Miscellaneous Natural Products for COVID-19

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Contributor: Syed A. A. Rizvi, George P. Einstein, Orien L. Tulp, Frantz Sainvil, Rolando Branly

Natural medicine has proven its effectiveness against various illnesses. Most of the pharmaceutical agents currently used can trace their origin to the natural products in one way, shape, or form. Using natural products, which is part of various traditional medical systems to prevent and/or treat diseases, dates back thousands of years in different parts of the world.

Keywords: natural products ; infectious disease ; COVID-19 ; immunity

1. Curcumin

Curcumin is one of the essential compounds in the turmeric rhizome (Curcuma longa), a yellow-orange crystalline material. It does not have a lot of different kinds. This product has been used as medicine for the last 4000 years, especially in South Asia [1]. It has been named the “Indian saffron” and the “Golden spice” because of its use as a potent agent in medicinal applications. The compound has been used in Unani, Ayurveda, and Chinese medicine. The discovery of the compound dated back 200 years when it was determined as a pure compound in 1842 [2]. There have been numerous studies showing this as a powerful medicinal agent including antimicrobial properties [3].

The geographical locations of its growth have tremendous effects on the quality of the plant and its nutrition composition [4]. It has been used to add flavor to rice, meat, pasta, and vegetable dishes. It is speculated that it has been used for over 2500 years to treat different diseases and illnesses. It has been used in Ayurveda and traditional Chinese medicine for different conditions. The importance of the plant in treatment is from its orange-yellowed color, which is the most potent component [5]. Studies on the plant have determined that curcumin has antimicrobial, antioxidant, anti-inflammatory, antiangiogenic, antiplatelet, and antimutagenic properties. These properties have preventive and protective abilities against various diseases such as autoimmune, neurological, metabolic, liver, lung, and cardiovascular. The examination of the effects of curcumin on health is therefore necessary [5].

Studies on curcumin’s physical, organic, and inorganic chemistry have established that the substance acts through various mechanisms; this knowledge has been used to develop nutraceuticals and curcumin-based therapeutic agents. The studies showed that curcumin could react with free radicals, form, and break down nonconjugated substances in the body. Curcumin has been established to be effective in treating lifestyle and chronic illnesses through its pharmacological and chemo-preventive abilities. It has also been used in traditional Indian medicine to expulse gas, strengthen the body’s energy, alleviate arthritis, improve digestion, and dissolve gall stones. In modern medicine, it has been used to heal wounds, stimulate the immune system, and decelerate aging [6].

Curcumin has limited bioavailability due to its insufficient absorption, high speed of metabolism, and elimination from the body. These properties make it have limited therapeutics effects in the body. However, new methods have been developed to increase its bioavailability. One of the commonly used interventions is in combination with piperine. The bioavailability of curcumin significantly increases with a combination of piperine; the mechanism is through the decreased glucuronidation of curcumin. The structural analogs of curcumin have been established to increase its bioavailability too [6].

Curcumin has been used in the Jiawei-Xiaoyao, a Chinese traditional treatment system, to treat several diseases such as stress, depression, and dyspepsia for thousands of years now. It has also been established that it is effective in treating neurological disease, cardiovascular disease, and other inflammatory diseases. It is also hypothesized to be effective against the pathogenesis of molecular targets to treat and prevent diseases [7]. The modulation of the molecular targets has a role in the development of the disease. Curcumin has been shown to play vital roles in regulating cytokines, kinases, growth factors, metastatic, receptors, and apoptotic molecules in most phases during most diseases’ development. The curcumin structure’s inclination increases its free radical scavenging activities to low-level hydrogenation and a high level of methoxylation [8]. The structure additionally enables the curcumin to have antioxidant, anticancer, and anti-inflammatory effects.

Studies have shown that curcumin has been effective against the COVID-19 variant [9]. The supplementation with curcumin modulates pathogens' inflammation and oxidative stress on the respiratory system. Studies have shown a direct effect of curcumin on the COVID-19 variant. It has been predicted that curcumin interacts with ACE2 protein and S protein and intervenes by inhibiting the entry of the virus into the lung cells. It has been postulated that curcumin may prevent the entry of the virus into the body and its replication [10].

2. Elderberry (Sambucus nigra)

This flowering plant belongs to the Adoxaceae family and is used as a supplement to treat flu and cold symptoms. The berries of this plant contain anthocyanin that has been shown to possess powerful antioxidant properties. Its therapeutic use has effectively treated obesity, influenza, upper respiratory infection, metabolic syndrome, gingival recession, and hyperlipidemia. The flowers and the plant's berries contain antibacterial, antioxidant, glucose-lowering anti-inflammatory, and immune-modulating properties. It can be used alone or combined with other agents to treat various health conditions [11].

The elderberry is an excellent source of free and conjugated amino acids, proteins, fiber fractions, vitamins, antioxidants, and unsaturated fatty acids. Its study shows biological activity elements, primary polyphenols, proanthocyanidins, phenolic acids, and flavonols. The presence of phenols makes the elderberry an ideal medicine and has high antioxidant properties [12].

Many factors affect the composition of the elderberry, such as the degree of ripeness, the variety, and climatic and environmental conditions. The protein nutrient composition is 2.7–2.9% in the fruits, 2.4% in the flowers, and the leaves contain 3.3%. The amino acids occur in the free or conjugated form in the leaves and the flowers. The protein component of the elderberry is complete; among 16 of all the amino acids that belong to the plant cannot be synthesized in the body and must be supplied in the diet, while there are nine amino acids in the leaves and the flowers. The lipids of the plant are usually located in the seeds. The seeds have an oil content of around 22.4%, and in meals produced from the seeds, around 15.9%. The fatty acids are dominantly made up of unsaturated fatty acids; linolenic, linoleic, and oleic acids. The dietary fiber is 7.4% of the total carbohydrate content of 18.4%. Some of the fiber fractions found in the fruit include pectic acid, pectin, calcium pectinate, and pectin. An amount of 6.8–11.5% of the fruits are made up of sugars. Vitamins A, B, and C are found in high amounts. Elderberry is an excellent source of flavonols and phenolic acids. Isorhamnetin, kaempferol, and Quercetin are the most predominant ones. Polyphenolic compounds are found in the leaves, flowers, and fruits. The flavanols are tenfold more in the flowers than the fruits and the leaves [13][14].

The elderberry has been used in folk medicine to treat many ailments and diseases. It has been heavily applied in managing respiratory infections, mainly in colds and cases of flu, but also in dislocations, burns, skin rashes, hemorrhoids, stings, insect bites, and swellings, among others. Traditional medicine recommends the utilization of the elderberry to manage respiratory illnesses such as cold and catarrh, influenza. It is also a laxative, anti-inflammatory, diuretic, and diaphoretic agent. Its components tackle the levels of reactive oxygen species in the body, reactive chlorine species, and reactive nitrogen species through its antioxidant activity [15].

A diet consisting of elderberry fruits is likely to be a potential protective agent against the unwanted effects of oxidative stress on the body and growth. The antioxidant activities are exhibited by the elderberry's extract, it scavenges hydroxyl radicals and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH•) while inhibiting the lipid peroxidation in the linoleic acid emulsion. Nitric oxide radicals have also been effectively scavenged by the extracts [16][17].

The elderberry has many beneficial effects on increasing the activity of antioxidant enzymes in the plasma, such as glutathione and reducing uric acid levels, reducing oxidative stress, and affecting the blood system. A positive effect of uric acid activity at higher levels has been shown to have antioxidative properties. Uric acid can scavenge ROS and chelate metals such as Fe and Cu. One of the properties that make it important for protection against vascular disease is its ability to penetrate the endothelial cells [18].

