirus Acute Lung Injury (SAFE EVICT CORONA-ALI)
	NCT04357782	Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation (AVoCaDO)
	NCT04342728	Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ)
	NCT04363216	Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment
	NCT04530539	The effect of melatonin and Vitamin C on COVID-19
	NCT04664010	Efficacy and safety of high-dose vitamin C combined with Chinese medicine against coronavirus pneumonia (COVID-19)
	NCT04279197	The Efficacy of Treating Pulmonary Fibrosis and Pulmonary Function Injury in COVID-19 With the Fuzheng Huayu Tablets: A Multicenter Randomized Controlled Trial
	NCT05029037	High-dose Intravenous Vitamin C (HDIVC) as Adjuvant Therapy in Critical Patients with Positive COVID-19. A Pilot Randomized Controlled Dose-comparison Trial. (HDIVC)
Vitamin D	NCT04334005	Effect of Vitamin D Administration on Prevention and Treatment of Mild Forms of Suspected Covid-19
	NCT04344041	COvid-19 and Vitamin D Supplementation: A Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)
	NCT04334512	A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Quintuple Therapy to Treat COVID-19 Infection
	NCT04351490	Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19 (ZnD3-CoVici)
	NCT04487951	N-terminal Pro-B-type natriuretic peptide and vitamin D Levels as Prognostic Markers in COVID-19 Pneumonia
	NCT04709744	Impact of Vitamin D Level and Supplement on SLE Patients During COVID-19 Pandemic
	NCT04536298	A Cluster-Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Vitamin D3 Supplementation to Reduce Disease Severity in Persons with Newly Diagnosed COVID-19 Infection and to Prevent Infection in Household Members
	NCT04449718	Vitamin D Supplementation in Patients With COVID-19: A Randomized, Double-blind, Placebo-controlled Trial
	NCT04868903	Low vs. moderate to high-dose vitamin D for prevention of COVID-19
	NCT04793243	Vitamin D3 Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation
Vitamin E	NCT04570254	Open Clinical Trial of the Use of Antioxidants and Pentoxifylline as Adjuvant Therapy to Standard Therapy in Patients with and Without Septic Shock Secondary to COVID-19 Severe Pneumonia
Vitamin K	NCT04770740	A Phase 2, double blind, randomized, placebo-controlled clinical trial to investigate the safety and effects of oral vitamin K2 supplementation in COVID-19
	NCT04780061	Dietary Supplements to Reduce Symptom Severity and Duration in People With SARS-CoV-2: A Randomized, Double Blind, Placebo Controlled Clinical Trial
Zinc	NCT04472585	Sub-cutaneous Ivermectin in Combination with and Without Oral Zinc: A Placebo Randomized Control Trial on Mild to Moderate COVID-19 Patients
	NCT04447534	Does Zinc Supplementation Enhance the Clinical Efficacy of Chloroquine/Hydroxychloroquine in Treatment of COVID-19?
	NCT04542993	Can SARS-CoV-2 Viral Shedding in COVID-19 Disease be Reduced by Resveratrol-assisted Zinc Ingestion, a Direct Inhibitor of SARS-CoV-2-RNA Polymerase? A Single Blinded Phase II Protocol (Reszinate Trial)
	NCT04959786	Effect of a Combination of Nitazoxanide, Ribavirin and Ivermectin Plus Zinc Supplement on the Clearance of COVID-19: Extension Study
	NCT04551339	Zinc Versus Multivitamin Micronutrient Supplementation to Support Immune Health in the Setting of COVID-19 Pandemic: A Randomized Study
	NCT04482686	A Phase II Double-Blind Randomized Placebo-Controlled Trial of Combination Therapy to Treat COVID-19 Infection
Copper	NCT04877509	Micronutrient Status Involved in Immunity in Elderly Patients With COVID-19
	NCT04870736	Mouth-to-mouth Ventilation Efficiency Through Breathable Self-Sterilizing Respirator During BLS in COVID-19 Pandemic: A crossover Simulation-based Study
	NCT04751669	Efficacy of Micronutrient Dietary Supplementation in Reducing Hospital Admissions for COVID-19: A Double-blind, Placebo-controlled, Randomized Clinical Trial
Selenium	NCT04869579	Selenium as a Potential Treatment for Moderately ill, Severely ill, and Critically ill COVID-19 Patients
	NCT04507867	Effect of a Nutritional Support System to Reduce Complications in Patients with Covid-19 and Comorbidities in Stage III
	NCT04323228	Anti-inflammatory/Antioxidant Oral Nutrition Supplementation on the Cytokine Storm and Progression of COVID-19: A Randomized Controlled Trial
	NCT04363606	Chronic Fatigue Etiology and Recovery in Covid-19 Patients: The Role of Fatigability and Stay in Intensive Care
Calcium	NCT04379310	Evaluation of Demographic and Clinical Parameters on Admission and Medications Used for Comorbidities in Patients with Covid-19 Pneumonia: A Single Center Experience in Turkey
	NCT04330300	The Coronavirus Disease 2019 Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Investigation (CORONACION) Randomized Clinical Trial

