Review

Health promoting properties and functions of medicinal and culinary mushrooms for the COVID-19 era. An appraisal: does the “anti” mantra stack up?

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Abstract

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. Some of the most notable benefits include such properties as anti-pathogenic, antioxidant, anti-inflammatory, immunomodulatory, gut microbiota enhancement, and angiotensin-converting enzyme 2 specificity. The use of medicinal mushrooms (MMs) as extracts in nutraceuticals and other 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. In the context of COVID-19, this review explores current research about MMs to identify the key properties claimed to confer health benefits. Considered also are barriers or limitations that may impact general recommendations on MMs as therapy. It is contended that the extraction method used to isolate bioactive compounds must be a primary consideration for efficacious targeting of physiological endpoints. Mushrooms commonly

available for culinary use and obtainable as a dietary supplement for medicinal purposes are included in this review. Specific properties related to these mushrooms have been considered due to their potential mediating effects on human exposure to the SARS CoV-2 virus and the ensuing COVID-19 disease processes.

Keywords: COVID-19, β -glucans, immunomodulation, anti-inflammation, antioxidant, ACE2 regulation.

Abbreviations: AbM, *Agaricus bisporus* Murril; ACE, angiotensin-converting enzyme; AGEs, advanced glycation end products; ARDS, acute respiratory distress syndrome; BP, blood pressure; BRMs, biological response modifiers; CD69, calcium dependent membrane bound type11 C-lectin receptor; COVID-19, corona virus disease 2019; CVD, cardiovascular disease; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; EMPs, edible mushroom polysaccharides; FS, fermented substrate; GLP, *G. lucidum* polysaccharide; GLUT4, glucose transporter type 4; GSK, glycogen synthase kinase; HbA1c, glycosylated haemoglobin A1c; HDL, high density lipoprotein; HIV, human immunodeficiency virus; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; IL, interleukin; LDL, low-density lipoprotein; MMs, medicinal mushrooms; NK, natural killer; NO, nitric oxide; PE, pressure-assisted extractions; PPR, pattern recognition receptor; PSK, polysaccharide Krestin; PSP, polysaccharopeptides; RAAS, renin-angiotensin-aldosterone-system; RNA, ribonucleic acid; ROS, reactive oxygen species; RRTI, recurrent respiratory tract infection; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus-2; SCFAs, short chain fatty acids; STZ, streptozotocin; T2DM, Type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; Th, helper T cell; TNF, tumour necrosis factor; TvM, *Trametes versicolor* mycelium.

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]. *Ganoderma lucidum*, for example, 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 plants or their derivatives might be harnessed and utilised as therapeutic agents. In particular, this pertains to their use in mitigating risk factors, preventing severe disease outcomes and improving recovery prospects. 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 plant-based food revolution, as dietary supplements, biocontrol agents, and cosmetics. Most pertinent is their use as nutraceuticals and pharmacological therapy, 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 [4,9]. The nomenclature may also be a problem as it affects accurate identification and, thus, attribution. As more research is achieved, commercialisation and application continue to increase, these variables must be addressed. Contended, however, is that more work may yet be required. Particular aspects such as extraction methods may be very pertinent in this quest.

In the broader context of COVID-19, this narrative review investigates the use of mushrooms as medicine, exploring the bioactive compounds they contain and the associated "anti" claims. Specific properties have been considered due to their potential mediating effects on human exposure to the SARS CoV-2 virus or the ensuing COVID-19 disease processes. Mechanisms of action, physiological effects, and potential capabilities such as antiviral, antioxidant, immunomodulatory, cardiovascular regulation, and health-promoting factors will be highlighted.

The research question has two parts; 1) does the research support the potential of MMs to ameliorate symptoms associated with COVID-19, and 2) what limitations currently impact utilising mushrooms as a reliable medicinal treatment. Research findings associated with specific mushrooms such as *Agaricus* spp. (e.g., *bisporus*, [common white button/brown]), *Cordyceps militaris*, *Flammulina velutipes/enokitake*

(Enoki), *G. lucidum* (Reishi), *G. frondosa* (Maitake), *Hericium erinaceus* (Lion's Mane), *Lentinus edodes* (Shiitake), *Pleurotus* spp. (e.g., [*ostreatus*, Oyster]), and *Trametes versicolor* (Turkey Tail) are considered.