There is enough evidence suggesting that treatment of colds and influenza has been effective with elderberry extracts. The extracts have exhibited antiviral and antibacterial activity. At higher concentrations, the elderberry inhibited the activity of influenza A. The compounds are directly bound to the H1N1 Viruses led to preventing their entry into the cells and subsequently prevent an infection [16]. The extracts have been observed to help the host avoid losing any weight in the disease process. It also stimulated the local and systemic immune system responses. Other studies have helped to show the strong inhibitory effects of the extracts on the feline immunodeficiency virus. The extracts have antibacterial activity against Gram-positive bacteria that cause frequent upper respiratory infections. The infusions made from the leaves showed great inhibitory effects on the growth of bacteria (*Bacillus subtilis*, *Bacillus megaterium*, *Escherichia coli*, and *Staphylococcus aureus*) and against yeast. There was also antibacterial against nosocomial pathogens, including methicillin-resistant *S. aureus.* The antimicrobial activity of the flower extracts was more pronounced than that of the fruit extracts [19].

The elderberry extracts stimulated the secretion of proinflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α (tumor necrosis factor) and cytokine IL-10. It increased the production of IFN-β interferon associated with upregulation of TLR-3 (toll-like receptor 3). Elderberry-derived polyphenols caused a 50% decrease in the levels of IL-1β that is responsible for the long-term inflammation in chronic illnesses. The elderberry also can increase the number of lymphocytes in the body [20].

The consumption of the elderberry is considered safe if it is eaten when cooked and consumed moderately. It is dangerous to consume it uncooked because of the potential cyanide toxicity. The intake should be cautiously monitored in diabetic patients to promote glucose and insulin metabolism. Some of the side effects that have been reported upon its use include nausea and vomiting, hypokalemia, dehydration, tachycardia, hypotension, and diarrhea [21].

3. Glutathione

This is an endogenous peptide that possesses both metabolic and oxidative properties. It has been used to prevent neurotoxicity induced by oxaliplatin and cisplatin [22]. It has also been used to prevent other adverse effects caused by radiation therapy and antineoplastic agents and other disorders like poisoning by heavy metals and other elements, corneal disorders, eczema, and liver disorders [23]. Furthermore, glutathione has been employed treat peripheral vascular disorders and idiopathic pulmonary fibrosis. It is a vital extracellular antioxidant of the lungs, and there is a high concentration of the substance in the epithelial lining fluid of the lungs. It has been shown that a deficiency of glutathione can contribute to the damage of the epithelial lining that is witnessed in different lung disorders. Patients with idiopathic pulmonary fibrosis and cystic fibrosis treated with glutathione had better results over time [24].

Two cytosolic enzymes, glutamylcysteine glutamate and GSH synthetase, catalyze glutathione synthesis from cysteine, glycine, and glutamate. Feedback inhibition, availability of cysteine, and enzyme activity have all been shown to affect glutathione synthesis. The role of substances in the metabolism of nutrients, defense against free radicals, and regulation of cellular events are all vital for the body. Deficiency of the substance leads to oxidative stress that plays a role in aging and the pathogenesis of many other illnesses such as liver disease, parkinsonism, Alzheimer's disease, and sickle cell anemia, among others [25].

There is a panoply of the roles played by glutathione in the body. First, it helps to get rid of free radicals and other reactive species of oxygen from the body directly and indirectly via enzymatic actions. The GSH is oxidized to GSSG and then reduced to GSH by NADPH-dependent glutathione reductase. Glutathione peroxidase catalyzes GSH reduction of hydrogen peroxide and other peroxides. Secondly, GSH reacts with several electrophiles and physiological metabolites such as prostaglandins, leukotrienes, melanins, and estrogen to form mercapturates. Glutathione-S-transferase initiates these reactions. The substance also conjugates with nitrogen oxide to form an S-nitrosoglutathione adduct cleaved by thioredoxin to release NO and GSH. NO and GSH are vital in the hepatic action of insulin-sensitizing agents that regulate the utilization of amino acids, glucose, and lipids. GSH serves as a substrate for formaldehyde dehydrogenase that converts GSH and formaldehyde to form S-formyl-glutathione. Formaldehyde is a carcinogen, and its removal from the body, is of great physiological importance as it is produced from the metabolism of choline, methanol, sarcosine, xenobiotics, and methionine [26].

It is required to convert prostaglandin H2 to prostaglandin D2 and E2 catalyzed by Endoperoxide isomerase. It is also involved in the glyoxalase system that converts methylglyoxal to D-lactate, a pathway often presents in microorganisms. Due to the vital role of glutathione in the body, adequate concentrations are essential for the proliferation of the cells, including the intestinal epithelial cells and lymphocytes. It is also involved in the process of spermatogenesis in males and the maturation of sperms. Similarly, glutathione is important in activating T-lymphocytes and polymorphonuclear leukocytes and the production of cytokines to mount immune responses against foreign pathogens. Since GSH affects the oxidative, which is an important aspect of the disease process, it can prevent ferocious effects induced by the produced chemicals [27].

Glutathione has been used as adjuvant therapy in the treatment of COVID-19 [28]. There are immunoinflammatory mechanisms that have been implicated in the pathophysiology of COVID-19. Oxidative stress is still a key factor in almost all disease processes; it affects the body's homeostasis. Glutathione and its precursors such as N-acetylcysteine have been considered for treatment because they influence the binding of the viral proteins to the ACE2 receptor proteins in the cells of the hosts that have been implicated in the COVID-19 infection [29]. The SGH is found in the cytosol of most cells in the body. It comprises three substances: glutamate, cysteine, and glycine. It also plays a role in DNA synthesis, a foreign mechanism that viruses used to replicate and induce an infection. It is the first line of defense against oxidative stress caused by foreign pathogens in the epithelial lining of the lower respiratory tract [30].

The concentrations of GSH in the epithelial fluids are 140 times higher than those found in the serum [29]. Low amounts of endogenous GSH have been implicated to be the cause of the pathogenesis of most illnesses that act through inflammation and oxidative stress, COVID-19 being one of them [31]. COVID-19 is more established in populations with natural or pathological depletion of GSH. The precursor is also important in activating other mechanisms that lodge attacks against the pathophysiological pathways of the vital attacks and the inflammation that follows. It can increase the response of the T cells and decrease the plasma levels of TNF. The precursor also has mucolytic properties that strengthen the protection against pulmonary diseases [32].

4. Medical Mushrooms

Edible mushrooms are known for their nutritional properties, therapeutic potential, and biological activities. They have emerged as important sources of compounds demonstrating antitumor, antioxidant, and antimicrobial properties [33]. Its bioactive properties enable them with an antioxidant capacity to prevent diseases related to increased oxidative stress and the formation of free radicals. The antimicrobial activities of the compounds and extracts from the mushrooms have been well documented over the years. The use of medical mushrooms has a long tradition in Asian countries. Medicinal compounds from the mushrooms are extracted in multiple ways, through cultivation in the farms or collection from the wild. The fruiting bodies of the mushroom are harvested, or the mycelium is cultivated in the fermenters with solid or liquid substrates. Components in the mushroom can mitigate assaults that make the body vulnerable to cardiovascular illnesses, cancer, and neurodegenerative and metabolic disorders [34].

The mushrooms have been an important therapeutic raw material in folk medicine; for instance, the reishi mushroom (Ganoderma lucidum) was regarded as a panacea in traditional Chinese medicine [35]. The therapeutic effects of the traditionally used species have been corroborated with modern research. The species used for food have good amounts of carbohydrates; their structure has chitin that fills the dietary role. They also have large amounts of proteins that contain essential amino acids and may be alternated with animal products. They have low-fat content making them a good source with low calories, but they have adequate stores of polyunsaturated fatty acids (PUFAs) which present many health benefits to the body. The medicinal and dietary uses of the edible mushrooms are supported by the fact that they contain numerous health-promoting and biologically active compounds. They have secondary metabolites that have a range of benefits, such as antiviral, antibacterial, antioxidative, anticancer, the ability to improve the functioning of the cardiovascular system, and anti-inflammatory properties. The most profound application of medical mushrooms is to prevent inflammation [36][37].