(continued on next page)

Table 1 (*continued*)

Food supplements	Identifier	Study
	NC T04610567	Two Phases Clinical Trial to Evaluate Safety and Efficacy of Methotrexate Associated to LDL Like Nanoparticles (LDE-MTX) in the Treatment of Patients with Mild Coronavirus-19 (COVID-19) Disease.

components, CCBs may act as a host-oriented treatment that suppresses virus reproduction by controlling the virus-dependent host machinery, and the risk of resistance mutants is reduced [135].

8. Towards nano-nutraceuticals approach

During infection treatment, and even after hospital release, the patient may have several illnesses at the same time for an extended period. Such complex medical problems are difficult to treat with standard antiviral medicines. As a result, scientists see a need for a new therapy that can perform many jobs at once. Considering developments and prospects, manipulative nanomedicine could be one of the prospective COVID-19 infection treatments [136]. To handle the COVID-19 pandemic, bio-nanotechnology must be optimized to create nanomedicine against SARS-CoV-2. Since we all are aware that SARS-CoV-2 virus strain varies depending on a variety of factors, the most important of which is personal medical history, making therapeutic optimization difficult [136]. Investigating highly precise nanomedicine as a means of controlling COVID-19 infection in a tailored manner is feasible through researching bio-nanotechnology and nanomedicine, both of which are created and developed for individualized health wellbeing [137]. Nanocarriers are studied to modify the pharmacokinetics aspects of the encapsulated nutraceutical medication and reduce the concentration of drug necessary for biological processes owing to prolonged and/or regulated administration. Furthermore, the use of targeted ligands on the surface of nanocarriers to recognize biological molecules of the targeted tissue is a very promising strategy for increasing antimicrobial properties [138, 139].

For the successful delivery of natural products from traditional medicine, various nanotechnology-based systems such as polymeric NPs, solid lipid NPs, magnetic NPs, metal, and inorganic NPs, nanospheres, nano capsules, quantum dots, nano emulsions, polymeric micelles, liposomes, and dendrimers have been employed [140]. Because of the unique character, nano-sized herbal medications have been created as nano-phytomedicines (Fig. 5). This introduces potential herbal drug-loaded pharmaceutical carriers for complementary alternative medicine to the contemporary system, potentially accelerating the battle against a variety of acute and chronic and pandemic global challenges such as COVID-19 [141, 142].

Stimuli-responsive polymers modify its characteristics in relation to the prevailing of external variables such as temperature, pH, electric or magnetic field, light, ultrasound, and salt content, among others (solubility, form, surface characteristics, etc.). Due to their unique characteristics, stimulus-responsive polymers provide several opportunities to include nanostructure functions and enable the creation of different intelligent systems for biomedical applications like as imaging, illness detection, controlled medication administration, and bio separation [143, 144]. Since the emergence of COVID-19, a wide range of herbal remedies have been utilised either alone or in line with the traditional management approaches. These herbal extracts may have anti-SARS-CoV-2 properties by interrupting the viral life cycle, making them a viable preventative and treatment option for the pandemic [145].