2 Research methods

Major databases were initially searched via Primo search tool of Charles Sturt University Library using the keywords "mushrooms" and "health" and "COVID-19" or SARS CoV-2". Further searches included specific mushroom species such as "Ganoderma spp" and compounds such as "β-glucans" and health effects such as "inflammation" or "immunomodulation". Reference lists associated with pertinent papers were examined extensively for additional source material.

3 SARS CoV-2 virus and COVID-19 infection

Human coronaviruses such as the common cold generally cause mild illnesses but can mutate over time [10]. SARS CoV-2, a novel species of the *Coronaviridae* family, is the infective agent that causes COVID-19. Structural elements of the virus critically enable attachment, cell activity, multiplication and infectiousness [11], with ACE2 being the primary entry receptor [12]. SARS CoV-2 has become a global concern due to its transmissibility, virulence factors, and the severity of the disease processes associated with its mutations [11]. SARS CoV-2 enters the lungs through the respiratory tract, directly infecting upper and lower tract cells. Infection typically

involves nasal ciliated epithelial cells and alveolar epithelial cells [12]. Also involved are other types of endothelial cells of the arteries, immune, smooth muscle and intestine [7]. This presents implications for systemic organ involvement, particularly through the pro-inflammatory immune response that characterises the disease sequelae.

Presentation of the disease can range from no symptoms (asymptomatic) to severe illness with potentially life-threatening complications or fatal outcomes [10]. Moreover, while most people who contract COVID-19 experience mild to moderate symptoms and recover, at increased risk are the elderly, male gender, and people with comorbid conditions such as cardiovascular diseases, diabetes, hypertension, and poor nutritional status [7,13,14].

4 Immune and inflammatory responses to COVID-19

Immune cell responses react to pathogenic invasion or tissue damage to fight against infection or other attacks. The optimal immune response in humans involves both activation and inhibition in a coordinated and balanced way. However, interference with, and aberration of, the immune response and associated hyperinflammation is a defining characteristic of COVID-19 pathogenesis [13,15]. Stimulation and recruitment of pro-inflammatory cytokines trigger an influx of immune cells in a highly organised cellular and molecular cascade, causing alterations of the circulatory system through endothelial cell

interactions and damage to vascular barrier, capillaries and organs [13,14]. Manifested is a hyper response from immune activity (cytokine storm) with possible life-threatening consequences. Respiratory complications include pneumonia and acute respiratory distress syndrome (ARDS). Other systemic manifestations involve severe inflammation of organ endothelium and disorders within the vascular system, dysregulation of the ACE2 receptor gateway and disruption of the renin-angiotensin-aldosterone system (RAAS) [13,14,16]. Furthermore, cardiometabolic disease risk factors are implicated in the increased severity, morbidity and mortality associated with COVID-19. These include high blood pressure, obesity and diabetes, as well as cardiovascular events such as myocardial infarction and inflammation, thromboembolism and vasculitis [7,17,18].

5 Mushrooms as prevention or treatment for COVID-19

5.1 General features

Mushrooms are macro-fungi with a distinctive fruiting body, either hypogeous (underground) or epigeous (aboveground). There are estimated around 140,000 known species of mushrooms 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 [4,6,19]. Some 2,000 are edible, and a few hundred wild and cultivated mushrooms have long been utilised as MMs [5,19]. Nutritionally, mushrooms are low in energy and are generally a good source of macro

and micronutrients and trace elements, although there is variability [20–23]. As functional foods, they are also anti-inflammatory and known to modulate gut bacteria [24]. 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 [2,16,25].

5.2 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 [1,2,5,6,19,26–28]. Pertinent to COVID-19 infection, these compounds demonstrated effects, notably inflammation regulation, immune and reactive oxygen species (ROS) modulation, involvement in host defence mechanisms, microbial activity, pulmonary cytoprotection, and ACE2 specificity or inhibition [4,16,29].

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 [2,16]. Lectins, for example, 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 [19]. With structural diversity and variability, mushroom polysaccharides have a high capacity to carry biological information, and via such function, they have antitumour, antioxidant, immunomodulatory, anti-inflammatory, anti-microbial, anti-obesity and anti-diabetic effects [17]. β -glucans (D fraction) deserve special attention as they highly illustrate MMs' therapeutic potential and the variabilities that need consideration for application.