The glucans and the chitosans have shown antilipemic effects as they decrease the LDL cholesterol levels and the absorption of fat in the gut [38]. They also regulate glycemia; therefore, they prevent the development of obesity, diabetes, and cardiovascular diseases. The β-Glucans, usually contained in the Basidiomycota species, are the biological response modifiers because of their broad-spectrum activities in the immune system [39]. Additionally, they have antioxidant properties, decrease carcinogenic elements' metabolite levels, and prevent DNA damage. They have also been shown to play a role in producing anti-inflammatory and pro-inflammatory cytokines in the body. They have a high binding affinity to the surface of the immune cell receptors with the pattern recognition receptors in the form of pathogen-associated patterns of molecules. Such receptors include dectins-1, toll-like receptors, and complementary receptor 3. Thus, the immune cells' maturation and proliferation, stimulation, and activation of the natural killer cells and the macrophages can be activated by β-glucans. Lentinan from the Lentinula species is one of the most typical β-glucan and has been used for a long in the medical realm [39].

The amino acids content in the edible mushrooms is also linked to the anti-inflammatory effects of the medical mushrooms; they have been shown to play a role in the metabolism of prostaglandins [40]. The anti-inflammatory properties of the oyster mushroom have been explained by the presence of isoleucine, tyrosine, phenylalanine, and leucine amino acids. The arginine can inhibit the growth of tumor cells and decrease the risk of developing metastases. Patients who have cancer and who are under arginine supplementation have shown to have a stronger immune system, gained body weight, and have a favorable prognosis than patients who are not under any supplementation. Ergothioneine in mushrooms is an essential amino acid and acts as an antioxidant. It is absorbed by the tissues from the food and is essential for cells prone to oxidative stress like the lens of the eye, semen, skin, and the erythrocytes. The presence of histidine derivatives in A. bisporus has been attributed to relieving oxidative stress. Ergothioneine is chemo and radio-protective and has antimutagenic activities [37][41].

Lectins contained in medical mushrooms can bind selectively with the membrane carbohydrates of different types of cells, playing an important role in the regulation of the immune system. They promote the process of adhesion of cells, and some of them have been shown to activate the lymphocytes, while others have strong anti-proliferative properties. Lectins that have been extracted from the mushrooms have been established as inhibiting the proliferation of tumor cells, especially in breast cancer, without inducing any toxicity. It has also been tested for use in treating psoriasis, eye disorders, especially glaucoma and diabetes [41][42].

The fatty acids of the mushrooms can support human anti-inflammatory processes due to their high composition of unsaturated fatty acids. The PUFAs are precursors of eicosanoids which play a role as signaling molecules necessary for cellular response regulation in the muscles, nerve cells, the immune system, and the blood vessels. They maintain an equilibrium between the anti-inflammatory and inflammatory responses. Therefore, having an adequate supply of fatty acids in the diet helps prevent cardiovascular diseases. α-Linolenic acid (ALA) has been an essential component for normal health and basic nutrition; it is a precursor of long-chained PUFAs [41][43].

It also has potent anti-inflammatory activities. Extracts of chanterelle revealed the presence of fatty acids that showed antagonistic activities towards the receptors activated by peroxisome proliferator-activated receptor γ (PPARγ). The latter plays a vital function in the metabolism of carbohydrates and lipids, in the differentiation of the adipocytes, and in monitoring the inflammation processes [41][42][43]. They inhibit insulin-resistance development; they are efficient against diabetes. They showcase a strong ability to the tumor and inflammation-associated diseases. The fatty acids present in the A. bisporus and other mushrooms can protect the body against hormone-dependent cancers of the breasts. The mechanism of action is by inhibiting aromatase activities, an enzyme involved in the synthesis of estrogen [44].

Among the important secondary metabolites, phenolic compounds are the most useful; they are found in fungal fruits. They contain both anti-inflammatory and antioxidative properties. They do this through multiple mechanisms. They can donate electrons that neutralize the reactive oxygen species and protect the cells against any damage. They can also chelate elements such as iron and copper, which are potential oxygen species generators. They protect the body against free radicals like lipoxygenase, NADH oxygenase, cyclooxygenase, and microsomal monooxygenase. Most of the enzymes are involved in inflammation processes. Some of the phenolic compounds found in the different mushrooms include gallic, cinnamic, caffeic acids, and protocatechuic. Caffeic acids are the most prominent phenolic compound in most mushroom species. The latter exhibited both inflammatory and antioxidative properties [45].

Dried edible mushrooms contain high levels of vitamin C, folic acid, thiamine, niacin, and relatively low amounts of α-tocopherol, riboflavin, and β-carotene. Dietary deficiency of folic acids is a common problem; therefore, these diets can be supplemented with edible mushrooms. The mushroom species are also excellent sources of tocopherols and carotenoids. These compounds have powerful anti-inflammatory and anticancer protection of the body. They also inhibit cellular membranes from peroxidation. The carotenoids are very vital for the normal functioning of the eyes with an added role as powerful antioxidants [37][46].

Several mushroom species contain vitamin D precursor ergosterol, ergocalciferol, and other sterols. Lately, as per studies, vitamin D deficiency has been on the rise. Vitamin deficiency can be attributed to diabetes, hypertension, cancer, and inflammation of the intestines that all are characterized by inflammation. Vitamin D is known for its anti-inflammatory properties. It inhibits the translocation of NF-κB to the nucleus of the cells; this prevents the expression of the pro-inflammatory genes [46].

Due to the well-known antiviral properties of the medical mushroom, they have been explored as potential therapy in fight against COVID-19 [47][48][49].

5. Astaxanthin

Astaxanthin (AX) pigment belongs to the xanthophylls family, the oxygenated carotenoid derivatives from the plants by lycopene synthesis. It is one of the major components included in the feeds of crustaceans and salmonids. The main role of the pigment is to provide a desirable reddish color to the organisms reared, as most of them do not have access to natural carotenoids [50]. Apart from the induction of pigments, it has antioxidant properties that have been reported to be stronger than those caused by α-tocopherol and β-carotene. Due to these properties, it has been said to protect the organisms from a wide range of diseases such as different types of cancer, cardiovascular-related illnesses, and diseases related to the immune system [51].

The normal aerobic metabolism in the body produces free radicals and reactive oxygen species. AX reacts with the free radicals to generate innocuous compounds by inhibiting the oxidation reactions [52]. However, apart from acting as antioxidants, the carotenoids can also induce oxidative stress on the cells. The AX antioxidative activity is more than ten times stronger than the other carotenoids [53]. It reacts vigorously with other free radicals, depending on the polyene system length and the terminal rings [54].

AX has been proven effective in managing Helicobacter pylori infections that induce gastritis, stomach cancer, and peptic ulcers in humans. The exact mechanism of action against these microorganisms is not known [55]. Due to known regulatory properties of AX for the expression of pro-inflammatory factors as well as antiviral effects, it has been explored as potential adjuvant therapy for COVID-19 disease [56][57][58].

6. Andrographis paniculata

Andrographis paniculata, commonly referred to as creat or green chiretta plant has been used as a medicinal food for many centuries now. The roots and leaves of the plants have been used for various medicinal purposes in Asia and Europe. It has been used for medicine because of its ‘cold property’ to remove heat and expel toxins from the body. It is being used to stimulate the immune system and manage myocardial ischemia, respiratory tract infections, and pharyngotonsillitis in modern medicine. It also contains anti-inflammatory, anti-microbial and anti-hyperglycemic, anti-sclerosis, antiplatelet, anticancer, choleretic, and anti-hyperglycemic properties. Its leaves and stems contain active phytochemicals such as flavonoids and diterpenoids [59][60].

