Medicinal Mushrooms and COVID-19

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Many mushroom species are consumed as food, while significant numbers are also utilised medicinally. Mushrooms are rich in nutrients and bioactive compounds. A growing body of in vitro, in vivo, and human research has revealed their therapeutic potentials, which include such properties as anti-pathogenic, antioxidant, anti-inflammatory, immunomodulatory, gut microbiota enhancement, and angiotensin-converting enzyme 2 specificity. The uses of medicinal mushrooms (MMs) as extracts in nutraceuticals and other functional food and health products are burgeoning. COVID-19 presents an opportunity to consider how, and if, specific MM compounds might be utilised therapeutically to mitigate associated risk factors, reduce disease severity, and support recovery. As vaccines become a mainstay, MMs may have the potential as an adjunct therapy to enhance immunity.

COVID-19 β-glucans immunomodulation anti-inflammation anti-oxidant ACE2 regulation

1. Introduction

Mushrooms have long been regarded as healthful and widely consumed for their culinary and nutritional values. Some species have an ancient tradition as medicinal therapies, and increasingly, this is being realised in a contemporary context [1][2]. However, until recently, the scientific understanding of mushrooms' application as a medicinal agent has been chiefly empiric [3]. Interest in advancing the health properties and pharmacological activities means that clinical research is growing, and much of the traditional knowledge is being documented and validated [4]. Indeed, there is an interdisciplinary field of science studying medicinal mushrooms (MMs), with an increasing number of human studies emerging. This, along with industry technological developments, means that some mushrooms are now regarded as a class of drugs called "mushroom pharmaceuticals" [1]. Physiological activities revealed from numerous studies include anti-pathogenic, antioxidant, anti-inflammatory, immunomodulatory, and anticoagulation effects, plus gut microbiota enhancement, pulmonary cytoprotection, and angiotensin-converting enzyme (ACE) 2 specificity [4][5]. These actions are mainly attributable to the bioactive compounds present in the fruiting bodies and the mycelium, depending on the species [2]. For example, Ganoderma lucidum contains more than 120 different triterpenes plus polysaccharides, proteins, and other bioactive compounds [6].

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), presents an opportunity to consider how macro-fungi or their derivatives might be harnessed and utilised as therapeutic agents. In particular, this pertains to their use in optimising health to avoid or mitigate risk factors, prevent severe disease outcomes, and improve recovery prospects as commonly noted or experienced. For example, the immune response is crucial in COVID-19 pathogenesis, and its modulation to control the hyperinflammatory response would be advantageous. Additionally, the virus appears to have a higher prevalence for and more severe outcomes in populations with particular risk factors and comorbidities associated with age, obesity, metabolic, cardiovascular, and inflammation-mediated conditions [7][8]. Many of these factors are known to respond to, and are modifiable through, dietary or lifestyle interventions. Therefore, with their potential and specific therapeutic effects, MMs seem well placed to be considered as nutraceutical options, or at the very least, as health-promoting food sources. Moreover, as vaccines become the mainstay for preventing severe outcomes, finding effective immune-enhancing adjuncts will be beneficial.

MMs are increasingly being utilised as a nutritional food source in the “food as medicine” health-promoting dietary approach [9]. They are also used as dietary supplements, biocontrol agents, and cosmetics. Most pertinent is their use as nutraceuticals and natural products for pharmacological therapy, which are valued for their immunological, anti-inflammatory, and health-promoting effects [4]. However, of prime consideration is that mushrooms’ properties, mechanisms of action, and potential efficacies can be influenced by many variables, including climate, location, cultivation, processing, and extraction techniques [4][10]. The nomenclature may also be a problem as it affects accurate identification and, thus, attribution. As more research is achieved, and commercialisation and application continue to increase, these variables must be addressed. However, more work may yet be required. Particular aspects such as extraction methods may be very pertinent in this quest.

2. Mushrooms as Prevention or Treatment for COVID-19

2.1. General Features

Mushrooms are macro-fungi with a distinctive fruiting body, either hypogeous (underground) or epigeous (aboveground). There are estimated to be around 140,000 known species of macro-fungi belonging mainly to the phyla Basidiomycetes and some to Ascomycetes. Many more hundreds of thousands of fungi are assumed yet to be identified and classified [4][6][11]. Some 2000 are edible, and a few hundred wild and cultivated mushrooms have long been utilised as MMs [5][11]. Nutritionally, mushrooms are low in energy and are generally a good source of macro and micronutrients and trace elements, although there is variability [12][13][14][15]. As functional foods, they are also anti-inflammatory and known to modulate gut bacteria [16]. Species-specific structural and maturation elements of fruiting bodies and mycelia, and potentially even the fermented substrate from which the prepared product may have been produced, impact effects. Variances involve the chemistry, bioactive fractions derived from them, and biological activity [2][17][18].