5.3 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. Glucans can be found in foods other than mushrooms, such as cereals. Thus, to be clear, the fungi glucans, in particular, β -glucans are discussed, and referred to as edible mushroom polysaccharides (EMPs). Molecular weight, the chain length, and side branching structures of mushroom β -glucans can be species- and cultivar-specific, influencing variance, complexity and biological activity [5,16,30,31]. Purity and purification processes are essential in characterising the structure [24]. Growing environments, drying conditions, and isolation/extraction methods are also crucial for the intensity of biological activities [17].

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 [32]. The immunomodulatory properties of mushroom-derived β -glucans exert more potent immunoinflammatory effects than other types and have long been recognised for this [30,33]. 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 [30,33]. They can also stimulate the activity of macrophages [34] and neutrophils, support natural killer (NK) cell activity, influence the production of cytokines and chemokines, and modulate antibody production, amongst many other functions [32].

Solubility and particulate size of β -glucans are important physical features as many receptors involved can activate different immune responses [30]. 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. Several authors have described the concept of trained immunity [13,33,35] 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 [35] cautioned that due

to the development of hyperinflammatory symptoms, such as may occur in COVID-19, the use of a therapy that may induce trained immunity effects warrants particular consideration. Notwithstanding, β -glucans have been used alongside parenterally administered vaccines, including hepatitis B and influenza vaccines. 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. [33].

6 Systemic “anti” responses and activities associated with specific MMs

The following synopsis examines the various “anti” effects and activities of specific mushrooms elucidated in research. **Table 1.** provides a selection of research findings exhibiting ‘anti’ effects and benefits resulting from bioactive compounds or secondary metabolites of selected MMs, which are deemed applicable for potential COVID-19 therapy consideration. These effects and potential benefits of MMs are also illustrated in

Figure 1.**6.1 Anti-pathogenic**

The viral replication cycle involves attachment, penetration, uncoating, replication, assembly, and release [36]. Mushroom extracts and bioactive compounds impede viral entry into host cells and multiplication, inhibit virus adsorption, replication, nucleic acid synthesis, and disrupt other pathogens [3,6,13]. As viral proteases are involved in viral replication, MMs may have therapeutic utility [13]. Protease inhibitors have been isolated from *G. lucidum*, *C. militaris* and *A. bisporus* [13]. 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 [37]. *Ganoderma* compounds isolated from *G. lucidum* effectively inhibited human immunodeficiency virus (HIV)-1 and HIV-1 protease [38]. 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* Murriel (AbM), *Hericium 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. [39] 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. Results showed the inhibition of bacterial (85%) and fungus (50%) and such effects compared favourably against Ciproflaxin, a broad-spectrum antibiotic deployed as the control. *P. ostreatus* extract showed minimal activity (3/39) of the same range of pathogens and did not inhibit any of the yeast and mould species. 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 [16].

6.2 Immune modulation

A response named “the lentinan antiviral effect”, acting as a BRM, has been attributed to innate immune responses and specific immunity regulation. 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, promote cytotoxicity and phagocytosis [2,40]. An in-house hot water extract of *L. edodes* was compared to a commercially sourced lentinan

extract (Carbosynth-Lentinan) 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 interleukin (IL)-1 β and IL-6 in lung injury and activated macrophages in vitro [16]. Oxidative stress was also reduced. Lectin derived from *P. ostreatus* has been studied as a hepatitis B virus DNA vaccine adjuvant and found to effectively enhance surface protein antibodies [41]. 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 RRTI, otitis media, tonsillopharyngitis, bronchitis, laryngitis, and other flu and cold like symptoms, plus fewer days off school [42–44].

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 [45–48]. AndosanTM, 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 [48]. *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 [48]. Further highlighting this, polysaccharides extracted from liquid-cultured mycelia and fruiting bodies of *G. frondosa* demonstrated antioxidant, antitumour, anti-inflammatory, hepatoprotection and immunostimulatory activity [49]. 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 tumour necrosis factor (TNF)- α expression [50].

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 [51]. 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 [52].