Curcumin, a pharmacological component of turmeric, has indeed been found to have antiviral properties towards a variety of viruses, suggesting that it might be used to treat COVID-19 infection [146]. In research, sinacurcumin, a curcuminoid nano micellar form with an average size of 10 nm, was used to boost curcuminoids' oral absorption. Curcumin is a lipophilic chemical with poor absorption from the gastrointestinal tract in conventional dosage forms like capsules and tablets due to its water insolubility. Nano micelles dissolve the active component, curcuminoids, in their lipophilic part with 100% encapsulation efficiency, substantially improving water solubility. Sinacurcumin soft gels completely dissolve in the stomach's acidic environment, releasing micro micelles that are stable for up to 6 h [147, 148].

Glycyrrhizic acid (GA) nanoparticles (GANPs) selectively target regions with significant inflammation, such as the lungs, in an MHV-A59-induced surrogate mouse model of COVID-19, which appeared to increase GANP accumulation and therapeutic efficacy. Furthermore, GANPs have antiviral and anti-inflammatory properties, reducing organ damage and providing sick mice with a substantial survival advantage [149]. The nanocomposite of GANPs greatly enhanced the biocompatibility of the raw material GA, providing a technological foundation for expanding GA's range of applicability. Furthermore, GANPs might target regions of inflammatory process via the EPR effect in the COVID-19 surrogate mouse model, which appeared to increase GANP accumulation in the lungs and livers, boosting the treatment's efficacy. A new therapeutic agent of this type can be easily produced into a viable therapy for COVID-19 [150–152].

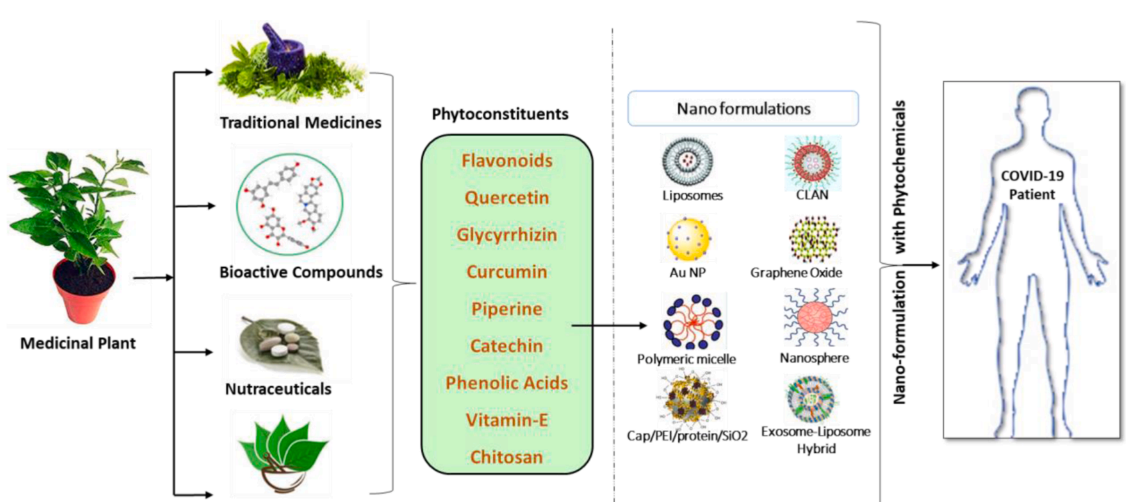

Fig. 5. Nano-approach for the targeted delivery of phytoconstituents in the body.

