Rationalization of Mushroom-Based Preventive and Therapeutic Approaches to COVID-19: Review

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ABSTRACT: Since December 2019, a *de novo* pattern of pneumonia, later named coronavirus disease 2019 (COVID-19), has caused grave upset throughout the global population. COVID-19 is associated with several comorbidities; thus, preventive and therapeutic strategies targeting those comorbidities along with the causative agent, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), seem imperative. In this state-of-the-art review, edible and medicinal mushrooms are featured in the treatment of SARS-CoV-2, COVID-19 pathomanifestations, and comorbid issues. Because this is not an original research article, we admit our shortcomings in inferences. Yet we are hopeful that mushroom-based therapeutic approaches can be used to achieve a COVID-free world. Among various mushroom species, reishi or lingzhi (*Ganoderma lucidum*) seem most suitable as anti-COVID agents for the global population.

KEY WORDS: ACE, ACE2, compromised immunity, immunomodulation, COVID-19, medicinal mushrooms, *Ganoderma lucidum*, protease inhibitor, SARS-CoV-2

ABBREVIATIONS: ACE, angiotensin-converting enzyme; **AD**, Alzheimer's disease; **ADAM**, a disintegrin and metalloproteinase; **ALI**, acute lung injury; **Ang**, angiotensin; **ARDS**, acute respiratory distress syndrome; **AT1R**, angiotensin receptor type 1; **CD**, cluster of differentiation; **COVID-19**, coronavirus disease 2019; **CVD**, cardiovascular disease; **DC**, dendritic cell; **FIP**, fungal immunomodulatory protein; **G-CSF**, granulocyte colony-stimulating factor; **GM-CSF**, granulocyte-macrophage colony-stimulating factor; **HIV**, human immunodeficiency virus; **IFN**, interferon; **IL**, interleukin; **IP**, IFN-γ–induced protein; **MasR**, muscarinic receptor; **MCP**, monocyte chemotactic protein; **MIP**, macrophage inflammatory protein; **NF-κB**, nuclear factor κB; **NK**, natural killer; **NO**, nitric oxide; **PRR**, pattern recognition receptor; **RAS**, renin angiotensin system; **RTI**, respiratory tract infection; **S protein**, spike protein; **SARS**, severe acute respiratory distress syndrome; **SARS-CoV-2**, severe acute respiratory distress syndrome coronavirus-2; **Th**, helper T cell; **TMPRSS2**, transmembrane protease serine 2; **TNF**, tumor necrosis factor; **TRIM**, trained immunity; **WHO**, World Health Organization

I. INTRODUCTION

Following the breakout of the novel coronavirus disease 2019 (COVID-19) in December 2019 in Wuhan, China, the virus is still shaking the global health care sector, economies, education, politics, as well as the global population. COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Although the initial signs and symptoms of COVID-19 in patients are fever, dry cough, and dyspnea, pneumonia in adverse states leads to severe acute respiratory syndrome (SARS) and death.[1] Development of antiviral agents against SARS-CoV-2 has become a global urgency and the development of different therapeutic strategies continues worldwide.[2] Unfortunately, to date there is hardly any single or combined medicotherapy available that could be prescribed to patients with COVID-19. The world has painstakingly awaited a vaccine against this pandemic, and vaccine distribution began in some parts of the world at the end of 2020. Because vaccine development requires a longer clinical trial period, the search for a currently usable medicotherapy that can withstand, albeit slow down, COVID-19 pathogenesis has

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gained momentum. In this context, nutraceutical or functional food–based approaches would benefit humans highly.[3] COVID-19 has manifested several comorbidities such as compromised immunity, depleted nutritional status, hypertension, cardiovascular diseases (CVDs), lipid profile, diabetes, noncommunicable diseases like Alzheimer's disease (AD), and old age.[4] Thus, integrative treatment strategies aimed directly at SARS-CoV-2 infection along with amelioration of these comorbidities seem pertinent.[5] The combination of both Eastern and Western medicotherapeutic approaches would greatly aid the COVID-19 affected population in overcoming this global crisis.[5] Inclusion of alternative and traditional medicine in COVID-19 treatment also seems beneficial.[6–8] In this context, edible and medicinal mushrooms are excellent as functional food–based and traditional medicotherapeutic agents against SARS-CoV-2 pathogenesis.[9,10] Thus, by pinpointing the SARS-CoV-2–related antiviral, immunomodulatory, nutritive, and COVID-19 comorbidity-ameliorating effects of different mushroom species, this review rationalizes the usage of mushrooms as a defense in the war against COVID-19.