2.2. Structural Elements and Bioactive Compounds

MMs produce bioactive primary and secondary metabolites and specific molecular weight compounds such as polysaccharides, polysaccharide–protein complexes, polyphenols, terpenoids, lectins, coumarins, ribosomal and non-ribosomal peptides, peptidoglycans, alkaloids, fatty acids, sterols, and antioxidants [1][2][5][6][11][19][20][21]. The most studied health-promoting properties and effects of MMs appear to be related to polysaccharides, lectins, protein complexes, sterols, and polyphenols such as terpenoids [2][17]. For example, lectins are non-immunoglobulin binding storage proteins that play a crucial role in such biological processes as cell signalling, cell–cell interactions in the immune system, and host defence mechanisms [11]. Mushroom polysaccharides have a strong ability to carry biological information, and via such function, they have antitumour, antioxidant, immunomodulatory, anti-inflammatory, antimicrobial, anti-obesity, and anti-diabetic effects [22]. To some extent, all of the bioactive compounds mentioned above have a body of knowledge that could be examined in respect of SARS CoV-2 virus protection and COVID-19 symptom reduction, as these compounds demonstrated beneficial effects that may be very helpful. Notably, these effects include inflammation regulation, immune and reactive oxygen species (ROS) modulation, host defence mechanisms involvement, microbial activity, pulmonary cytoprotection, and ACE2 specificity or inhibition [4][17][23].

However, *β*-glucans (D fraction) appear to have wide-ranging effects and benefits that deserves further examination. Additionally, mushroom-derived *β*-glucans are becoming more common in nutraceutical products and are promoted in a functional culinary sense. The limitations that may impact the appropriate application must also be considered. For example, their efficacy is very dependent on species, extraction techniques, and methods.

2.3. *β*-Glucans

Glucans are heterogeneous polysaccharides, with short or long-chain glucose polymers linked by large numbers of glucose sub-units, different branching, branch linkage, and backbone structures. They are a natural component of the cell walls. In addition to mushrooms, glucans are also a constituent of foods such as cereals. Thus, to be clear, the fungi glucans, in particular, *β*-glucans, are discussed and referred to as edible mushroom polysaccharides (EMPs).

The molecular weight, chain length, and side-branching structures of mushroom *β*-glucans can be species and cultivar specific, influencing variance, complexity, and biological activity [5][17][24][25]. The purity and purification processes are essential in characterising the structure [16]. Growing environments, drying conditions, and isolation/extraction methods are also crucial for the intensity of β-glucans' activities [22]. The solubility and particulate size of β-glucans are important physical features as many receptors involved can activate different immune responses [24]. For example, particulate β-glucans are known to directly stimulate immune cell activation through a dectin-1 pathway, while soluble *β*-glucans require complement receptor-3 dependent pathway activation.

The immunomodulatory properties of mushroom-derived *β*-glucans exert more potent immunoinflammatory effects than other types and have long been recognised for this [24][26]. Immunomodulation is characterised by the ability to correct deviated immune functions. This may be through supporting declined or suppressed parameters or normalising overactive or increased functions [27]. Notably, due to their confirmed complex mode of action, *β*-glucans are recognised as biological response modifiers

(BRMs). They induce epigenetic programming in innate immune cells to produce a more robust immune response and act as pathogen-associated molecular patterns, binding to specific pathogen recognition receptors, inducing innate and adaptive immune responses [24][26]. They can also stimulate the activity of macrophages [28] and neutrophils, support NK cell activity, influence the production of cytokines and chemokines, and modulate antibody production, amongst many other functions [27].

Several authors have described the concept of trained immunity [26][29][30] as being a modified and epigenetic innate immune response capable of producing antibody-free memory to a secondary heterologous stimulus that is more robust. However, Geller and Yan [30] cautioned that due to the development of hyperinflammatory symptoms, such as those that may occur in COVID-19, the use of a therapy that could induce trained immunity effects warrants particular consideration. Notwithstanding, due to their immune enhancement benefits, studies examined the use of biomacromolecule compounds, including polymers such as β-glucans and chitosan as vaccine adjuvants [31][32][33]. Moreover, the potential of using β-glucans as a wide-spectrum immune-balancing food-supplement-based enteric vaccine adjuvant for COVID-19 was explored by Ikewaki et al. [26].