Chitosan nanoparticles can be primarily used to treat responses in the digestive system induced by the emergence of COVID-19 because of their mucoadhesive characteristics. According to Zuo and colleagues, SARS-CoV-2 infection in gastrointestinal tissues produces alterations in the fecal microbiota, which persist yet after SARS-CoV-2 has been eradicated, with the assessed sufferers continuing to have deficient symbiotic organisms and intestinal microbiomes [153]. Furthermore, the prevalence of certain bacteria, such as *Clostridium ramosum, Clostridium hathewayi*, and *Coprobacillus* appears to be linked to the severity of COVID-19 [154, 155].

Dormont et al. loaded nanoparticles with the anti-inflammatory medicine's adenosine and alpha tocopherol (vitamin E) for targeted activity in areas of acute inflammation with squalene, an endogenous lipid [156]. Mice experiencing a cytokine storm were given squalene nanoparticles, which decreased pro-inflammatory cytokines and increased IL-10, reducing uncontrolled inflammation [157].

9. Challenges and alternative approaches

Nanoparticle-based medication development is receiving a lot of attention these days, and it might lead to the development of new, safer medicinal medicines (i.e., alternative antiviral and antimicrobial agents). Ag-NPs, Cu-NPs, Co-NPs, and ZnO—NPs, for example, have appealing physio-chemical characteristics, such as aggregation, agglomeration, crystallinity, chemical composition, form, size, surface charge, and area [158]. Many difficulties linked to the components of the nano-biofortification process, such as which nano-nutrients are necessary for human health, have been identified behind the COVID-19 and nano-nutrients subject. What nutrients must be biofortified, and how should they be biofortified? Is it possible to transform all nutrients to nanoparticles? Is this method feasible, and how much will it cost? All of the preceding concerns pose major problems, particularly for developing nations, and may be influenced by COVID-19′s worldwide position. However, another problem with treating COVID-19 is that certain drugs lose their efficacy when the virus-compound combination dissociates after dilution. As a result, when the virus is no longer bound, it may continue the reproductive cycle. The use of nanoparticles has the potential to limit viral pathogenicity substantially, as nanoparticles inflict lasting harm to the virus [154, 159].

10. Toxicity

With the fast progress of nanoscience in the field of medicine, numerous researchers are assessing its detrimental effects and toxicities at the same time. Their interaction at nonspecific target locations rises for the same reasons that contribute to its enhanced effectiveness, namely, small size, higher surface area, particular geometries, and surface charges [160]. The primary mechanism responsible for nanomaterial toxicity is thought to be increased production of osmotic damage and proinflammatory cytokines in numerous organs, which harm the biomolecules of the cell, notably proteins, lipids, and DNA [161]. The liver, lungs, spleen, kidney, and heart are among the most perfused organs in the body. As a result, they receive the maximum quantity of any absorbed or injected substance. The liver is the primary location for the buildup of reactive oxygen species. Hepatotoxicity, nephrotoxicity, cardiotoxicity, immunotoxicity, and genotoxicity are all possible side effects of nanomaterials [162]. In addition to their beneficial effects, certain multifunctional food sources may be harmful to the human body if consumed in large quantities. For instance, licorice and glycyrrhizin can negatively affect human health if consumed in large quantities and for an extended period. Although it is widely established that licorice has fewer adverse effects when given orally rather than intraperitoneally or intravenously, even oral treatment over several weeks or longer might induce hazardous consequences [163, 164].

11. Manufacturing

Despite a large body of literature demonstrating the significant benefits of nanotechnology-based methods for diagnosing and treating viral infections, just a few items have made it to clinics. The lack of a clear methodology for trial and characterization, as well as the complexity, unpredictability, and heterogeneity of the techniques, have made repeatability and scale-up a major issue [165]. Controlling crucial parameters throughout production and the impact of even slight variations on the product's overall safety and efficacy is a major issue in nanomedicine development [166]. In *in-vitro* tests can be used to anticipate how nanomaterials will interact with the body as a first step. However, when exposed to toxics, the human body has physiological mechanisms, which is a major flaw in this paradigm. Furthermore, they take less time, are less expensive, are easier to use, and provide for better control of the experimental settings [166, 167].