II. MOLECULAR MECHANISM OF SARS-COV-2 PATHOGENESIS

SARS-CoV-2 possesses four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Fig. 1). Binding of SARS-CoV-2 to the host cell receptor is S protein mediated.[11] Entry of coronavirus into host cells requires S protein priming by cellular proteases such as transmembrane protease, serine 2 (TMPRSS2).[12] S protein is cleaved by proteases into S1 and S2 subunits (Fig. 2). Initially, through the receptor binding domain in the S1 subunit, the S protein binds to the ACE2 receptor of the host.[11] Then, the S2 subunit fuses with the cell membrane and viral entry occurs, followed by attachment of the viral genome (ssRNA) with the host's ribosomes and translation (Fig. 2).[11] Later, proteolysis of two coterminal and large polyproteins into smaller components facilitates folding and packaging into virions.[11] Virions exert both cytocidal and immunomodulatory effects on host cells (Fig. 2). Cytopathic effects (apoptosis and cell lysis) and syncytia formation, especially in the lungs, also occur.

SARS-CoV-2 pathogenesis involves both innate and adaptive immune responses (Fig. 2). Cytokines, produced by innate (macrophages, dendritic cells [DCs], natural killer [NK] cells) and adaptive (B and T lymphocytes) immune cells, are important components of inflammatory responses to viruses. Pattern recognition receptors (PRRs) of innate immune cells recognize and bind pathogen-associated molecular patterns of the invading virus that trigger inflammatory responses yielding inflammatory cytokines (Figs. 2 and 3).[13,14] Interleukin (IL)-1, tumor necrosis factor (TNF)-α, and IL-6 are the most important proinflammatory cytokines of the innate immune response (Figs. 2 and 3).[13,14] Circulatory levels of other elevated

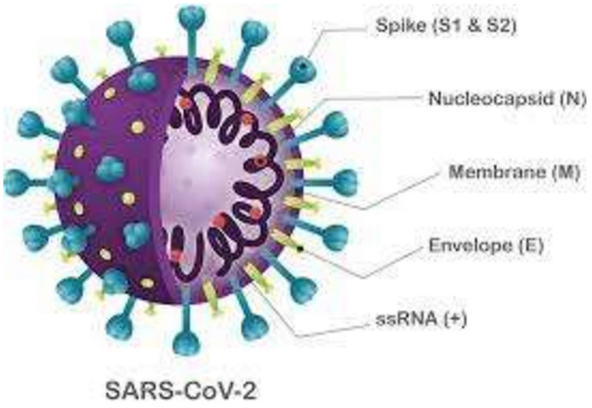

FIG. 1: Structure of SARS-CoV-2

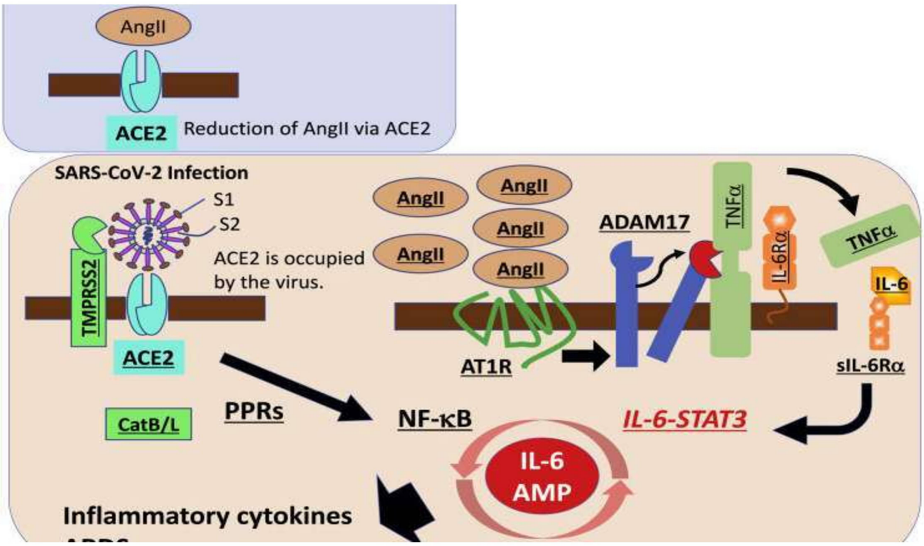

FIG. 2: Molecular mechanism of SARS-CoV-2 pathophysiology. CatB/L, cathepsin B/L.