3. Systemic Pro-Health Responses and Activities Associated with Specific MMs

The following synopsis examines the various pro-health effects and activities of specific macro-fungi elucidated in research that may have applications to the pathological sequelae and outcomes associated with COVID-19. The effects and potential benefits of MMs are illustrated in **Figure 1**.

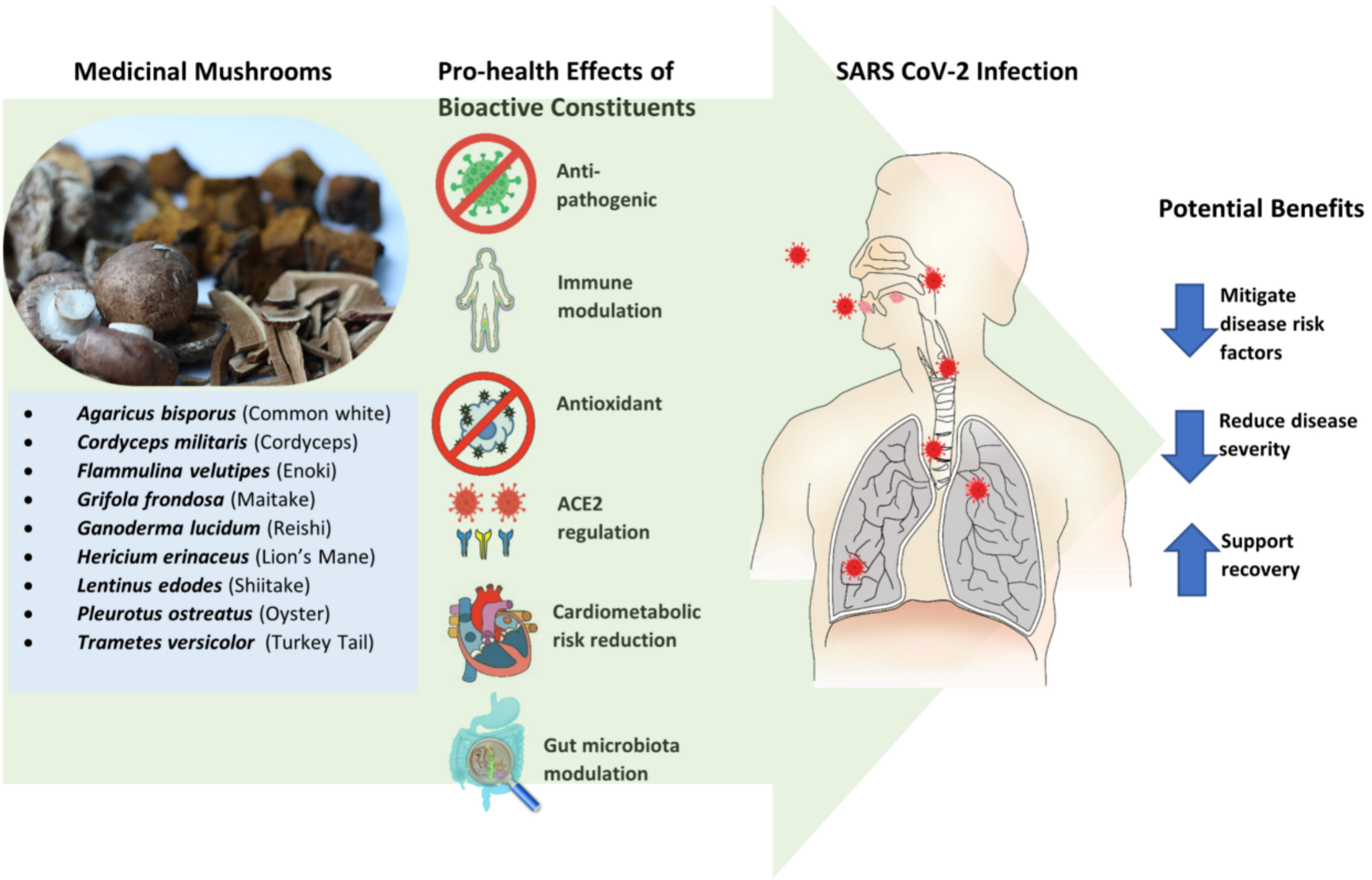

Figure 1. Medicinal mushrooms demonstrated modulatory and regulatory effects via the actions of bioactive compounds. These effects may apply in the pathophysiology and sequelae of SARS CoV-2 infection in humans. Potential benefits to consider and investigate specifically in this context involve mitigating disease risk factors, reducing disease severity, and supporting recovery.