The major constituent of the plant is andrographolide (a labdane diterpenoid) and has been used as an herbal medicine in Asia for a long time. It has beneficial effects against virus infection, bacteria dysentery, fever, laryngitis, herpes, and rheumatoid arthritis. The compound protects the body against inflammation by binding to the adenosine A2A receptor, inducing the nuclear factor, subsequently inactivating GSK3β, which causes the upregulated expression of heme oxygenase 1. The process regulates the body against oxidative stress from diseases like diabetes, neurodegenerative diseases, and osteoporosis. It can also control inflammation by regulating the expression of proteins (Dai et al., 2019).

The plant’s active compound has been implicated in treating colitis, long-term inflammatory disease of the intestines with limited treatment options. *A. paniculata* mitigates the extension of inflammation of the intestine in colitis induced by transfer of naïve T cells. It does this by affecting the early proliferation and differentiation of the T cells. Additionally, it decreases cytokine expression and splenic cell counts and CD4+ IFN-γ + T cells within 4–7 weeks of undergoing treatment [60][61].

The active compound of *A. paniculata* has been shown to protect the body against infectious agents that destroy the central nervous system. In the process of a CNS disease, the immune responses that protect the body may turn against the host leading to death and morbidity. The plant can prevent the anti-nociceptive activity on hyperalgesia caused by nitroglycerine administration by inhibiting the action of interleukin 6 (IL-6) in the cerebrum and the expression of TNF-α mRNA in the mesencephalon only. Andrographolide can decrease the LPS-induced expression of the cortical C-X-C and C-C subfamily chemokine in vivo [62]. It can also decrease inflammation of the astrocytes and oxidative stress by mediating the out of the cell signal-regulated kinase and Nrf2-p38-MAPK signaling pathways in the primary astrocytes. Regulating the p38-MAPK signaling pathway can protect the MCAO-induced brain injury. It is also involved in suppressing the generation of free radicals, brain infarction, and the blood-brain barrier disruption. It has also shown tremendous benefits in Alzheimer’s diseases; patients prescribed with andrographolide recover spatial memory, learning performance, and synaptic basal transmission. The compound has also shown neuroprotection on the regulation of the synaptic proteins, reduction of the phosphorylated tau proteins, and the maturation of the amyloid-beta aggregate in the aged degus [62].

Recently, peroxisome proliferator-activated receptor-gamma (PPARγ) agonism has been shown as a new strategy to address alcohol use disorder (AUD) and possibly to other addictive substances [63]. The administration of *A. paniculata* extract or andrographolide activates the transcription factor PPARγ [64].

The extractions from A. paniculata have been implicated in the studies concerning the management of the virus. In the studies, the post-infection treatment of the Calus-3 cells significantly prevented the production of infectious virions as per the assays used. In summary, the experimental evidence favored the andrographolide and *A. paniculata* for the advanced users as a monotherapy and combination with other drugs against the COVID-19 virus [65][66].

7. Propolis

This is a resinous material well known and collected by the bees from the plant exudates and the buds. It is mixed with the wax, the pollen, and the bee enzymes. The bees use it in smoothening the out internal walls, carver the carcasses of the intruders in the hive to prevent them from decomposing, and sealing the holes present in the honeycombs. Due to its antimicrobial and antiseptic properties, it protects the colonies of bees from infection. Since antiquity, propolis has been used by different civilizations to manage colds, ulcers, and wounds because of its local anesthetic and antiseptic properties. It was used to embalm the death by the Egyptians and recently in the Boer War to regenerate the tissues and heal wounds. Its uses have also been applied in contemporary medicine owing to its anti-inflammatory, antioxidant, antitumor, and immune-modulatory activities. Its chemical and biological compositions have been studied to gain more insight into it [67][68].

The use of propolis has not shown any notable side effects after administration. No alterations in enzyme activities were reported. After administration, only a few minor side effects have been reported in treating stomatitis, prevention of otitis media, and mouth ulcers. It protects the renal tissue against free radicals, toxicity, and other adverse effects caused by diatrizoate. Some of the different forms of propolis from Taiwan protected the liver from developing fibrosis [68].

Propolis may directly act on microorganisms in vitro. It can stimulate the immune system in vivo and activate the mechanisms involved in killing microorganisms. The use of antimicrobial drugs with propolis is still being investigated. Findings indicated the ability of propolis to decrease the resistance of the walls of the bacteria to the therapeutically administered antibiotics and caused synergistic effects when administered with antibiotics on the ribosome but do not have any interaction with drugs acting on the DNA or folic acid [69]. It also shows antiviral properties. It exerts the antiviral action by partially blocking the entry of viruses within the cells; this affects the replication steps of the virus into the cells and leads to the degradation of the RNA before the virus enters into the cells or after supernatant is released by the cells. Antifungal properties of propolis have been documented as well; it inhibits the aflatoxigenic fungi, decreasing the percentage of germination of conidia in isolates of flavus. Some of the different types also exerted effects against Candida albicans [69].

A potential pharmacological approach to treat COVID-19 aims at downstream effectors like p21-activated kinases. Caffeic acid phenethyl ester (CAPE), one of the most beneficial components of propolis, has shown the ability to downgrade the RAC, a signaling protein in human cells [25]. It is hypothesized to act as a RAC/CDC42-activated inhibitor of the kinase. This experimental evidence suggests that CAPE can help inhibit fibrosis induced by the COVID-19 virus. However, hypersensitivity reactions should be considered when using it for treatment [70][71].

8. Probiotics

Probiotics are living nonpathogenic microorganisms taken to maintain microbial balance, especially in the gastrointestinal tract. They are composed of Saccharomyces boulardii yeast or lactic acid bacteria such as Bifidobacterium and Lactobacillus species, usually through diet supplements and foods. They exert their beneficial effects via various mechanisms like lowering the pH of the intestines, preventing and decreasing invasion by pathogenic organisms, and modifying the hosts' immune response [72][73][74].

Not all species of probiotics have all the beneficial effects. The best-documented effectiveness of probiotics is in treating acute diarrhea caused by pouchitis and rotavirus. However, there is a knowledge gap in clarifying the roles of probiotics in preventing diarrhea related to the use of antibiotics, irritable bowel syndrome, Crohn's disease, vulvovaginal candidiasis, and traveler's diarrhea. When ingested, there is no consensus on the least number of microorganisms to obtain a beneficial effect. Some scientists are looking into using probiotics to address COVID-19 [75][76]. A recently published report on a randomized, quadruple-blinded, placebo-controlled trial reported a notable increase in specific IgM and IgG against SARS-CoV-2 using a four-strain probiotic composition, indicating its effects on host's immune system. The COVID-19 outpatients and early viral and symptomatic remission [77].

9. N-Acetyl Cysteine (NAC)

For decades, N-acetyl cysteine has been used to treat multiple disorders such as intoxication of paracetamol, stable angina pectoris, acute respiratory distress syndrome, doxorubicin-induced cardiotoxicity, HIV/AIDS, radio-contrast induced nephropathy, toxicity from heavy metals, and psychiatric disorders such as bipolar, addiction, and schizophrenia. It is the precursor of amino acid L-cysteine and is available in intravenous, oral, and inhalation forms. Its toxicity is relatively low and presents mild side effects such as nausea, vomiting, tachycardia, pruritus, and rhinorrhea [78].