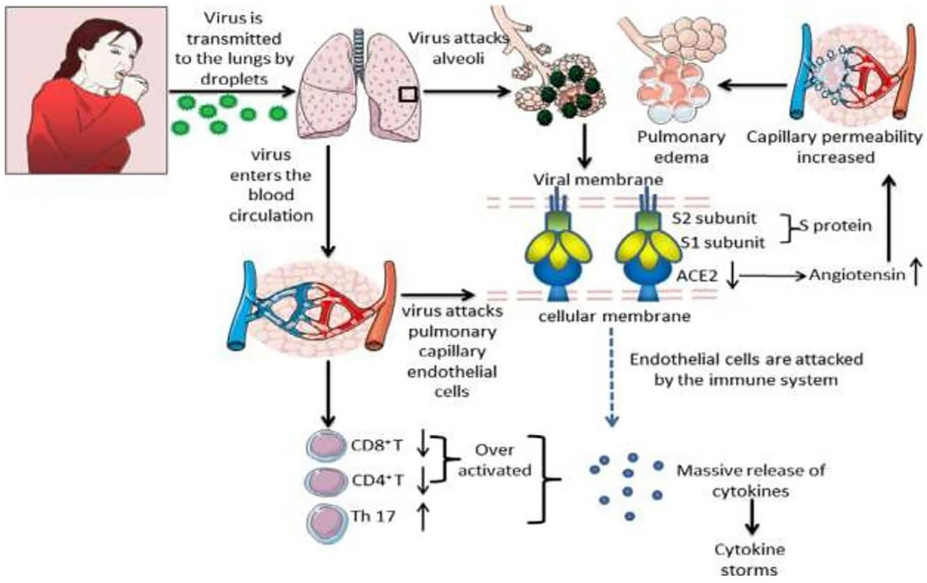

FIG. 3: SARS-CoV-2 pathophysiology

proinflammatory cytokines found in patients with COVID-19 are IL-1b, IL-7, IL-8, IL-9, fibroblast growth factor, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, IFN-γ–induced protein (IP)-10, monocyte chemotactic protein (MCP)-1, macrophage inflammatory proteins (MIP)-1A and MIP1-B, platelet-derived growth factor, and vascular endothelial growth factor (Figs. 2 and 3).[13,14] The state of transient increased levels of circulatory proinflammatory cytokines is referred to as the "cytokine storm" (Figs. 2 and 3). The cytokine storm triggers an influx of immune cells (macrophages, neutrophils, and T cells) to the infection site, which associates perturbed

endothelial cell-to-cell interactions and damage of the vascular barrier and capillaries (Figs. 2 and 3).[15] Alveolar damage, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and ARDS-mediated hypoxia are the most notorious effects of the cytokine storm that culminate in the death of persons with SARS-CoVID-19 infection (Figs. 2 and 3).[15]

III. PERTURBED ACE/ACE2 RATIO AND COVID-19 PATHOPHYSIOLOGY

Renin angiotensin system (RAS) dysregulation has been considered as a pathophysiological factor of COVID-19–led ALI and ARDS. In RAS, angiotensin-converting enzyme (ACE) converts angiotensin (Ang) I to AngII and ACE2 converts AngII to angiotensin 1-7 (Ang1-7) (Fig. 4A). ACE2 is expressed highly in alveolar epithelial cells, vascular endothelial cells, cardiomyocytes, intestinal epithelial cells, and renal proximal tubular cells.[16] AngII, through agonism at AngII receptor type 1 (AT1R), mediates vasoconstrictive, proinflammatory, and pro-oxidative effects (Fig. 4B and 4C).[17] On the other hand, Ang1-7, binding at the muscarinic receptor (MasR), provides anti-inflammatory, antioxidative, and vasodilatory

