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Possible Use of *Ganoderma* Mushroom Extracts for the Treatment of Some Chronic Risk Factors Associated with Severe Covid-19

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Review Article

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Abstract

The novel coronavirus (SARS-CoV-2) emerged in Wuhan, China in December 2019 causing the coronavirus disease 2019 (COVID-19). The disease has caused a pandemic that had disrupted social and economic life globally. Intense research is ongoing to understand the nature of the virus and pathogenesis as well as the development of drugs and vaccines. Ample evidence suggests that the elderly people, those with pre-existing chronic medical conditions, such as lung disease, heart disease, diabetes, obesity, chronic kidney disease, compromised immunity and even men may be at higher risk of serious illness and intensive care. The virus tends to trigger the over-production of pro-inflammatory cytokines, which results in multiorgan damage, resulting in death. Following this review, we proposed the use of *Ganoderma* mushroom extracts, which have certain properties relevant to the management of COVID-19 complications including anti-inflammatory, antiviral, immune modulatory, and antioxidant, anti-aging and multiorgan protection. Most of this research has been done on rodent models with few clinical trials. Since, the mushroom is generally regarded as safe (GRAS) and have been used for centuries in Asian traditional medicine, we recommend the use of this mushroom in the management of the disease including as active ingredients in COVID-19 drugs, and alternatives to synthetic drugs, health supplements, adjuvant therapy or functional foods.

Keywords: Anti-Inflammatory; Antiviral; Chronic Diseases; Cytokine Release Syndrome; *Ganoderma Lucidum*, Multiorgan Damage; Pre-Existing Conditions; Traditional Medicine

Introduction

The novel coronavirus (nCoV), which was later identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China late last year, is the causative agent of Corona Virus Disease 2019 (COVID-19). The outbreak, which was officially reported in December last year, within less than three months, have spread round the world and was subsequently declared a pandemic by the World Health Organization (WHO). The pandemic has disrupted social and economic activities round the world, affecting virtually every facet of society. Response to the pandemic led to lockdowns and disruption of economic activities. Health systems became stretched and overwhelmed in many countries. As of 26 August 2020, the virus has caused 24 million infections with over 820,000 deaths worldwide.

It is suspected that that the virus originated in bats and spilled over to humans. Human to human transmission is suspected to occur via droplets, air transmission and contacts. Global economic integration and international travel may have facilitated the spread of the virus. With so much fear and anxiety concerning the virus, scientists all over the world are working to study the pattern of pathology and to identify the risk factors that can complicate the infection. Studies have found that age, gender, and pre-existing health conditions such as asthma, pulmonary diseases, kidney diseases, hypertension, diabetes, cancer, tuberculosis and HIV/AIDS are risk factors. The elderly especially above 55

years old [1,2] are at increased risk. Men are at higher risk than women Poletti, et al. & Williamson, et al. [1,3] studies have also shown that lifestyle such as alcoholism and smoking are important risk factors for COVID-19 Poortmans, et al. Environmental factors of temperature, humidity, ultra-violet radiation, which are variable across the Earth could affected the spread of the virus and could become an important risk factor. Social activities, which bring people together such as open markets, religious activities, sporting events, festivals, carnival, conferences, and elections are also important risk factors. More risk factors are continually being discovered as the virus spreads from place to place.

A recent study by the United States Center for Disease Control and Prevention (CDC) suggest that race could become a risk factor for COVID-19. The study found that in the US, African-Americans and Latinos are more affected by coronavirus infections. The study found that black and brown communities have been "disproportionately affected" by the pandemic. They showed that African-Americans, which accounted for only 13.4% of the U.S, accounted for 22% of coronavirus infections. Latinos, which represented 18.3% of the population, accounted for 33% of coronavirus infection. On the other hand, Native Americans, which represent 1.2% of the population, accounted for 1.3% of infections. White Americans, which represents 76.5% of the population, accounted for 36 percent of coronavirus infections [4].

Currently, there are no globally approved drugs or vaccines for the control of the diseases. Hence, in an attempt to control the disease, several measures should be instituted. First is to break the transmission chain of the virus. Many countries all over the world, embarked on lockdowns, physical distancing, enforcement of strict hygiene, fumigation of the environment, hand washing, and the use of alcohol-based sanitizers, face shield and masks. The drug strategy was to repurpose existing drugs, while researching novel therapeutics. Subsequently, several repurposed drugs have been tested and found to be effective in reducing the severity of the disease, which increases the chances of survival. Some of the more commonly repurposed drugs are in clinical trials for the treatment of COVID-19 including Redemsevir, Favipiravir, lopinavir/ritonavir, Umifenovir, and Ribavirin [5,6]. Redemsevir, was initially developed to treat Ebola during the outbreak in West Africa in 2014 and is now the first and only drug that has received approval of the US Food and Drug Administration, and European Medical Agency.