Studies on the NAC have shown that it interacts with several pathways of metabolism that include regulation of apoptosis and the cell cycle, progression of tumors, expression of genes, immune modulation, and mitochondrial functions. Its half-life is an average of 5.6 h, and it is cleared in the kidneys. This low bioavailability is due to its N-deacetylation in the mucosa of the intestines and first-pass metabolism in the liver. The plasma acts as a pro-oxidizing medium; a redox exchange reaction occurs between cysteine proteins, NAC, and cystine in the plasma to produce NAC–cysteine, NAC–NAC, and cysteine [79]. The latter goes through the epithelial cell membranes and helps synthesize glutathione, an important antioxidant in several physiological processes in the body [80]. Some of these processes include detoxification of the electrophilic xenobiotics, regulations of the immune responses, leukotriene and prostaglandin metabolism, redox-regulated signal transduction modulation, antioxidant defense, signaling of neurotransmitters, and modulation of the proliferation of the cells [81][82].

N-acetyl cysteine is also known to exhibit antiviral properties [83], not surprisingly, it has also shown great promise in addressing the COVID-19 pandemic mostly by diminishing the cytokine storm and thus preventing acute respiratory distress syndrome (ARDS), the leading cause of death from SARS-CoV-2 infection [84][85][86][87].

10. Quercetin

Quercetin is an aglycon flavonoid and is widely found in various fruits, plants, medicinal plants including apples, wild berries, brassica vegetables, tea, as well as in many seeds, nuts, Ginkgo biloba and elderberry, etc. It is an auxin transport inhibitor and reported to exhibit useful pharmacological properties such antioxidant, antiprotozoal, anticancer, antiviral, anti-inflammatory, immunoprotective, antidiabetic, etc. [88][89]. Quercetin exhibits low oral bioavailability (~2%) and gets rapidly eliminated in urine and feces. The absorbed Quercetin goes through II metabolism and gets excreted in urine through kidney and bile through liver [90].

Due to its known antiviral properties [91], Quercetin was also extensively evaluated as possible adjuvant therapy and a preventive measure against COVID-19 [92][93][94][95]. Quercetin is a potent nuclear factor erythroid-derived 2-like 2 (NRF2) agonists and these agonists are known to prevent SARS-CoV-2 replication in vitro [96][97]. Quercetin has prevented various zoonotic coronaviruses as well as other viruses' entry into host cells [98][99]. Quercetin is a potent immune modulator, it inhibits inflammatory pathways leading to cytokine storm, and also reduces the dendritic cells stimulation and expression of major histocompatibility complex (MHC) class II [100]. Quercetin has shown strong inhibitory activity against human angiotensin-converting enzyme 2 receptors (hACE2) expression, thus blocking the SARS-CoV-2 entry in the human cells [101]. Further, querceitin has been shown to target the Chymotrypsin-like Protease (3CL^{pro}), Papain-like protease (PL^{pro}), and Spike protein (S protein) of the SARS-CoV-2 [102].

Since Quercetin is a safe and known natural product that has previously demonstrated antiviral capabilities including the novel SARS-CoV-2, it was evaluated in various clinical trials [103]. The results show, using Quercetin alone and in combination with other natural products (curcumin, zinc, vitamin C, etc.) and drugs, results in lessening the clinical manifestations [93][104].

References

1. Sharifi-Rad, J.; Rayess, Y.E.; Rizk, A.A.; Sadaka, C.; Zgheib, R.; Zam, W.; Sestito, S.; Rapposelli, S.; Neffe-Skocińska, K.; Zielińska, D.; et al. Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Front. Pharmacol. 2020, 11, 01021.
2. Kunnumakkara, A.B.; Bordoloi, D.; Padmavathi, G.; Monisha, J.; Roy, N.K.; Prasad, S.; Aggarwal, B.B. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. Br. J. Pharmacol. 2017, 174, 1325–1348.
3. Adamczak, A.; Ożarowski, M.; Karpiński, T.M. Curcumin, a Natural Antimicrobial Agent with Strain-Specific Activity. Pharmaceuticals 2020, 13, 153.
4. Dosoky, N.S.; Setzer, W.N. Chemical Composition and Biological Activities of Essential Oils of Curcuma Species. Nutrients 2018, 10, 1196.
5. Quispe, C.; Herrera-Bravo, J.; Javed, Z.; Khan, K.; Raza, S.; Gulsunoglu-Konuskan, Z.; Daştan, S.D.; Sytar, O.; Martorell, M.; Sharifi-Rad, J.; et al. Therapeutic Applications of Curcumin in Diabetes: A Review and Perspective. BioMed Res. Int. 2022, 2022, 1375892.
6. Patel, S.S.; Acharya, A.; Ray, R.S.; Agrawal, R.; Raghuwanshi, R.; Jain, P. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. Crit. Rev. Food Sci. Nutr. 2020, 60, 887–939.

7. Hu, J.; Teng, J.; Wang, W.; Yang, N.; Tian, H.; Zhang, W.; Peng, X.; Zhang, J. Clinical efficacy and safety of traditional Chinese medicine Xiao Yao San in insomnia combined with anxiety. Medicine 2021, 100, e27608.
8. Nelson, K.M.; Dahlin, J.L.; Bisson, J.; Graham, J.; Pauli, G.F.; Walters, M.A. The Essential Medicinal Chemistry of Curcumin. J. Med. Chem. 2017, 60, 1620–1637.
9. Pawar, K.S.; Mastud, R.N.; Pawar, S.K.; Pawar, S.S.; Bhoite, R.R.; Bhoite, R.R.; Kulkarni, M.V.; Deshpande, A.R. Oral Curcumin with Piperine as Adjuvant Therapy for the Treatment of COVID-19: A Randomized Clinical Trial. Front. Pharmacol. 2021, 12, 669362.
10. Sharma, V.K.; Prateeksha; Singh, S.P.; Singh, B.N.; Rao, C.V.; Barik, S.K. Nanocurcumin Potently Inhibits SARS-CoV-2 Spike Protein-Induced Cytokine Storm by Deactivation of MAPK/NF-κB Signaling in Epithelial Cells. ACS Appl. Biomater. 2022, 5, 483–491.
11. Młynarczyk, K.; Walkowiak-Tomczak, D.; Łysiak, G.P. Bioactive properties of Sambucus nigra L. as a functional ingredient for food and pharmaceutical industry. J. Funct. Foods 2018, 40, 377–390.
12. Marţiş, G.S.; Mureşan, V.; Marc, R.M.; Mureşan, C.C.; Pop, C.R.; Buzgău, G.; Mureşan, A.E.; Ungur, R.A.; Muste, S. The Physicochemical and Antioxidant Properties of Sambucus nigra L. and Sambucus nigra Haschberg during Growth Phases: From Buds to Ripening. Antioxidants 2021, 10, 1093.
13. Perkins-Veazie, P.; Thomas, A.L.; Byers, P.L.; Finn, C.E. Fruit Composition of Elderberry (Sambucus spp.) Genotypes Grown in Oregon and Missouri, USA. Acta Hortic. 2015, 1061, 219–224.
14. Vulić, J.; Vračar, L.; Šumić, Z. Chemical characterictics of cultivated elderberry fruit. Acta Period. Technol. 2008, 39, 85–90.
15. Wieland, L.S.; Piechotta, V.; Feinberg, T.; Ludeman, E.; Hutton, B.; Kanji, S.; Seely, D.; Garritty, C. Elderberry for prevention and treatment of viral respiratory illnesses: A systematic review. BMC Complement. Med. Ther. 2021, 21, 112.
16. Tiralongo, E.; Wee, S.S.; Lea, R.A. Elderberry Supplementation Reduces Cold Duration and Symptoms in Air-Travellers: A Randomized, Double-Blind Placebo-Controlled Clinical Trial. Nutrients 2016, 8, 182.
17. Sidor, A.; Gramza-Michalowska, A. Advanced research on the antioxidant and health benefit of elderberry (Sambucus nigra) in food—A review. J. Funct. Foods 2015, 18, 941–958.
18. Hawkins, J.; Baker, C.; Cherry, L.; Dunne, E. Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. Complement. Ther. Med. 2019, 42, 361–365.
19. Fink, R.C.; Roschek, B., Jr.; Alberte, R.S. HIV type-1 entry inhibitors with a new mode of action. Antivir. Chem. Chemother. 2009, 19, 243–255.
20. Putra, W.E.; Rifa'i, M. Immunomodulatory Activities of Sambucus javanica Extracts in DMBA-Exposed BALB/c Mouse. Adv. Pharm. Bull. 2019, 9, 619–623.
21. Ulbricht, C.; Basch, E.; Cheung, L.; Goldberg, H.; Hammerness, P.; Isaac, R.; Khalsa, K.P.; Romm, A.; Rychlik, I.; Varghese, M.; et al. An evidence-based systematic review of elderberry and elderflower (Sambucus nigra) by the Natural Standard Research Collaboration. J. Diet. Suppl. 2014, 11, 80–120.
22. Avan, A.; Postma, T.J.; Ceresa, C.; Avan, A.; Cavaletti, G.; Giovannetti, E.; Peters, G.J. Platinum-induced neurotoxicity and preventive strategies: Past, present, and future. Oncologist 2015, 20, 411–432.
23. Mitchell, J.B.; Russo, A. The role of glutathione in radiation and drug induced cytotoxicity. Br. J. Cancer 1987, 8, 96–104.
24. Grey, V.; Mohammed, S.R.; Smountas, A.A.; Bahlool, R.; Lands, L.C. Improved glutathione status in young adult patients with cystic fibrosis supplemented with whey protein. J. Cyst. Fibros. 2003, 2, 195–198.
25. Narayanankutty, A.; Job, J.T.; Narayanankutty, V. Glutathione, an Antioxidant Tripeptide: Dual Roles in Carcinogenesis and Chemoprevention. Curr. Protein Pept. Sci. 2019, 20, 907–917.
26. Lushchak, V.I. Glutathione homeostasis and functions: Potential targets for medical interventions. J. Amino Acids 2012, 2012, 736837.
27. Burgess, J.R.; Yang, H.; Chang, M.; Rao, M.K.; Tu, C.P.; Reddy, C.C. Enzymatic transformation of PGH2 to PGF2 alpha catalyzed by glutathione S-transferases. Biochem. Biophys. Res. Commun. 1987, 142, 441–447.
28. Linani, A.; Benarous, K.; Bou-Salah, L.; Yousfi, M.; Goumri-Said, S. Exploring Structural Mechanism of COVID-19 Treatment with Glutathione as a Potential Peptide Inhibitor to the Main Protease: Molecular Dynamics Simulation and MM/PBSA Free Energy Calculations Study. Int. J. Pept. Res. Ther. 2022, 28, 55.