T. versicolour 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 anti-microbial, antiviral, antitumour, anti-inflammatory, antioxidant, hepatoprotective, bone

protective, and notably immunopotentiality. [53,54]. Two bioactive mycelia extracts of protein bound polysaccharides from *T. versicolour*, namely polysaccharopeptide (PSP) and polysaccharide krestin (PSK), are currently utilised medicinally in some countries as integrated cancer therapy and adjuncts for chemotherapy and radiotherapy [2,53,55]. From a range of randomised and non-randomised controlled trials, PSK and PSP were both found to promote positive impacts on anticancer effects [56]. Deemed resulting from 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 [55–57]. Additionally, antitumour and antimetastatic effects were noted through direct tumour inhibiting experiments in vivo [56]. Of interest in the context of COVID-19 application is the mechanisms of *T. versicolour*. 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-1 α and 1 β and IL-6, plus prostaglandin E2, histamine, activation of complement-3 and T cell proliferation [53,55,57]. While this may be desired to improve cancer outcomes, such as enhancing the immunosuppressive status, a cautionary approach in applying *T. versicolour* 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 COVID-19 recovery or playing a role as a vaccine adjuvant.

6.3 Antioxidant

The antioxidant/ROS system plays a significant role in pathogenic protection, regulation, and homeostasis in the human body. For example, 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 [58]. The antioxidant capacity of MMs has been demonstrated in various studies through radical scavenging, lipid peroxidation inhibition, and increasing antioxidant enzyme activities [29,50,59,60]. Bioactive compounds such as phenolics, indoles, flavonoids, glycosides, polysaccharides, tocopherols, glutathione and ergothioneine, ascorbic acid, carotenoids, vitamin D, copper, manganese, zinc, selenium in MMs all participate in reducing oxidative stress [58,61]. 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-2-methylglutaryl coenzyme A (HMG-CoA) reductase activity [62]. Several bioactive compounds with antioxidant activity were isolated, in particular ergosterol. Hexane solvent fraction demonstrated the most potent inhibiting oxidation of LDL and HMG-CoA reductase activity. This indicates a possible role in

preventing oxidative stress-mediated vascular disease processes [62].

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* [63]. Fourteen selected culinary-MMs were evaluated for in vitro antioxidant and ACE inhibitory activities [29]. The mushrooms were extracted by boiling water for 30 minutes. 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 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* showed relatively high compared to the other mushrooms [29].

6.4 ACE2 regulation

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 hyper inflammation and oxidative stress. Additionally, RAAS maintains dynamic control of vascular function. The deleterious effects of COVID-19, such as those associated

with cardiometabolic and other hallmark disorders, demonstrate dysregulation of this homeostatic function [7,12,64,65]. MMs have been investigated for ACE inhibitory, antiplatelet, anti-inflammatory and antioxidant activity [29,66,67]. For example, Cheah and Halliwell [59] made a compelling case for applying ergothioneine (high levels in mushrooms) in the array of COVID-19 pathologies. In MMs, bioactive compounds such as triterpenes, sterols, phenolic compounds, and polysaccharide fractions possess metabolic modulating capabilities [50]. These include blood pressure, glycaemia, cholesterol, triglyceride, and weight lowering activities. ACE inhibitory activity of several mushroom species was assessed via hot water and alcohol extracts [29]. *G. lucidum* particularly as a hot water extract, and *Pleurotus* spp. demonstrated potent ACE inhibitory activity, assumed due to the phenolic content and antioxidant capacity. However, variations existed between species and depended on the extraction method [29]. In vitro digestion of *P. ostreatus* identified several peptides known to be ACE inhibitors [68]. 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) [64]. 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 [64]. For example, excessive sodium ions can impair the endothelial vasculature and risk hypertension, but manifestations may be ameliorated with higher potassium ion levels. Hence, the high potassium and low sodium content of mushrooms may be an excellent nutritional source for ACE inhibition [1,23].

6.5 Cardiometabolic risk reduction

Fruiting bodies and mycelium extracts of edible mushrooms (some more than others) can be a valuable source of lovastatin, a statin group compound [69]. This compound inhibits HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. Thus, MMs with activity associated with lovastatin's mechanisms of action may be a promising source of anti-hypercholesterolaemic agents. Most notably, such cholesterol lowering potential has been observed in the fruiting bodies of *Pleurotus* spp. and others, including *A. bisporus* and *H. erinaceus* [62,68–71]. This potential, along with the absorption and stimulatory effect of dietary fibres and gut effects on faecal excretion, makes for a promising functional food application.