In the ongoing response to COVID-19, several herbal remedies were also tried in many African countries including ginger, garlic, turmeric, bitter kola, and artemisia. In Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) is currently processing twenty-one (21) herbal medicinal products for 'safety listing' status to treat symptoms associated with COVID-19. According to the Agency, many of the applicants claim that their products are immune boosters and anti-infectives useful for relief of symptoms that could be associated with COVID-19. However, no clinical study has been done on any of the products to prove their claim of efficacy, and no approvals given. Prominent among the listed herbal remedies was Pax Herbal Cugzin capsule 290mg, which consists of ginger, turmeric and bitter kola.

Antibody therapy was also considered. But it faced with several challenges. The virus is poorly immunogenic, immunity developed after recovery from infection is short-lived, typically within 2-3 months, hence, there were suspected cases of re-infection or reactivation. This became a challenge for relying on herd immunity for the control of the disease. Recent studies have shown that a cocktail of antibodies especially from llamas could be a promising treatment Huo, et al. [7], but it has to be further developed.

There are speculations that full economic and social activity cannot be restored globally until an effective vaccine is discovered. Several scientific researches have led to the discovery of promising vaccine candidates, which are in different stages of testing, with most in preclinical, while a few are at different stages of clinical trials. As of 21 July 2020, about 165 vaccine candidates are under various stages of development and licensure with 140 in preclinical i.e. animal trials, 19 in phase I, 13 in phase II and 4 in phase III. Among the four front-runners, two of the vaccines is based on virus vector using modified human Adenovirus (CanSino Biologics, China,) and chimpanzee Adenovirus (University of Oxford and AstraZeneca, UK), while the other two (US Pfizer/German BioNTech; Moderna / US National Institute of Allergy and Infectious Disease) are based on mRNA technology [8]. Preliminary results from clinical trials is quite encouraging and some of the leading vaccines are preparing for mass production.

Because there is presently no vaccine, antibody or drug therapies licensed for COVID-19, there is an urgent need to address the risk factors associated with the disease in order to save lives. The chronic risk factors are among the most threatening especially heart diseases, kidney diseases, diabetes, pulmonary diseases and cancers. Also, diseases that weaken the immunity such as HIV are important, though with less risk than the chronic diseases. Meanwhile, *Ganoderma* mushrooms have been shown to be antiviral Bharadwaj, et al. & Lu, et a. [9,10] boost immunity Murray, et al. [11], or have anti-inflammatory properties (Wei et al 2018) may be effective in treating certain chronic diseases Bulam, et al. [12] and thus a viable option for the management of COVID-19 [13]. The aim of this paper is therefore to present arguments for the consideration of *Ganoderma* as a potential option for

the management of COVID-19 and complications.

Covid-19 Chronic Risk Factors and Complications

COVID-19 mortality has rapidly increased worldwide and there is urgent need to understand who is most at risk [3]. Based on the pattern of mortality observed globally, chronic risk factor associated with death for COVID-19 patients include diabetes, kidney diseases. Hypertension, other respiratory and diseases heart diseases such as asthma, obesity, HIV/AIDS, tuberculosis. Apart from HIV/AIDS and tuberculosis, most of these chronic diseases are associated with old age. Several studies have shown that the risk of severe COVID-19 if an individual becomes infected with the virus, is higher in older individuals, males and those with pre-existing chronic health conditions. According to the National Council on Aging, 85% of adults 65 years and older have at least one condition, while 68% have two or more of the following disease conditions, which were ranked among the ten most common health diseases of adults; hypertension (58 %), high cholesterol (47%), arthritis (31%), ischemic heart disease (29%), diabetes (27%), chronic kidney diseases (18%), heart failure (14%), depression (14%), chronic obstructive pulmonary disease (11%) and Alzheimer disease (11%) (https://www.ncoa.org/blog/10-common-chronic-diseases-prevention-tips/). All these conditions apart from Alzheimer disease, depression and arthritis are known risk factors of COVID-19. While analyzing the 5,484 contacts of SARS-CoV-2 index cases detected in Lombardy, Italy, Poletti, et al. [1] quantified the probability of developing symptoms either respiratory infection or fever ≥37.5 °C, requiring intensive care or death. SARS-CoV-2 positive subjects older than 60 years with risk of symptoms developed critical disease, with males at significantly higher risk.