3.1. Anti-Pathogenic

The basic viral cycle, also associated with SARS CoV-2, involves attachment, penetration, uncoating, replication, assembly, and release [34]. Mushroom extracts and bioactive compounds impede viral entry into host cells and multiplication, inhibit virus adsorption, replication, nucleic acid synthesis, and disrupt other pathogens [3][6][29]. It is known that proteolytic enzymes facilitate the cleavage of S glycoprotein, which is a critical step in SARS CoV-2 viral attachment [35]. Since protease inhibitors have been isolated from *G. lucidum*, *C. militaris*, and *A. bisporus* [29], MMs may have therapeutic utility.

Cordycepin isolated from C. militaris exerted an antiviral effect through a protein kinase inhibitory mechanism and an inhibitory role towards ribonucleic acid (RNA) synthesis and Epstein–Barr virus (EBV) replication [36]. Ganoderma compounds isolated from G. lucidum effectively inhibited human immunodeficiency virus (HIV)-1 and HIV-1 protease [37]. Additionally, various triterpenoids (isolated from G. lucidum and other Ganoderma species) were active against HIV-1, influenza type A, and herpes simplex type 1 [6]. In vitro and in vivo studies on a range of common viral agents from Agaricus spp. including Agaricus blazei Murril (AbM), H. erinaceus, and G. frondosa demonstrated antiviral properties [3].

MMs are also purported to have anti-bacterial functions [1]. To confirm this potential, Hearst et al. [38] conducted an in vitro microbiological assessment using aqueous extracts of L. edodes and P. ostreatus. The aqueous extract of L. edodes demonstrated potent activity when tested in culture against 29 bacterial isolates (Gram-positive and Gram-negative) and 10 fungal/yeast agents. Here, 85% of the bacterial and 50% of the fungal organisms were inhibited by the L. edodes extract. The results compared favourably against Ciproflaxin, which is a broad-spectrum antibiotic that was deployed as the control. In contrast, P. ostreatus aqueous extract showed minimal activity on the same range of pathogens, with only three out of 39 samples inhibited, while none of the yeast and mould species was affected. Additionally, a purified source of lentinan, a specific class of *β*-glucan, reduced populations of multiple antibiotic-resistant clinical isolate Klebsiella pneumoniae in an in vivo lung infection model and showed potential for treating sepsis-induced lung injury and boosting type 1 interferon response to RNA viruses such as influenza and coronavirus [17].

3.2. Immune Modulation

A response elicited from L. edodes named “the lentinan antiviral effect” has been attributed to innate immune responses and specific immunity regulation. Acting as a BRM, lentinan can promote T helper cell (Th) type 1 response and improve Th1/Th2 balance. It may also activate inflammasomes, enhance immune cells, activate the complement system, and promote cytotoxicity and phagocytosis [2][39]. An in-house hot water extract of L. edodes was compared to a commercially sourced lentinan extract (Carbosynth–Lentinan (CL)) to investigate if isolates could alleviate the immune cascade in conditions experienced by COVID-19 patients, such as ARDS. *β*-glucans from L. edodes reduced IL-1β and IL-6 in lung injury and activated macrophages in vitro [17]. *β*-glucans were also used to investigate oxidative stress alleviation in H2O2-treated THP-1 cells. Viability, apoptosis and necrosis were assessed. CL extract attenuated oxidative stress-induced early apoptosis, and the in-house lentinan extract attenuated late apoptosis [17].

Lectin derived from P. ostreatus has been studied as a hepatitis B virus DNA vaccine adjuvant and demonstrated effectiveness in enhancing surface protein antibodies [40]. Studies utilising pleuran (insoluble *β*-glucans derived from P. ostreatus) administered in oral liquid syrup form have suggested numerous positive immunomodulatory effects in recurrent upper and lower respiratory tract infection (RRTI). Demonstrated effects of pleuran, particularly in studies with children, include reduced incidences of RRTI, otitis media, tonsillopharyngitis, bronchitis, laryngitis, and other flu and cold-like symptoms, plus fewer days off school [41][42][43].