The effects of various MMs have also been studied with other cardiometabolic parameters. Dicks and Ellinger [68] undertook a systematic review of eight clinical studies of subjects with and without type 2 diabetes mellitus (T2DM) using fresh, cooked or dry powder *P. ostreatus*. These studies seemed to reveal beneficial effects,

though in most studies risk of bias was high or unclear due to methodological weaknesses and/or inadequate reporting. Nevertheless, observed were effects in glycaemic control (reduction in fasting and/or 2 h postprandial glucose), lipids metabolism (decrease in total cholesterol, LDL-cholesterol and/or triglycerides), some lowering in blood pressure, antioxidant effects, a reduction in food intake, but no weight change [68]. Administration of total polysaccharides extracted from *P. ostreatus* was given for four weeks in a high-fat diet and streptozotocin (STZ)-induced type 2 diabetic rats [72]. Found was that elevated blood glucose levels reduced, insulin resistance improved, and glycogen increased. The mechanisms occurred through activation of GSK-2 phosphorylation in the liver and GLUT4 translocation in muscle tissue. In high fat fed rats, *A. bisporus* demonstrated increased high-density lipoprotein (HDL) along with reductions in total cholesterol (TC) and LDL, and additionally, in type 2 diabetic rats induced by STZ, glucose levels decreased [73]. The anti-hyperglycaemic effect, along with antioxidant protection on the pancreas, kidney and liver, were also demonstrated with *H. erinaceus* polysaccharides on STZ-induced rats [74].

The pharmacological effects of *C. militaris* SU-12 residue polysaccharide were investigated using high-fat emulsion-induced hyperlipidaemic mice models. Identified were the characteristics of the polysaccharides, concluding these to have demonstrable antihyperlipidemic, hepatoprotective activities, and an increase in

antioxidant activity when serum and liver sections were analysed [75]. STZ-induced type 1 diabetic rats were used in a study that compared *G. frondosa* (water-soluble powdered whole Maitake fraction SX), two anti-diabetic drugs and a control to assess circulating glucose levels and blood pressure (BP) [76]. All treatments generally decreased circulating glucose levels compared to control. However, only the Maitake group consistently demonstrated enhanced insulin sensitivity, significantly lowered systolic BP, decreased RAAS, and increased nitric oxide system activity. *F. velutipes* powder and extract were shown to have good antioxidant activity, were a source of rich dietary fibre and mycosterol capable of impacting and reducing cardiometabolic disease parameters such TC, LDL cholesterol, and triglycerides (TGs) [77]. However, *G. lucidum* has produced less consistent results. In a study with high fat fed rabbits, Li et al. [78] found that atherosclerotic plaques were attenuated along with a reduced generation of ROS and malondialdehyde.

In contrast, no positive results were found in a prospective double-blind randomised placebo-controlled trial of 84 subjects with type 2 diabetes mellitus and metabolic syndrome over 16 weeks using *G. lucidum*, *G. lucidum* with *C. sinensis*, or a placebo [79]. The primary outcome measures were blood glucose biomarkers (glycosylated haemoglobin [HbA1c] and fasting plasma glucose), and secondary outcome measures were HDL and LDL, TGs, BP, C-reactive protein and apolipoproteins A and B markers. When the two

intervention groups were combined due to sample size inadequacy, there was no effect on the primary or secondary outcomes [79]. In a secondary analysis to investigate the benefits of daily intake of *A. bisporus* on cardiometabolic risk, stored serum of prediabetic patients with features of metabolic syndrome were analysed. No significant changes to body weight, cardiovascular or metabolic parameters were observed, and plasma leptin did not change. Nevertheless, ergothioneine concentrations, oxygen radical absorbance capacity and adiponectin were increased with a reduction of advanced glycation end products (AGEs) [80].

6.6 Gut microbiota modulation

The intestinal flora structure, the abundance and diversity of microbiota or activity can influence positive or negative health outcomes. Positive effects are reduced risk of cardiovascular and other metabolic diseases, lowered postprandial blood glucose, increased satiety for weight management, and improved laxation [81]. Aberrances of gut microbiota may contribute to chronic inflammatory diseases such as atherosclerosis, thrombosis, diabetes and asthma, which may be in part due to oxidative stress [82]. Fortunately, the functions and diversity of gut microbiota are influenced by the non-digestible and digestible fibres and prebiotic properties of mushrooms. Ma et al. [24] reviewed collated studies from various disease models that demonstrated health improvement from EMPs. There were correlations between EMPs and beneficial host-microbiota regulation effects [24]. Similar effects may also be

induced via mannitol, raffinose, resistant starch and chitin found in mushrooms [81]. Benefits of EMPs highlighted by Ma et al. were metabolic improvements such as reduction in TC and other lipid markers, anti-obesity activities, inflammation and insulin resistance, improved gut mucosa integrity and intestinal morphology, signalling pathways and pro-inflammatory cytokines inhibition [24].