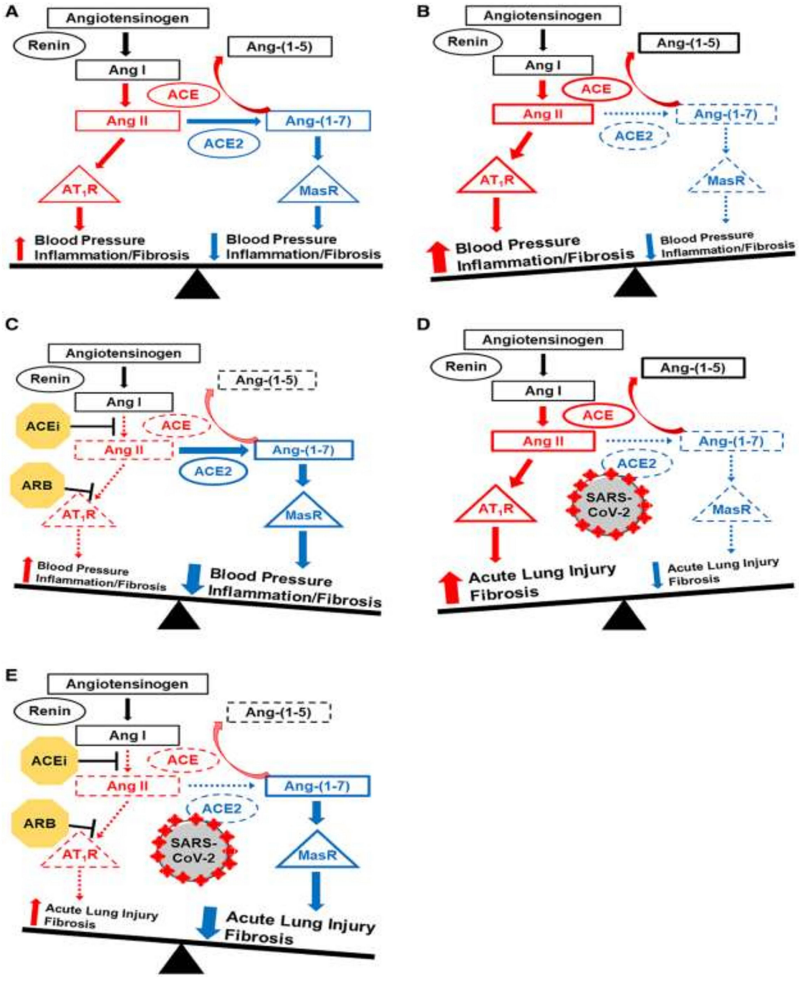

FIG. 4: ACE/ACE2 ratio in normal physiology and SARS-CoV-2 pathophysiology. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor binding domain.

effects (Fig. 4D).[18] Thus, the ACE2/Ang1-7/MasR and ACE/AngII/AT1R triads exert opposite effects (Fig. 4D and 4E). In patients with COVID-19, binding of SARS-CoV-2 to ACE2 attenuates ACE2 activity and shifts the ACE/ACE2 ratio disproportionately such that signaling of the ACE/AngII/AT1R triad predominates, resulting in overproduction of vasoconstrictor Ang and lowered production of vasodilator Ang1-7 (Fig. 4D and 4E). Signaling through AT1R, AngII acts as a proinflammatory cytokine (Fig. 4D and 4E).[16] Further activation of nuclear factor κB (NF-κB) and a disintegrin and metalloprotease ADAM17 by the Ang Ⅱ-AT1R axis triggers production of the mature form of epidermal growth factor receptor ligands and TNF-α as well as the gp130-mediated activation of STAT3.[19] Consequently, activation of the IL-6 amplifier leads to a hyperinflammatory state with increased pulmonary vascular permeability (Figs. 2–5).[20] Severe immune injury occurs from hyperactivation of T cells producing proinflammatory helper T cell Th17 and highly cytotoxic cluster of differentiation $CD8^+$ T cells and rapid activation of $CD4^+$ T lymphocytes into pathogenic Th1 cells and inflammatory $CD14^+$ $CD16^+$ monocytes (Fig. 5).[21,22] Elevated levels of plasma/serum cytokines and chemokines such as IL-2, IL-7, G-CSF, GM-CSF, IP-10, MCP-1, MIP-1a, and TNF-α lead to the cytokine storm described earlier (Figs. 2–5).[14,15]