From various studies, age has emerged as a consistent risk factor for illness and death from COVID-19. Davies, et al. [2] reported age-dependent effects in the transmission and control of COVID-19 epidemics. From epidemic data obtained from China, Italy, Japan, Singapore, Canada and South Korea, they estimated the susceptibility to SARS-CoV-2 infection and found that individuals under 20 years of age is approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% of infections in 10-19 year old, rising to 69% of infections in people aged over 70 years. Data from University of Oxford (2020) show that men, older people, those with uncontrolled diabetes and severe asthma are at increased risk of death from COVID-19. Zhang, et al. [14] observed that male gender, severe COVID-19, expectoration, muscle ache, and decreased albumin were independent risk factors that influence the improvement of COVID-19 patients. Williamson, et al. [3], while analyzing primary healthcare records of over 17 million adults in the UK, pseudonymously linked to nearly 11,000 COVID-19-related deaths, found that the death was associated with: being poor, older and male, and with diseases such as diabetes, severe asthma and various other medical conditions.

Studies from China show that people who have high blood pressure may be twice as likely to die from COVID-19 [15]. The risk of death among those with high blood pressure was found to vary depending on the antihypertensive treatment the patients were receiving [16]. In addition, the study found that patients with high blood pressure who were not taking medication to control the condition were at even greater risk of dying from COVID-19. Obesity is another risk factor for COVID-19 fatality. This could be due to the relationship between obesity and stress on the heart. Evidence from observational studies suggests that maternal pre-pregnancy overweight and obesity are also associated with offspring cardiovascular risk factors in childhood and cardiovascular diseases in adulthood Gaillard, et al.

Clark et al. analyzed the data of 1.7 billion people comprising 22% of the global population, and found that at least one underlying condition that puts them at increased risk of severe COVID-19 if infected (ranging from <5% of those younger than 20 years to >66% of those aged 70 years or older). The analysis shows that the number of individuals at increased risk was most sensitive to the prevalence of chronic kidney disease, diabetes, cardiovascular disease, and chronic respiratory disease. About one in five individuals worldwide could be at increased risk of severe COVID-19, should they become infected, due to underlying health conditions, which varies considerably by age.

In New York, Lighter, et al. [17] analyzed some COVID-19 patients younger than 60 year and found that those who were obese i.e. with BMI 30 -34 kg/m^2 were twice as likely as non-obese individuals (BMI < 30 kg/m^2) to be hospitalized and were 1.8 times as likely to be admitted into intensive critical care. Reports from other countries have also shown similar pattern of increased risk of COVID-19 associated with overweight and obesity in patients including France Simonnet, et al. [18] and China [19].

Preliminary data from studies carried out in South Africa show that persons living with HIV or active tuberculosis (TB) had increased likelihood of dying from COVID-19. However, the effect is smaller compared with other known risk factors such as old age and diabetes [20].

Studies have also shown that cancer is an important risk for COVID-19. While, analyzing all-cause mortality within 30 days of COVID-19 diagnosis, Poortmans, et al. reported an increased mortality associated with age, male gender, smoking, comorbidities, active cancer, region of residence,

and receipt of azithromycin plus hydroxychloroquine, but not with anticancer therapy. Lee, et al. found that mortality from COVID-19 in cancer patients appears to be principally driven by age, gender, and comorbidities. Kuderer, et al. found that among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general risk factors and risk factors unique to patients with cancer. On the other hand, Poortmans, et al. found that, although the risk of death was significantly associated with age, male gender, and comorbidities, no correlation was found between anticancer treatments within 4 weeks before testing positive for SARS-CoV-2 and COVID-19 morbidity or mortality.