Short chain fatty acids (SCFAs), including acetic acid, propionic acid, butyric acid and valeric acid, are known to provide beneficial health effects such as nutrient supply to the colonic epithelium, oxidative stress reduction, immune stimulation, and colonic pH modulation [82]. However, the proportion of SCFAs varies depending on the EMPs from different mushrooms [24]. *G. lucidum* appears most significant for microbiota derived health effects. Specifically, *G. lucidum* polysaccharide (GLP) appeared to have notable anti-diabetic and anti-obesity effects [83,84]. For example, Chen et al. [85] found GLP restored the gut microbiota of T2DM rats to a normal level and modified metabolites. Li et al. [82] found that *G. lucidum* mycelium polysaccharide strain S3 (GLPS3) increased the relative abundance of beneficial bacteria *Lactobacillus*, *Roseburia* and *Lachnospiraceae* in mice induced with repetitively intraperitoneal injection of diethylthiocarbamate. An increase in *Roseburia*, an SFCA-producing bacteria, after dietary administration with GLPS3, was considered an indicator of the health promoting activities of the SCFAs, and possibly also of immune stimulation.

Contrasting findings were reported by Lee et al. [86] when examining results from the Nurses' Health Study (for women) and the Health Professionals Follow Up Study (for men). In these studies, respondents were asked how often they consumed fresh, cooked or canned mushrooms (species unidentified). Data collected were short and long-term changes in biomarkers such as lipids, insulin or inflammation or cardiovascular risks such as sex, lifestyle factors and certain medical conditions. The authors found no benefit of mushroom consumption on cardiovascular disease and T2DM, and instead, a potential inverse relationship to T2DM.

7 Limitations and barriers for consideration

7.1 Isolation and extraction methods and techniques

A variety of isolation methods and assay techniques to extract and examine bioactive compounds are employed to study and commercialise MMs. Appropriate separation, recovery, and purification processes are necessary for obtaining maximum output from their usage [62]. Emphasis for this review is on the extraction methods for isolating the compounds rather than assays. Extraction methods vary and include solid-state fermentation, liquid-liquid partitioning, solubility in aqueous, ethanol, methanol and hot water broth, enzyme facilitated extraction, acidic/alkaline extraction, supplementation of liquid cultures, and aromatic analysis of dried states, amongst others [5,28,51]. As an example, Pop et al. [87] demonstrated the extraction

protocol on *Trametes* spp. using three different extraction solvents of water, ethanol, and methanol to isolate a range of phenolic acids, flavanols, flavones, and bioflavonoids. The properties and activity within the same species might differ depending on the type of extraction (water or ethanol/methanol) and the structure/section of the fruiting body [51,63]. This could have ramifications for creating medicinal therapies and targeting their mechanisms of action if undefined or not fully elucidated. Following are some other examples of extraction methods applied in research to demonstrate the variabilities in methodology and associated findings.

Friedman's review [28] on *H. erinaceus* identified specific bioactive secondary metabolites isolated in many ways and according to the different plant structures such as mycelia and the polysaccharide fractions. Bioactive compounds included ergosterol content and new sterols identified in cultivated *H. erinaceus* mycelia using salicylic acid, methyl jasmonate, water and ethanol. Antioxidant properties in a water-soluble polysaccharide were identified, but not in an ethanol extraction of another polysaccharide within the same species. Ma et al. [24] comprehensively examined the role EMPs have in their activities against obesity, inflammatory bowel disease, and cancer. EMPs display complicated and diverse characterisation correlating to their biological actions. Derived from various studies, they characterised the type of polysaccharide along with the extraction method. This demonstrated that the carbohydrate

structure and chemistry, and thus the methods to isolate, are vital information for assigning effect. Martel et al. [51] surveyed studies on cells, animals and humans utilising various constituents of mushrooms and plants. They found that effects on a wide variety of immune cell types could be stimulatory or inhibitory depending on the extraction method. The dichotomy appeared to be due to the differential solubility and potency of the main constituents in the extracts. Even within the same species, water-soluble polysaccharide extracts activated immune responses, but ethanol extracts inhibited them, although there were a few exceptions.