IV. MUSHROOMS IN MAINTAINING ACE/ACE2 BALANCE

Because the impaired ACE/ACE2 ratio has been linked with the COVID-19 pathomechanism, treatment strategies targeting this ratio have received immense attention.[23] ACE inhibitory proteins have been isolated from different edible and medicinal mushrooms, of which the most notable are *Ganoderma lucidum*, *Grifola frondosa*, *Agrocybe* species, *Auricularia auricula-judae*, *Hericium erinaceus*, *Hypsizygus marmoreus*, *Pleurotus cystidiosus*, *P. eryngii*, *P. flabellatus*, *P. florida*, *P. sajor-caju*, *Schizophyllum commune*, *Tricholoma giganteum*, and *Volvariella volvaceae.*[24–29] In addition to peptides and proteins, ACE inhibitory triterpenes have also been extracted from *G. lucidum*.[30] The ACE inhibitory effect of these mushrooms can restore the ACE/ACE2 ratio indirectly and would thus provide a COVID-19-ameliorating effect.[23] In addition, by allowing less conversion of AngI to AngII through ACE inhibition, usage of mushrooms seems apt in COVID-19 therapeutics. As chemically synthesized ACE inhibitors have side effects such as dry cough, an alternative medicinal approach incorporating mushrooms seem promising.[31] On the other hand, increasing ACE2 levels would also increase the susceptibility of SARS-CoV-2 binding to host cells, making the process a double-edged sword. Thus, further research is warranted in this aspect.

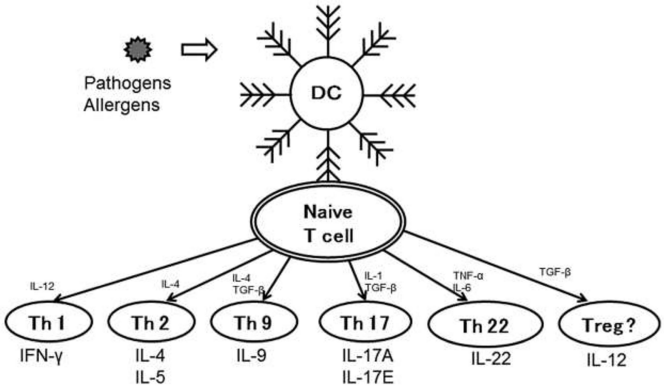

FIG. 5: Hyperactivation of T cells generating a series of Th cells and proinflammatory cytokines. TGF, tumor growth factor; Treg, regulatory T cell.

V. ANTIVIRAL PROPERTIES OF MUSHROOMS

Mushroom extracts and biocomponents can impede viral multiplication through their inhibitory roles toward virus adsorption and entry into host cells, viral replication, and nucleic acid synthesis.[32] Viral proteases are important for replication and proteolytic cleavage-led production of infectious viral particles. Inhibitors of those proteases are of paramount choice in antiviral drug development. The U.S. Food and Drug Administration has permitted the use of human immunodeficiency virus (HIV)-1 protease inhibitors (tipranavir, saquinavir, ritonavir, nelfinavir, lopinavir, indinavir, darunavir, atazanavir, and amprenavir) for treatment against SARS-CoV-2.[33] In addition, RNA-dependent RNA polymerase inhibitors (remdesivir and favilavir) have been applied as a COVID-19 treatment in different countries.[34] Different protease inhibitors have been isolated from edible and medicinal mushrooms such as *G. lucidum*, *G. colossum*, *G. sinense*, *Lignosus rhinoceros*, *A. polytricha*, *Russula paludosa*, *Cordyceps militaris*, and *Agaricus bisporus.*[35–45] Ganomycin I and ganomycin B from *G. colossum* are reported to have anti–HIV-1 protease with half maximal inhibitory concentration values of 7.5 and 1.0l μg/ml, respectively.[39] Ganoderone A, ganoderol B, lucialdehyde B, lucidadiol, lucialdehyde, amantadine sulfate applanoxidic acid G, and ergosta-7,22-diene-3b-ol isolated from *G. pfeiffery* have shown antiviral effects against influenza A virus.[46] Compared to others, *Ganoderma* species seem promising in protease inhibition–based antiviral therapeutic approaches. Up to the present day, biocomponents derived from *Ganoderma* (ganocompounds) have been found effective in thwarting HIV-1 protease, which corroborates utilization of ganocompounds against SARS-CoV-2. Cordycepin (3′-deoxyadenosine), isolated from *C. militaris*, exerts an antiviral effect through a protein kinase inhibitory mechanism.[47] Also, its inhibitory role toward RNA synthesis has been implicated in influenza virus multiplication.[48] The epigenetic mode of antiviral effects has also been linked with cordycepin.[49]