Rothan, et al. [21] listed both the systemic and respiratory disorders associated with COVID-19. The systemic disorders include cough, fevers, headache, fatigue, haemoptysis, hypoxaemia, dyspnoea, lymphopenia and diarrhoea, while the respiratory disorders include pneumonia, acute respiratory distress syndrome (ARDS), sneezing, sore throat, Rhinorrhoea and ground glass opacity. Puelles, et al. [22] observed that though SARS-CoV-2 preferentially infects cells in the respiratory tract, but it also targets other organs. From autopsy series of 27 patients, they found that the virus multiplied extensively and destroyed other organs of the body including the kidney, liver, brain and heart in addition to the lungs and larynx. Their conclusion was that the virus exhibits renal and multi-organ tropism, which influences the course of the disease and possibly aggravates pre-existing conditions that ultimately results to death. The SARS-CoV-2 genome encodes for a group of accessory proteins that help them modify the inside environment of an infected cell making it easier for the virus to replicate. Among them is the ORF3a protein, which creates a hole in the membrane of an infected cell, triggering inflammation leading to multi-organ damage and also making it easier for progeny viruses to be released and spread [23].

Generally, COVID-19 produces mild to moderate symptoms in most people, but can cause severe medical complications leading to death in some older adults or people with pre-existing chronic medical conditions. The complications of COVID-19 appear to be caused by a condition known as cytokine release syndrome (CRS), which disrupts the immune system resulting in the release of pro-inflammatory proteins called cytokines (cytokine storm), which is associated with multiorgan damage including the lungs, heart, liver, and kidneys. Brain damage and neurological disorders associated with COVID-19 have been recorded in some cases. Other complications include venous thromboembolism, cardiovascular complications, neurologic complications, septic shock, disseminated intravascular coagulation, acute respiratory failure and general weakening of the immune system, which can predispose someone to other microbial attacks. A detailed review on the effects of COVID-19 on the immune system can be found in Yazdanpanah, et al. [24]. Studies have linked the disease severity and mortality of COVID-19 to the levels of cytokines especially interleukin-6 (IL-6) and IL-8, a phenomenon that was also observed with other human coronaviruses including Middle East respiratory syndrome (MERS) and SARS [25].

Coronavirus infection results in monocyte, macrophage and dendritic cell activation, which caused the over-production and release of pro-inflammatory cytokines including IL-1α, IL1β, IL-2, IL-6, IL-8 and IL-10, tumor necrosis factor alpha (TNF-α), interferon gamma (IFNγ), granulocyte-macrophage colony stimulating factor (GM-CSF) and M-CSF, induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory proteins (MIP1α) responsible for the pathophysiology of severe COVID-19 including acute respiratory distress syndrome (ARDS), hypertension, multiorgan damage and death [21-26-28], which is a trend that has been observed in about 15- 20% of cases. Miao, et al. [25] also linked lung injury and multiorgan damage to CRS and also noticed that patients requiring intensive critical care (ICC) showed higher concentrations of pro-inflammatory cytokines compared with those not requiring ICC.

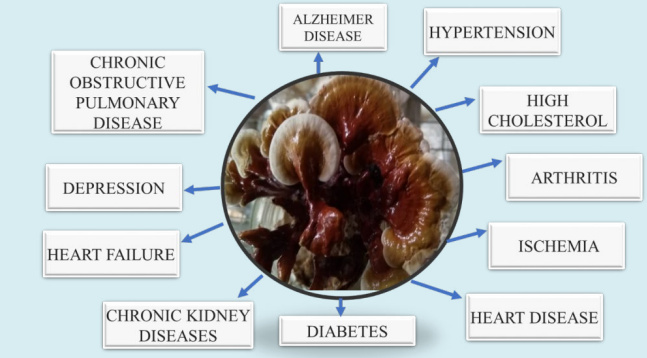

Figure 1: Diseases addressed by *Ganoderma* mushroom for tackling the common health problems of the elderly.

Elevated systemic IL-6 levels in patients with COVID-19 has been considered as a possible contributor to disease exacerbation. Elevated level is a relevant parameter in predicting most severe course of disease and the need for intensive care and also suggests a potential therapeutic approach [29]. Hence, targeting and controlling cytokines during the management of COVID-19 patients especially for severe cases, could improve survival rates and reduce mortality [25,26]. IL-6 antagonists such as tocilizumab, sarilumab and siltuximab are used to treat CRS [27]. Here, we consider the possibility of using extracts from *Ganoderma* mushroom to treat CRS, symptoms of severe COVID-19, rejuvenate organs and address other complications.