12. Conclusion and viewpoint

In lieu of the renin-angiotensin system being implicated in COVID-19, with angiotensin converting enzyme-2 (ACE-2) being the primary target, phytoconstituents must have antiviral, anti-inflammatory, antioxidant, and effects on cardiovascular targets to be a successful therapeutic in the treatment of COVID-19. Many therapies based on natural products or food supplements with immune-stimulatory and antiviral actions capable of supporting and increasing the body's immune defenses may be able to reduce the duration and severity of symptoms associated with colds, flu, and respiratory viruses in general, as well as prevent the onset of serious complications [168]. With the potential and difficulties of nanotechnology, nanomedicine, and biotechnology in mind, the healthcare industry should indeed engage in nanotherapies to control COVID-19. Therefore, understanding the essential characteristics and relevant receptors and drivers associated with novel coronaviruses is critical for gaining insight of how nutraceuticals or phytomolecules might successfully operate against them [169].

Furthermore, knowing the mechanism of action of conventional antivirals and potential targets for drug development might aid in the creation of a COVID-19 treatment regimen derived from natural products. By improving the safety to risk ratio of nanostructures, the present pandemic issue may be viewed as a great opportunity for the revolution of nanomedicine. To make such compounds effective, extensive investigative research, and sharing of experiences along with information among various nationalities, agencies, and enterprises, particularly regulatory agencies, is necessary and should be the focus of future approaches [142, 170].

Producing nano delivery systems for herbal remedies has a numerous advantage in phytoformulation studies, such as improved absorption and bioavailability, toxicological safety, pharmacodynamic action augmentation, stability enhancement, improved cellular macrophage variability, sustained delivery, protection from physiochemical deterioration, and so forth. As a result, nanosized drug delivery systems for medicinal herbs may have a bright future in terms of improving activity and overcoming adversity connected with herbal formulations. As a result, including nanocarriers as a novel drug discovery system into the standard medical system is critical to combating more chronic illnesses such as asthma and diabetes, COVID-19, cancer etc. [171]. The SARS-CoV-2 is observed to mutate contiously and the newly emerged variants for example Delat and Omicrin are possessing higher infectivity and transmissivity causing adverse health effects [172–174]. Presently, managing this new pahse on COVID-19 infection is challenging and raised the demand to develop efficient biosensor for POC detection of SARS-CoV-2 [175,176], anti-viral and anti-bectarial materials for eradicating SARS-CoV-2 [173], and nanotheranostics needed for trapind and eradication of muated SARS-CoV-2 [177]. Alongwith technological developments and the scenerio of SARS-CoV-2 infection due to new varinats, novel nanotechnology supported nutraceuticals should be promoted as a part of therapy to manage newly emerged health consiquences [172,173].

Keeping these aspects and concerns into consideration, this article summarizes the potential of neutraceutucals and manage pre/post or both COVID-19 infection consequences. As SARS-CoV-2 is known to affect most of the organs of the body and in such situation, the delivery of an optimized therapeutic agent is crucial due to various barriers present in body. To improve the delivery of nutraceuticals, retain their structure and functionality even for a longer time, develop a longer therapeutic approach via optimization encapsulation and controlled release, and scaling-up production, an approach of nanomedicine is presented here briefly along with the potential challenges. These systems can control the SARS-CoV-2 infection and provide a support to immune system to patient during infection and after the infection for a better recovery. The is serious concern because majority of patient recovering from the infection are showing other disorders associated with lung, eye, and sometime neurological. Therefore, an alternative and main therapy, we are posing using of nano nutraceutical of a better management of SARS-CoV-2 infection needed for a better recover with no side-effects.

Declaration of Competing Interest

The authors do not declare any conflict of interest.

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