29. Lana, J.F.S.D.; Lana, A.V.S.D.; Rodrigues, Q.S.; Santos, G.S.; Navani, R.; Navani, A.; da Fonseca, L.F.; Azzini, G.O.M.; Setti, T.; Mosaner, T.; et al. Nebulization of glutathione and N-Acetylcysteine as an adjuvant therapy for COVID-19 onset. Adv. Redox Res. 2021, 3, 100015.

30. Ghezzi, P. Role of glutathione in immunity and inflammation in the lung. Int. J. Gen. Med. 2011, 4, 105–113.

31. Polonikov, A. Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients. ACS Infect. Dis. 2020, 6, 1558–1562.

32. Silvagno, F.; Vernone, A.; Pescarmona, G.P. The Role of Glutathione in Protecting against the Severe Inflammatory Response Triggered by COVID-19. Antioxidants 2020, 9, 624.

33. Anusiya, G.; Gowthama Prabu, U.; Yamini, N.V.; Sivarajasekar, N.; Rambabu, K.; Bharath, G.; Banat, F. A review of the therapeutic and biological effects of edible and wild mushrooms. Bioengineered 2021, 12, 11239–11268.

34. Valverde, M.E.; Hernández-Pérez, T.; Paredes-López, O. Edible mushrooms: Improving human health and promoting quality life. Int. J. Microbiol. 2015, 2015, 376387.

35. Wang, L.; Li, J.Q.; Zhang, J.; Li, Z.M.; Liu, H.G.; Wang, Y.Z. Traditional uses, chemical components and pharmacological activities of the genus Ganoderma, P. Karst.: A review. RSC Adv. 2020, 10, 42084–42097.

36. Sande, D.; Oliveira, G.P.; Moura, M.A.F.E.; Martins, B.A.; Lima, M.T.N.S.; Takahashi, J.A. Edible mushrooms as a ubiquitous source of essential fatty acids. Food Res. Int. 2019, 125, 108524.

37. Muszyńska, B.; Grzywacz-Kisielewska, A.; Kała, K.; Gdula-Argasińska, J. Anti-inflammatory properties of edible mushrooms: A review. Food Chem. 2018, 243, 373–381.

38. Sima, P.; Vannucci, L.; Vetvicka, V. β-glucans and cholesterol (Review). Int. J. Mol. Med. 2018, 41, 1799–1808.

39. Vetvicka, V.; Teplyakova, T.V.; Shintyapina, A.B.; Korolenko, T.A. Effects of Medicinal Fungi-Derived β-Glucan on Tumor Progression. J. Fungi 2021, 7, 250.

40. Ayaz, F.A.; Chuang, L.T.; Torun, H.; Colak, A.; Sesli, E.; Presley, J.; Smith, B.R.; Glew, R.H. Fatty acid and amino acid compositions of selected wild-edible mushrooms consumed in Turkey. Int. J. Food Sci. Nutr. 2011, 62, 328–335.

41. Sharma, D.; Singh, V.P.; Singh, N.K. A Review on Phytochemistry and Pharmacology of Medicinal as well as Poisonous Mushrooms. Mini Rev. Med. Chem. 2018, 18, 1095–1109.

42. Coelho, L.C.B.B.; Silva, P.M.D.S.; Lima, V.L.D.M.; Pontual, E.V.; Paiva, P.M.G.; Napoleao, T.H.; Correia, M.T.D.S. Lectins, Interconnecting Proteins with Biotechnological/Pharmacological and Therapeutic Applications. Evid. Based Complement. Alternat. Med. 2017, 2017, 1594074.

43. Fontes, A.; Alemany-Pagès, M.; Oliveira, P.J.; Ramalho-Santos, J.; Zischka, H.; Azul, A.M. Antioxidant Versus Pro-Apoptotic Effects of Mushroom-Enriched Diets on Mitochondria in Liver Disease. Int. J. Mol. Sci. 2019, 20, 3987.

44. Wińska, K.; Mączka, W.; Gabryelska, K.; Grabarczyk, M. Mushrooms of the Genus Ganoderma Used to Treat Diabetes and Insulin Resistance. Molecules 2019, 24, 4075.

45. Ganeshpurkar, A.; Rai, G.; Jain, A.P. Medicinal mushrooms: Towards a new horizon. Pharmacogn. Rev. 2010, 4, 127–135.

46. Chaturvedi, V.K.; Agarwal, S.; Gupta, K.K.; Ramteke, P.W.; Singh, M.P. Medicinal mushroom: Boon for therapeutic applications. Biotech 2018, 8, 334.

47. Hetland, G.; Johnson, E.; Bernardshaw, S.V.; Grinde, B. Can medicinal mushrooms have prophylactic or therapeutic effect against COVID-19 and its pneumonic superinfection and complicating inflammation? Scand. J. Immunol. 2021, 93, e12937.

48. Arunachalam, K.; Sasidharan, S.P.; Yang, X. A concise review of mushrooms antiviral and immunomodulatory properties that may combat against COVID-19. Food Chem. Adv. 2022, 1, 100023.