Novel techniques are being developed to remedy disadvantages associated with the extraction of bioactive compounds, such as long extraction times, low selectivity and solubility. Examples include high pressure assisted hot water extraction (PE) and the sequential application of microwave hydrogravity, supercritical CO₂ extraction and autohydrolysis. These green technologies have demonstrated effective extraction of polysaccharides such as polyphenols and ergothioneine from several species, including *H. erinaceus*, *L. edodes*, *Pleurotus* spp. and *A. bisporus* [49,88]. Wu et al. [49] undertook a study to evaluate the anti-inflammatory effects of total polysaccharides and β -glucans extracted from *G. frondosa* mycelia. The potential mechanisms were evaluated by examining effects on nitrite, prostaglandin₂, pro-inflammatory cytokines (TNF- α , IL-6 and IL-1 β), and intracellular reactive oxygen species in lipopolysaccharide-induced

macrophage cells. They compared a conventional extract method using ethanol with three different high pressure-assisted extractions (PE-200, PE-400, PE-600). Found was that the PE method in each case yielded greater extraction and content of polysaccharides and β -glucans and exerted stronger anti-inflammatory activities than the conventional method. Benson et al. [25] demonstrated that three components of *T. versicolor* (mycelium, initial substrate and fermented rice flour substrate), plus different extractions and combinations, could produce varied immune responses and activities when tested on human peripheral blood mononuclear cell cultures.

7.2 Environmental and other factors, including pharmacological

Other factors such as geographic region, temperature, cultivation practices and production methods also impact the characterisation of species, yield or nutrient content [4,28,89,90]. In a study by Cohen et al. [91], fifteen dried and crushed Basidiomycetes MM strains, fruiting bodies and mycelia were analysed. Found was that the protein and carbohydrate content ranged from 8.6-42.5% and 42.9-83.6%, respectively. Varying results for macro and micronutrients, and of concern, possible toxic elements, were reported as well. These results seem consistent with previous findings [23]. Additionally, mathematical modelling and comprehensive data collection as well as robust studies would all benefit and strengthen the claims and thus applications. This would optimise the potential of the health and

nutritional values and, therefore, their relationships to health benefits and effects.

Beyond this, pharmacokinetics, the timing of administration, dosage, mode, and formulation are all factors that must be considered in the therapeutical application of any compound [26].

Figure 2. summarises important considerations and some potential limitations presented in this appraisal.

8 Conclusion

This review identified major findings of in vitro, in vivo, and human studies for mushrooms utilised in the medicinal context. Particular species were used as examples and examined for their health effects due to their ready availability and/or

use in nutraceutical products. COVID-19 pathogenesis presents a spectrum of systemic health impacts for consideration. In particular, this relates to the aberrant immune and inflammatory responses that can lead to severe and detrimental effects. Demonstrated was that specific bioactive compounds derived from mushrooms are capable of inducing a physiological effect that can be considered helpful in COVID-19. These activities include anti-pathogenic, anti-inflammatory, immune-modulatory, antioxidant and ACE inhibitory. Thus, MMs are well placed to be a possible therapeutic option due to these functions and properties. Additionally, via their polysaccharide and various phenolic content, MMs may benefit in various important ways, notably for cardiometabolic risk parameter improvement. Hence, MMs consumed regularly and preferably cooked in a broth would be a beneficial dietary inclusion that could greatly improve comorbidity conditions in general and those with COVID-19 specifically.

Importantly though, some fundamental aspects and factors must still be considered. This includes enabling technologies and methods to fully characterise and then standardise each isolate to its functions and mechanisms of action. Furthermore, compound or singular synergies or the multiple physiological pathways may influence outcomes. Additionally, not all effects associated with these bioactive compounds will be appropriate in every health context, and in some cases, maybe detrimental. Thus, the mechanisms of action must be clearly understood.

A particular nuance of this review has been discussion about extraction amongst other potential limitations. The methods can significantly impact the physiological effects of MMs, and the variation alone can result in different, even oppositional effects. To fully expose, clarify and develop the efficacy of MMs as a reliable medicinal adjunct or option for use in pandemics such as COVID-19, this aspect must be of primary consideration. Structure of plant, part of plant, growing conditions, process and production optimisation are also important considerations. Beyond this are the pharmacokinetics, dosing and formulations to factor in. Increasingly, MMs are being commercialised and promoted for their health-promoting benefits. Thus, continued efforts must be applied to realising more research, particularly in human subjects, with all these variables and factors in mind.