Ganoderma Treatment of Chronic Disease Conditions

Ganoderma lucidum (Fr.) mushroom, which is called Reishi in Japanese and Lingzhi in Chinese, has been used in traditional medicines in the treatment of several diseases in many Asian countries for centuries Dudhgaonkar, et al. & Meschino, et al. [30,31] and has become famous worldwide [32]. Many authors mentioned that the mushroom have been used in traditional medicinal for over 2000 years [33-35] and some have referred to the fungus as mushroom of immortality due to its use in the rejuvenation of health [36,37]. *Ganoderma* mushrooms are widely used as food, tea, dietary supplement and medicine in Oriental countries [38]. Diverse bioactivity activities have been demonstrated in studies of response in rodents and a few clinical trials (Table 1). The extracts of the mushroom are active against diseases including those affecting elderly persons including hypertension, high cholesterol, arthritis, ischemic heart disease, diabetes, chronic kidney diseases, heart failure, depression, chronic obstructive pulmonary disease and Alzheimer disease (Figure 1) and is suspected that the extract could treat many chronic problems such as, heart diseases, diabetes, and obesity. In addition, the mushroom extract is immunity boosting, antiaging, antiviral, and anti-inflammatory (Figure 2).

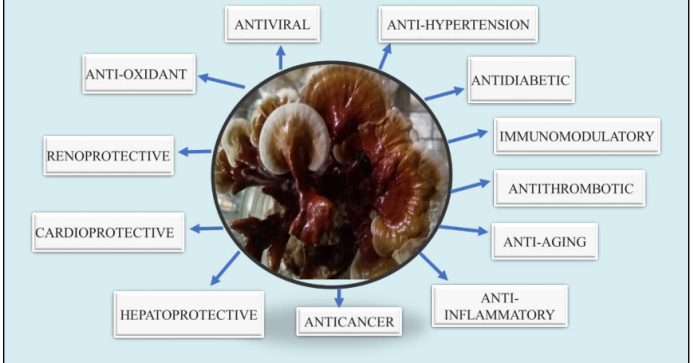

Figure 2: *Ganoderma* mushroom pharmacological effects for treating coronavirus risk factors

Ganoderma mushroom contain about 400 different bioactive substances including triterpenes, steroids, phenols, tannins, alkaloids, flavonoids, terpenoids, phenol, triterpenes, sterols nucleotides, glycoproteins, fatty acids, proteins/peptides and trace elements [36,39,40]. Of these, the pharmacological effects of the mushroom are attributable mostly to the presence of triterpenes and polysaccharides [32,41]. Specific polysaccharides that occur in the form of beta-D-glucans bound to amino acids (peptidoglycans) possess immune-modulating and anticancer properties [37].

Lu, et al. [10] isolated and identified 12 aromatic compounds, called lucidumins and lucidimine. Wong, et al. [42] reported several bioactive compounds in *Ganoderma* mushrooms that can play a role in the suppression of breast cancer including polysaccharides, ergosterol, ergosterol peroxide, and triterpenes such as Ganodermanontriol, Ganoderic acid and Ganoderiol A, et al. & Choi, et al. [43] identified 12 lanostane triterpenes from *G. lucidum* useful for suppressing inflammations. Over 120 triterpenoids have been identified from this mushroom species [40]. Ahmad, et al. [44] presented a review of the biologically active compounds of different medicinal mushrooms and their pharmacological activities.

The genus *Ganoderma* is comprised of species that possess several pharmacological properties that could be useful in the management of COVID-19 complications. Mushroom in general and *Ganoderma* in particular have the potential to reduce some chronic risk factors, complications and symptoms associated with COVID-19. Since, the development of CRS is correlated with the severity of COVID-19, the pro-and anti-inflammatory properties of the mushroom could therefore play an important role in tackling complications of the disease. Especially because there is not yet an available vaccine, the treatment of chronic risk factors may be an effective way of improving the outcome of covid-19 infections.

Anti-Inflammatory Effects and Tackling of Cytokine Storm Syndrome

Inflammation is part of a complex host immune defense mechanism triggered against invading microorganism, cancer or trauma. But the over production of some pro-inflammatory cytokines can lead to chronic diseases of inflammatory origin [45]. This is thought to be the mechanism for severe COVID-19. The anti-inflammatory effects of medicinal plants are thought to occur at different stages of the inflammation process and can generally inhibit the formation of a wide variety of cytokines by immune cells to either prevent the inflammatory reaction cascade from happening or running its full course [45].

Studies have attributed the anti-inflammatory activity of *Ganoderma* mushrooms to the presence of triterpenoids Choi, et al. & Wu, et al. [38,43] and polysaccharides [46]. Choi, et al. [43] identified 12 lanostane triterpenes from *G. lucidum* useful for suppressing inflammation. One of the triterpenes called butyl lucidenate D2 inhibited the production of TNF-α and IL-6, induce nitric oxide (NO) synthase and cyclooxygenase-2 expression, which could be useful in the tackling of cytokine storm syndrome associated with severe COVID-19.