AbM extract is another rich source of BRMs. Via the actions of, for example, proteoglycans, *β*-glucans, and ergosterol, anti-inflammatory, anti-pathogenic, and immunomodulatory cytokine effects were stimulated, vaccine efficacy was improved, and cytotoxic effects were induced [44][45][46][47]. Andosan™, a product primarily manufactured from AbM extract, combined with *H. erinaceus* and *G. frondosa*, has been investigated in clinical studies [3]. Independently, these three mushrooms have demonstrated efficacy for their immunomodulatory, anti-infective, antitumour, and anti-inflammatory effects with reduced pro-inflammatory cytokines and oxidative stress, and beneficial gut microbiota responses [47]. *H. erinaceus* contains aromatic compounds such as hericerins and erinacines that appear to function as a nerve growth factor as well as the beneficial immunomodulating and antitumour properties derived from the glycoproteins and polysaccharides [47]. Further highlighting this, polysaccharides extracted from liquid-cultured mycelia and fruiting bodies of G. frondosa demonstrated antioxidant, antitumour, anti-inflammatory, hepatoprotection, and immunostimulatory activity [48]. Grifolan, a β-glucan isolated from G. frondosa, showed enhanced cellular immunity and modulation activities evidenced by increasing IL-2 and IL-10 production and augmentation of IL-6, IL-1, and TNF-*α* expression [49].

Water extract of four different MMs, including G. lucidum, caused NK cell-induced cytotoxicity against cancer cells, but an ethanol extract did the opposite by reducing intracellular pathway activation [50]. Various triterpene acids and sterols isolated from G. lucidum fruiting bodies revealed antitumour and anti-inflammatory effects as demonstrated via induction of EBV early antigen by 12-O-tetradecanoylphorbol-13-acetate [51].

T. versicolor has a long traditional history of use to promote health, strength, and longevity. More recently, numerous studies, including clinical trials, suggest properties and effects that include antimicrobial, antiviral, antitumour, anti-inflammatory, antioxidant, hepatoprotective, bone protective, and notably immunopotentiation [52][53]. Two bioactive mycelia extracts of protein bound polysaccharides from *T. versicolor*, namely polysaccharopeptide (PSP) and polysaccharide krestin (PSK), are currently utilised medicinally in some countries as integrated cancer therapy and adjuncts for chemotherapy and radiotherapy [2][52][54]. From a range of randomised and non-randomised controlled trials, both PSK and PSP promoted positive impacts on anticancer effects [55]. Deemed resulting from the immunomodulation and potentiation of immune surveillance, PSK and PSP positively affect immune parameters, haematological function, performance status, quality of life, body weight, fatigue, pain, nausea, anorexia, and median survival [54][55][56]. Additionally, antitumour and antimetastatic effects were noted through direct tumour-inhibiting experiments in vivo [55]. Of interest in the context of COVID-19 application is the mechanisms of *T. versicolor*. This appears to be through the inducement of predominantly pro-inflammatory cytokines: not only those associated with TNF-*α* and NK cells but also pleiotropic cytokines such as IL-1α and 1β and IL-6, plus prostaglandin E2, histamine, activation of complement-3, and T cell proliferation [52][54][56]. While this may be desired to improve cancer outcomes, such as enhancing the immunosuppressive status, a cautionary approach in applying *T. versicolor* due to the hyperinflammatory response associated with COVID-19 progression should be taken. However, perhaps, there may be a place for consideration in the context of long COVID or playing a role as a vaccine adjuvant.