VI. IMMUNOMODULATORY ROLE OF MUSHROOMS

COVID-19 manifests a multitude of illnesses, some of which are symptomatic while others are asymptomatic.[50] Among them, immunological deregulation (i.e., the cytokine storm) is the most notable manifestation of COVID-19.[50] Thus, modulation of the compromised immune system has become the focal point in combating COVID-19. Immunomodulation is the regulatory process that maintains a balanced immune system: it does not allow all immune cells to be active altogether. In this regard, food and nutraceutical-based approaches boosting immune defense and modulating compromised immunity seem apt as a defense against COVID-19.[51] Immunomodulators are biocomponents able to lower immune stimulation (immunosuppressant), promote innate immune response (immunostimulants), or enhance vaccine efficacy (immunoadjuvants).[52] Mushroom-based immunomodulators can be classified into four categories: lectins, proteins, polysaccharides, and terpenoids.[52] Fungal immunomodulatory protein (FIP)-fve isolated from *Flammulina velutipes* could suppress replication of respiratory syncytial virus, a bronchiolitis agent. FIP-fve also lowered IL-6 expression and inflammation through inhibition of NF-κB translocation.[53] Trained immunity (TRIM) is a modified and epigenetic innate immune response that is capable of producing antibody-free memory to the pathogen and lasts for several months.[54] β-D-glucan has been implicated in enhancing TRIM through epigenetic mechanisms and metabolic regulation.[55] Respiratory tract infection (RTI), especially lung infection, is a grave concern of COVID-19 manifestations. Mushroom-derived β-glucan has been found to ameliorate both upper and lower RTIs and boost immunity.[56–58] Common cold or flu-like symptoms are the general features of COVID-19. Oral administration of β-D-glucan was shown to lower the level of common cold events by one-fourth, as evidenced in randomized, double-blind, placebo-controlled studies.[59,60] These effects have been deemed to arise through TRIM effects of β-D-glucan.[61] The β-D-glucan level is reported to be 54.0, 50.5, 34.3, and 32.8 g/100 g of dry weight of *G. lucidum*, *Trametes versicolor*, *G. frondosa*, and *C. militaris*, respectively.[62] Hot water extract of *G. lucidum* has been found to alleviate

influenza in H1N1 and H5N1 virus-induced influenza model rats.[63] Although the exact mechanism of antiviral effect is not yet known, overall enhanced immunity seems apt. This enhancement might occur either through direct immune stimulation or through TRIM. Thus, usage of β-D-glucan as both a therapeutic and prophylactic agent seems apposite.