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Conflicting Interests

The authors declared that there is no conflict of interest.

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Table 1. Research findings for specific mushroom species demonstrating beneficial effects and activities for potential “anti” therapeutic application.

Mushroom	Bioactive compound	“Anti” effects	References
<i>A. bisporus</i> Common white	Phenolics e.g., Ergothioneine	Antioxidant; increased ORAC activity; increased adiponectin; reduced AGEs; increased glutathione reductase and catalase activities	[59,63,80]
	Polysaccharides	Gut microbiota regulation; intestinal barrier integrity	[24]
	Secondary metabolites	Anti-hyperglycaemic; inhibitory effects on LDL oxidation; reduced HMG-CoA reductase activity; LPS reduction; ACE2 inhibition; cardiometabolic parameters improvement	[29,71,73,74]
	Ergosterol	Cytotoxic	[47]
Andosan™	Commercial extract <i>AbM</i> + <i>H. erinaceus</i> and <i>G. frondosa</i>	Immunomodulatory; anti-inflammatory; anti-tumour	[45]
Tomeka™	Commercial extract <i>A. bisporus</i> + <i>soy</i>	Anti-pathogenic	[3,28]
<i>C. militaris</i> Cordyceps	Cordycepin	Antiviral; RNA synthesis inhibition; suppressed EB viral replication; cytotoxic	[13,37]
		Antioxidant; anti-hyperlipidaemic; hepatoprotective	[75]

Mushroom	Bioactive compound	“Anti” effects	References
	SCFAs	Immune regulation and health promoting	[24]
<i>F. velutipes</i> Enoki	Polysaccharides/ dietary fibre	Reduced cardiometabolic parameters	[77]
	Mycosterol	Antioxidant	[77]
<i>G. frondosa</i> Maitake	Polysaccharides	Anti-inflammatory; antioxidant; immunomodulatory	[30,49]
		Increased insulin sensitivity; decreased systolic BP; decreased RAAS; increased NO	[76]
<i>G. lucidum</i> Reishi	Polysaccharides	SCFAs production; gut microbiota regulation; anti-obesity; anti-inflammation; reduced metabolic endotoxaemia; decreased FBG and insulin levels	[82–85]
	Ganodermic compounds – triterpenoids, other phenolics	Antioxidant; atherosclerotic plaque attenuation; anti-tumour; anti-inflammation; anti-viral HIV-1 and HIV-1 protease inhibition	[29,38,52,60,78]
	Mycelia fractions	ACE inhibition	[66]
<i>H. erinaceus</i> Lions Mane	Mycelia polysaccharide fractions	Anti-hyperglycaemic; improved antioxidant enzymatic activities	[62,74]
		LDL oxidation inhibition; HMG-CoA reductase inhibition	

Mushroom	Bioactive compound	“Anti” effects	References
	Fruiting body solvent fractions		
<i>L. edodes</i> – Shiitake	Polysaccharides; β -glucans	Antiviral; antioxidant; immunomodulation; cytotoxic; anti-inflammatory; microbiome regulation	[1,2,6,16,24,40]
	Aqueous extract	Anti-bacterial; anti-fungal	[39]
	Lovastatin	Hypolipidaemic	[69]
<i>P. ostreatus</i> Oyster	B glucans- pleuran	Immunomodulatory	[35,42–44]
	Lectins	Vaccine adjuvant	[19,41]
	Phenolics, peptides	ACE2 inhibition	[29,68]
	Lovastatin	HMG-CoA reductase inhibition	[68–70]
	Polysaccharides	Cardiometabolic parameter improvements	[68,72]
<i>T. versicolour</i> Turkey Tail	PSP, PSK	Cancer therapy/adjuvants; Immunomodulatory	[53,55–57]
		Gut microbiota modulation	[24]
	Glucans, phenolics	Antioxidant	[58]

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.

Figure 2. Factors to consider if MMs are to be utilised for therapeutic and treatment purposes. Extraction methods, in particular, appear to be very important. Even extracts from the same species produced with different approaches can exert contrasting activity.