3.3. Antioxidant

The antioxidant/ROS system plays a significant role in pathogenic protection, regulation, and homeostasis in the human body. For example, the increased activity of ROS is a key feature in the pathogenesis and progression of many disease states such as atherosclerosis, arterial thrombosis, hyperlipidaemia, hypertension, cancer, obesity, insulin resistance, diabetes mellitus, hepatic and renal conditions, amongst many others [57]. These disease states are representative comorbidities associated with SARS CoV-2 and COVID-19 sequalae and experience. The antioxidant capacity of MMs has been demonstrated in various studies through radical scavenging, lipid peroxidation inhibition, and increasing antioxidant enzyme activities [23][49][58][59]. Bioactive compounds such as phenolics, indoles, flavonoids, glycosides, polysaccharides, tocopherols, glutathione and ergothioneine, ascorbic acid, carotenoids, vitamin D, copper, manganese, zinc, and selenium in MMs all participate in reducing oxidative stress [57][60]. Ergothioneine deserves special mention, as it has a vast array of unique cytoprotective properties pertinent to COVID-19 pathologies, including scavenging reactive oxygen and nitrogen species. It is able to modulate inflammation, inhibit the expression of vascular adhesion proteins, and protect against respiratory burst, amongst many other antioxidant activities [58]. Notable amounts of bioavailable ergothioneine were demonstrated in the fruiting bodies of *A. bisporus* [61], *L. edodes*, *P. ostreatus*, and mycelia of *C. militaris* (strain cm5), *H. erinaceus*, and *P. eryngii* [62][63].

Liquid–liquid partitioned fractions of *H. erinaceus* were evaluated for their anti-atherosclerotic potential through evaluation of in vitro inhibitory effect on low-density lipoprotein (LDL) oxidation and 3-hydroxy-2methylglutaryl coenzyme A (HMG-CoA) reductase activity [64]. Several bioactive compounds with antioxidant activity were isolated, in particular ergosterol. Hexane solvent fraction demonstrated the most potent inhibiting oxidisation of LDL and HMG-CoA reductase activity. This indicates a possible role in preventing oxidative stress-mediated vascular disease processes [64].

Radical scavenging properties associated with catalase activity, glutathione reductase, and glutathione peroxidase activities were demonstrated in varying degrees from methanol and water extracts isolated from the gills, stipe, and caps of two wild strains and one cultivated strain of *A. bisporus* [65]. Fourteen selected culinary MMs were evaluated for in vitro antioxidant and ACE inhibitory activities [23]. The mushrooms were extracted by boiling water for 30 min. The total phenolic content was determined with G. lucidum demonstrating the highest phenolic content and the most potent ACE inhibitor. Antioxidant capacity was carried out via measuring the free radical scavenging effect, *β*-carotene, lipid peroxidation, reducing power ability, cupric-ion-reducing antioxidant capacity, and ACE inhibition. An antioxidant index was determined based on the average percentage relative to quercetin. G. lucidum and *H. erinaceus* were shown to be relatively high compared to the other mushrooms [23].

3.4. ACE2 Regulation

The deleterious effects of COVID-19, such as those associated with cardiometabolic and other hallmark disorders, demonstrate dysregulation of the homeostatic function within the RAAS [7][66][67][68]. RAAS maintains dynamic control of vascular function. ACE2 is an integral membrane protein present in the lungs, liver, heart, kidney, and endothelium. ACE2 dysregulation appears to strongly impact the RAAS, manifesting effects involving hyperinflammation and oxidative stress. MMs have been investigated for ACE inhibitory, antiplatelet, anti-inflammatory, and antioxidant activity [23][69][70].

In MMs, bioactive compounds such as triterpenes, sterols, phenolic compounds, and polysaccharide fractions possess metabolic-modulating capabilities [49]. These include blood pressure, glycaemia, cholesterol, triglyceride, and weight-lowering activities. The ACE inhibitory activity of several mushroom species was assessed via hot water and alcohol extracts [23]. G. lucidum, particularly as a hot water extract, and Pleurotus spp. demonstrated potent ACE inhibitory activity, which is assumed to be due to the phenolic content and antioxidant capacity. However, variations existed between species and depended on the extraction method [23]. In vitro digestion of P. ostreatus identified several peptides known to be ACE inhibitors [71]. A randomised, double-blind prevention trial is underway in the Democratic Republic of the Congo involving Tomeka®, a herbal mixture containing *A. bisporus* and other food-based nutrients such as soy, which is regarded for its potent ACE2 inhibition. The study aims to assess the intervention effect on COVID-19 markers of the RAAS, such as angiotensin-II and angiotensin-(1-7) [67]. Nutritional elements may support ACE inhibition indirectly by intercepting viral entry or via regulation and improvements in biomarkers associated with the involvement of the various systems [67]. For example, excessive sodium ions can impair the endothelial vasculature and risk hypertension, but manifestations may be ameliorated with higher potassium ion levels. Hence, mushrooms, which generally contain high potassium and low sodium may be a good nutritional source for ACE inhibition as well [1][15].

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