49. Slomski, A. Trials Test Mushrooms and Herbs as Anti-COVID-19 Agents. JAMA 2021, 326, 1997–1999.

50. Donoso, A.; González-Durán, J.; Muñoz, A.A.; González, P.A.; Agurto-Muñoz, C. Therapeutic uses of natural astaxanthin: An evidence-based review focused on human clinical trials. Pharmacol. Res. 2021, 166, 105479.

51. Higuera-Ciapara, I.; Félix-Valenzuela, L.; Goycoolea, F.M. Astaxanthin: A review of its chemistry and applications. Crit. Rev. Food Sci. Nutr. 2006, 46, 185–196.

52. Brotosudarmo, T.H.P.; Limantara, L.; Setiyono, E.; Heriyanto. Structures of Astaxanthin and Their Consequences for Therapeutic Application. Int. J. Food Sci. 2020, 2020, 2156582.

53. Ambati, R.R.; Phang, S.M.; Ravi, S.; Aswathanarayana, R.G. Astaxanthin: Sources, extraction, stability, biological activities and its commercial applications—A review. Mar. Drugs 2014, 12, 128–152.

54. Fakhri, S.; Abbaszadeh, F.; Dargahi, L.; Jorjani, M. Astaxanthin: A mechanistic review on its biological activities and health benefits. Pharmacol. Res. 2018, 136, 1–20.

55. Kang, H.; Kim, H. Astaxanthin and β-carotene in Helicobacter pylori-induced Gastric Inflammation: A Mini-review on Action Mechanisms. J. Cancer Prev. 2017, 22, 57–61.

56. Talukdar, J.; Bhadra, B.; Dattaroy, T.; Nagle, V.; Dasgupta, S. Potential of natural astaxanthin in alleviating the risk of cytokine storm in COVID-19. Biomed. Pharmacother. 2020, 132, 110886.

57. Ahmadi, A.R.; Ayazi-Nasrabadi, R. Astaxanthin protective barrier and its ability to improve the health in patients with COVID-19. Iran. J. Microbiol. 2021, 13, 434–441.

58. Sivarajan, R.; Oberwinkler, H.; Roll, V.; König, E.M.; Steinke, M.; Bodem, J. A defined anthocyanin mixture sourced from bilberry and black currant inhibits Measles virus and various herpesviruses. BMC Complement. Med. Ther. 2022, 22, 181.

59. Akbar, S. Andrographis paniculata: A review of pharmacological activities and clinical effects. Altern. Med. Rev. 2011, 16, 66–77.

60. Dai, Y.; Chen, S.R.; Chai, L.; Zhao, J.; Wang, Y.; Wang, Y. Overview of pharmacological activities of Andrographis paniculata and its major compound andrographolide. Crit. Rev. Food Sci. Nutr. 2019, 59 (Suppl. 1), S17–S29.

61. Naomi, R.; Bahari, H.; Ong, Z.Y.; Keong, Y.Y.; Embong, H.; Rajandram, R.; Teoh, S.H.; Othman, F.; Hasham, R.; Yin, K.B.; et al. Mechanisms of Natural Extracts of Andrographis paniculata That Target Lipid-Dependent Cancer Pathways: A View from the Signaling Pathway. Int. J. Mol. Sci. 2022, 23, 5972.

62. Lu, J.; Ma, Y.; Wu, J.; Huang, H.; Wang, X.; Chen, Z.; Chen, J.; He, H.; Huang, C. A review for the neuroprotective effects of andrographolide in the central nervous system. Biomed. Pharmacother. 2019, 117, 109078.

63. Islam, M.T. Andrographolide, a New Hope in the Prevention and Treatment of Metabolic Syndrome. Front. Pharmacol. 2017, 8, 571.

64. Stopponi, S.; Fotio, Y.; Cifani, C.; Li, H.; Haass-Koffler, C.L.; Cannella, N.; Demopulos, G.; Gaitanaris, G.; Ciccocioppo, R. Andrographis paniculata and Its Main Bioactive Ingredient Andrographolide Decrease Alcohol Drinking and Seeking in Rats Through Activation of Nuclear PPARγ Pathway. Alcohol Alcohol. 2021, 56, 240–249.

65. Sa-ngiamsuntorn, K.; Suksatu, A.; Pewkliang, Y.; Thongsri, P.; Kanjanasirirat, P.; Manopwisedjaroen, S.; Charoensutthivarakul, S.; Wongtrakoongate, P.; Pitiporn, S.; Chaopreecha, J.; et al. Anti-SARS-CoV-2 Activity of Andrographis paniculata Extract and Its Major Component Andrographolide in Human Lung Epithelial Cells and Cytotoxicity Evaluation in Major Organ Cell Representatives. J. Nat. Prod. 2021, 84, 1261–1270.

66. Intharuksa, A.; Arunotayanun, W.; Yooin, W.; Sirisa-Ard, P. A Comprehensive Review of Andrographis paniculata (Burm. f.) Nees and Its Constituents as Potential Lead Compounds for COVID-19 Drug Discovery. Molecules 2022, 27, 4479.

67. Kuropatnicki, A.K.; Szliszka, E.; Krol, W. Historical aspects of propolis research in modern times. Evid. Based Complement. Alternat. Med. 2013, 2013, 964149.

68. da Silva Barboza, A.; Aitken-Saavedra, J.P.; Ferreira, M.L.; Fábio Aranha, A.M.; Lund, R.G. Are propolis extracts potential pharmacological agents in human oral health?—A scoping review and technology prospecting. J. Ethnopharmacol. 2021, 271, 113846.

69. Almuhayawi, M.S. Propolis as a novel antibacterial agent. Saudi J. Biol. Sci. 2020, 27, 3079–3086.

70. Berretta, A.A.; Silveira, M.; Cóndor Capcha, J.M.; De Jong, D. Propolis and its potential against SARS-CoV-2 infection mechanisms and COVID-19 disease: Running title: Propolis against SARS-CoV-2 infection and COVID-19. Biomed. Pharmacother. 2020, 131, 110622.

71. Maruta, H.; He, H. PAK1-blockers: Potential Therapeutics against COVID-19. Med. Drug Discov. 2020, 6, 100039.

72. Williams, N.T. Probiotics. Am. J. Health Syst. Pharm. 2010, 67, 449–458.

73. Shi, L.H.; Balakrishnan, K.; Thiagarajah, K.; Mohd Ismail, N.I.; Yin, O.S. Beneficial Properties of Probiotics. Trop. Life Sci. Res. 2016, 27, 73–90.

74. Plaza-Diaz, J.; Ruiz-Ojeda, F.J.; Gil-Campos, M.; Gil, A. Mechanisms of Action of Probiotics. Adv. Nutr. 2020, 11 (Suppl. 1), S49–S66, published correction appears in Adv. Nutr. 2020, 11, 1054.

75. Antunes, A.E.C.; Vinderola, G.; Xavier-Santos, D.; Sivieri, K. Potential contribution of beneficial microbes to face the COVID-19 pandemic. Food Res. Int. 2020, 136, 109577.

76. Bottari, B.; Castellone, V.; Neviani, E. Probiotics and COVID-19. Int. J. Food Sci. Nutr. 2021, 72, 293–299.

77. Gutiérrez-Castrellón, P.; Gandara-Martí, T.; Abreu, Y.; Abreu, A.T.; Nieto-Rufino, C.D.; López-Orduña, E.; Jiménez-Escobar, I.; Jiménez-Gutiérrez, C.; López-Velazquez, G.; Espadaler-Mazo, J. Probiotic improves symptomatic and viral

clearance in Covid19 outpatients: A randomized, quadruple-blinded, placebo-controlled trial. Gut Microbes 2022, 14, 2018899.