Corticosteroids prescribed against severe ALI and ARDS hamper host antiviral immunity; thus, their usage against SARS-CoV-2 seems unwise.[64] Also, proximal immune response inhibition through IFN-related PRR activation would deregulate the host immune system.[65] Therefore, immunomodulatory treatment strategies targeted at proinflammatory and Th2 cytokine (IL-1, IL-4, IL-6, IL-8, IL-21, TNF-α, oxygen radicals) production seem apt.[66] Various anti-inflammatory biocomponents such as polysaccharides, terpenoids, phenolics, glycerides, and other low molecular weight substances have been isolated from Basidiomycetes mushrooms.[9,10,66] β-D-glucan extracted from *Lentinus edodes* is found to reduce inflammation in human alveolar epithelial A549 cells, as evidenced by reduced cytokine-induced NF-κB activation and attenuated proinflammatory cytokine production (TNF-α, IL-8, IL-2, IL-6, IL-22) oxidative stress-induced early and late apoptosis.[67] Thus, modulation of the cytokine storm through β-glucan–mediated controlled expression of pro- and anti-inflammatory cytokines could aid in withstanding COVID-19 pathogenesis.[66,67] Mushroom biocomponents (polysaccharides such as α- or β-glucans, proteins, or glycoproteins) exert immunomodulatory pursuits through regulation of cytokine (IL-10, IL-12p70, and IL-12p40) production by DCs; production of TNF-α, IL-1, IL-6, IL-8, IL12p40, and nitric oxide (NO); expression of inducible nitric oxide synthase by macrophages; and activation of NK cells.[68] Most of these effects have been reported for *G. lucidum*, *Phellinus linteus*, *A. blazei*, and *G. frondosa.*[68] Basidiolipids from *Agaricus* species of mushrooms have been found to have immunoadjuvant activity.[69] Through enhanced production of IFN-γ (inducer of DC maturation) and TNF-α (stimulator of IL-2 production), *A. bisporus* increased NK cell activity in mice.[70] NF-κB and AP-1 signaling has been associated with the anti-inflammatory potential of *P. ostreatus*.[71] Novel lentinal (LNT-1) extracted from *L. edodes* significantly downregulated expression of proinflammatory cytokines (TNF-α, IL-2, IL-11) and upregulated that of immunomodulatory, anti-inflammatory, and antiproliferative cytokines such as IFN-1 and IFN-γ.[72] DCs are potent antigen-presenting cells capable of activating naïve T cells (Fig. 5). Protein-bound polysaccharide K derived from *Coriolus versicolor* aids in the maturation of DCs along with overcoming the defective phagocytosis of DCs.[73,74] Inflammatory amelioration of *Inonotus obliquus* polysaccharides is linked with JAK-STAT signaling pathway inhibition and the associated release of T_h subsets, especially $CD4^+$ T cells.[75] Downregulation of IL-1, IL-6, IL-8, IL-17, MMP-9, NO, TNF-α, and IFN-γ and upregulation of IL-2 and IL-10 by *G. lucidum* as well as downregulation of IL-8, NF-κB, TNF-α, and MCP-1 by *G. frondosa* have been observed.[76]

VII. MUSHROOMS IN AMELIORATION OF COVID-19 COMORBIDITIES AND AS A NUTRITIONAL SUPPLEMENT FOR PATIENTS WITH COVID-19

Most patients with COVID-19 are aged > 65 years. Some people in this age range suffer from AD. AD, CVD, diabetes mellitus, hypercholesterolemia, and hypertension are common comorbidities of COVID-19. Patients with COVID-19 and comorbidities require nutritional supplementation in support of their fight against SARS-CoV-2 and diminished homeostasis.[77] As a functional food, both edible and medicinal mushrooms are highly effective in supplementing nutritional deprivation.[78–83] Polysaccharides (especially β-D-glucan), polyphenols, triterpenes, proteins, vitamins, and minerals present in mushrooms would support treatment of patients with COVID-19 and comorbidities.[83] As the preparation of mushroom powder is simple and does not require sophisticated handling and preservation processes, supplying mushroom powder to patients with COVID-19 and comorbidities around different parts of the globe would also be less cumbersome for aid agencies. Thus, we recommend quick actions in preparing mushroom-based food items for COVID-19 sufferers and request that the World Health Organization (WHO) and other health care

management agencies take the necessary steps to disseminate a mushroom-based therapeutic and preventive approach against SARS-CoV-2.

VIII. CONCLUSIONS

Different aspects of biomedical, biopharmaceutical, nutritional, immunological, and antiviral approaches link both edible and medicinal mushrooms in treatment to combat COVID-19. The contents of proteins, triterpenes, viral replication inhibitory proteins, and immunomodulatory polysaccharides like β-D-glucan found in mushrooms as well as nutritional supplements place mushrooms in superb stead in this global crisis. Among different mushroom species, *G. lucidum* stands out as the best in terms of COVID-19 preventive and curative agents. However, we must disclose that appropriate clinical studies are quintessential. Thus, we request that the WHO and health care agencies provide necessary measures in formulating mushroom-based anti-COVID preventive and therapeutic strategies.

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