78. Tenório, M.C.D.S.; Graciliano, N.G.; Moura, F.A.; Oliveira, A.C.M.; Goulart, M.O.F. N-Acetylcysteine (NAC): Impacts on Human Health. Antioxidants 2021, 10, 967.
79. Papi, A.; Di Stefano, A.F.D.; Radicioni, M. Pharmacokinetics and Safety of Single and Multiple Doses of Oral N-Acetylcysteine in Healthy Chinese and Caucasian Volunteers: An Open-Label, Phase I Clinical Study. Adv. Ther. 2021, 38, 468–478.
80. Lu, S.C. Glutathione synthesis. Biochim. Biophys. Acta 2013, 1830, 3143–3153.
81. Dodd, S.; Dean, O.; Copolov, D.L.; Malhi, G.S.; Berk, M. N-acetylcysteine for antioxidant therapy: Pharmacology and clinical utility. Expert Opin. Biol. Ther. 2008, 8, 1955–1962.
82. Mokhtari, V.; Afsharian, P.; Shahhoseini, M.; Kalantar, S.M.; Moini, A. A Review on Various Uses of N-Acetyl Cysteine. Cell J. 2017, 19, 11–17.
83. Schwalfenberg, G.K. N-Acetylcysteine: A Review of Clinical Usefulness (an Old Drug with New Tricks). J. Nutr. Metab. 2021, 2021, 9949453.
84. Wong, K.K.; Lee, S.; Kua, K.P. N-Acetylcysteine as Adjuvant Therapy for COVID-19—A Perspective on the Current State of the Evidence. J. Inflamm. Res. 2021, 14, 2993–3013.
85. Mohanty, R.R.; Padhy, B.M.; Das, S.; Meher, B.R. Therapeutic potential of N-acetyl cysteine (NAC) in preventing cytokine storm in COVID-19: Review of current evidence. Eur. Rev. Med. Pharmacol. Sci. 2021, 25, 2802–2807.
86. Izquierdo, J.L.; Soriano, J.B.; González, Y.; Lumbreras, S.; Ancochea, J.; Echeverry, C.; Rodríguez, J.M. Use of N-Acetylcysteine at high doses as an oral treatment for patients hospitalized with COVID-19. Sci. Prog. 2022, 105, 368504221074574.
87. Sanchez-Gonzalez, M.A.; Moskowitz, D.; Issuree, P.D.; Yatzkan, G.; Rizvi, S.A.A.; Day, K. A Pathophysiological Perspective on COVID-19's Lethal Complication: From Viremia to Hypersensitivity Pneumonitis-like Immune Dysregulation. Infect. Chemother. 2020, 52, 335–344.
88. Yang, D.; Wang, T.; Long, M.; Li, P. Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine. Oxid. Med. Cell Longev. 2020, 2020, 8825387.
89. Batiha, G.E.; Beshbishy, A.M.; Ikram, M.; Mulla, Z.S.; El-Hack, M.E.A.; Taha, A.E.; Algammal, A.M.; Elewa, Y.H.A. The Pharmacological Activity, Biochemical Properties, and Pharmacokinetics of the Major Natural Polyphenolic Flavonoid: Quercetin. Foods 2020, 9, 374.
90. Muñoz-Reyes, D.; Morales, A.I.; Prieto, M. Transit and Metabolic Pathways of Quercetin in Tubular Cells: Involvement of Its Antioxidant Properties in the Kidney. Antioxidants 2021, 10, 909.
91. Di Petrillo, A.; Orrù, G.; Fais, A.; Fantini, M.C. Quercetin and its derivates as antiviral potentials: A comprehensive review. Phytother. Res. 2022, 36, 266–278.
92. Manjunath, S.H.; Thimmulappa, R.K. Antiviral, immunomodulatory, and anticoagulant effects of quercetin and its derivatives: Potential role in prevention and management of COVID-19. J. Pharm. Anal. 2022, 12, 29–34.
93. Imran, M.; Thabet, H.K.; Alaqel, S.I.; Alzahrani, A.R.; Abida, A.; Alshammari, M.K.; Kamal, M.; Diwan, A.; Asdaq, S.M.B.; Alshehri, S. The Therapeutic and Prophylactic Potential of Quercetin against COVID-19: An Outlook on the Clinical Studies, Inventive Compositions, and Patent Literature. Antioxidants 2022, 11, 876.
94. Munafò, F.; Donati, E.; Brindani, N.; Ottonello, G.; Armirotti, A.; De Vivo, M. Quercetin and luteolin are single-digit micromolar inhibitors of the SARS-CoV-2 RNA-dependent RNA polymerase. Sci. Rep. 2022, 12, 10571.
95. Aucoin, M.; Cooley, K.; Saunders, P.R.; Cardozo, V.; Remy, D.; Cramer, H.; Abad, C.N.; Hannan, N. The effect of quercetin on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review. Adv. Integr. Med. 2020, 7, 247–251.
96. Bahoosh, S.R.; Shokoohinia, Y.; Eftekhari, M. Glucosinolates and their hydrolysis products as potential nutraceuticals to combat cytokine storm in SARS-COV-2. Daru 2022, 30, 245–252.
97. Jia, H.; Zhang, Y.; Si, X.; Jin, Y.; Jiang, D.; Dai, Z.; Wu, Z. Quercetin Alleviates Oxidative Damage by Activating Nuclear Factor Erythroid 2-Related Factor 2 Signaling in Porcine Enterocytes. Nutrients 2021, 13, 375.
98. Yi, L.; Li, Z.; Yuan, K.; Qu, X.; Chen, J.; Wang, G.; Zhang, H.; Luo, H.; Zhu, L.; Jiang, P.; et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J. Virol. 2004, 78, 11334–11339.
99. Catalano, A.; Iacopetta, D.; Ceramella, J.; Maio, A.C.; Basile, G.; Giuzio, F.; Bonomo, M.G.; Aquaro, S.; Walsh, T.J.; Sinicropi, M.S.; et al. Are Nutraceuticals Effective in COVID-19 and Post-COVID Prevention and Treatment? Foods 2022, 11, 2884.

100. Verna, G.; Liso, M.; Cavalcanti, E.; Bianco, G.; Di Sarno, V.; Santino, A.; Campiglia, P.; Chieppa, M. Quercetin Administration Suppresses the Cytokine Storm in Myeloid and Plasmacytoid Dendritic Cells. Int. J. Mol. Sci. 2021, 22, 8349.
101. Alshrari, A.S.; Hudu, S.A.; Imran, M.; Asdaq, S.M.B.; Ali, A.M.; Rabbani, S.I. Innovations and development of COVID-19 vaccines: A patent review. J. Infect. Public Health 2022, 15, 123–131.
102. Mouffouk, C.; Mouffouk, S.; Mouffouk, S.; Hambaba, L.; Haba, H. Flavonols as potential antiviral drugs targeting SARS-CoV-2 proteases (3CLpro and PLpro), spike protein, RNA-dependent RNA polymerase (RdRp) and angiotensin-converting enzyme II receptor (ACE2). Eur. J. Pharmacol. 2021, 891, 173759.
103. Pawar, A.; Russo, M.; Rani, I.; Goswami, K.; Russo, G.L.; Pal, A. A critical evaluation of risk to reward ratio of quercetin supplementation for COVID-19 and associated comorbid conditions. Phytother. Res. 2022, 36, 2394–2415.
104. Khan, A.; Iqtadar, S.; Mumtaz, S.U.; Heinrich, M.; Pascual-Figal, D.A.; Livingstone, S.; Abaidullah, S. Oral Co-Supplementation of Curcumin, Quercetin, and Vitamin D3 as an Adjuvant Therapy for Mild to Moderate Symptoms of COVID-19-Results From a Pilot Open-Label, Randomized Controlled Trial. Front Pharmacol 2022, 13, 898062.