Dudhgaonkar, et al. [30] evaluated the anti-inflammatory effects of the triterpene extract from *G. lucidum* in lipopolysaccharide (LPS)-stimulated macrophages and showed that *G. triterpenes* markedly suppressed the secretion of inflammatory cytokine including TNF-α and IL-6, and inflammatory mediator nitric oxide and prostaglandin E (2) from LPS- stimulated murine RAW264.7 cells. *Ganoderma triterpenes* also down-regulated the LPS-dependent expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) in RAW264.7 cells. Similarly, Wu, et al. [38] isolated 33 triterpenoids from *Ganoderma*, and of these, Compound 4 exhibited the most potent inhibition of nitric oxide production induced by LPS in RAW264.7 macrophage cells. The production of IL-6 and IL-1β, as well as the expression of iNOS, COX-2, and NF-κB were dose-dependent, in addition, phosphorylations of IκBα and IKKβ in LPS-induced macrophage cells were blocked. They concluded that this triterpenoid could be used as a potential anti-inflammatory candidate, which can be developed as value-added functional food for the prevention of inflammation. Again, these studies show that *Ganoderma* mushroom can be developed to prevent or counter cytokine storm experienced in severe COVID-19 cases.

Geng, et al. [47] investigated the anti-inflammatory activity of n-hexane, chloroform, ethyl acetate, and methanol extracts of *G. lucidum* and four other commercially available medicinal mushrooms, namely *Cephalosporium sinensis, Cordyceps mortierella, Hericium erinaceus* and *Armillaria mellea*. They found that the anti-inflammatory activities were due to the inhibition of the production of LPS-induced nitric oxide in murine macrophage-like cell line RAW264.7 cells, of which the chloroform extract from *G. lucidum* was the most effective inhibitor. Based on their results, it was suggested that the mushroom extracts could provide therapeutic and preventive approach to various inflammation-related diseases such as COVID-19. Many other scientists have identified and characterized various triterpenes that control nitric oxide and other pro-inflammatory substances. Su, et al. [48] isolated and identified 5 lanostane triterpenoids from the fruiting bodies of *G. lucidum*, and determined their anti-inflammatory activities by observing their inhibitory effects on nitric oxide production in RAW264.7 cells activated by a LPS. They found that Ganoluciduone B exhibited moderate inhibitory activity on nitric oxide production. Lu, et al. [10] isolated and identified 12 aromatic compounds, called lucidumins A-D (1-8) and lucidimine E (9-12), from *G. lucidum*, was characterized and exhibited significant anti-inflammatory activities against LPS-induced nitric oxide production in RAW264.7 macrophages.

Wei, et al. [46] evaluated therapeutic potential of *Ganoderma* polysaccharides to alleviate dextran sulfate sodium (DSS)-induced colitis in mice. They showed that the *Ganoderma* polysaccharide markedly suppressed the secretions of TNF-*α*, IL-1*β*, IL-6, IL-17A, and IL-4 and significantly affected populations of Th17 cells, B cells, NK cells, and NKT cells in the lamina propria lymphocytes. They concluded that *Ganoderma* polysaccharide prevented inflammation, maintained intestinal homeostasis, and regulated the intestinal immunological barrier functions in mice with DSS-induced colitis. Based on clinical, pharmacological trials and longstanding traditional use in folk medicine, Ahmadi Renani, et al. [44] recommended the use of medicinal plants in treatment of chronic inflammatory diseases.

Immune Boosting

Ganoderma lucidum is widely used and recommended by Asian physicians and naturopaths for its immune boosting effects [49]. *Ganoderma* polysaccharides and triterpenoids exert positive effects on the immune system in several ways, which could be relevant in the management of COVID-19 complications. Murray, et al. [11] reported that the beta-glucans from *Ganoderma* can activate white blood cells by binding to receptors on the outer membranes of neutrophils, macrophages, natural killer cells, and cytotoxic T cells, which could trigger a chain of reactions leading to increased immune activity. The anti-inflammatory property of the mushroom extract can boost the immune system. Murray, et al. [11] reported that *Ganoderma* can enhance innate immunity by increasing the ability of the neutrophils and macrophages to bind and destroy invading microbes, cancer cells, and other foreign bodies, which stimulates the production of cytokines such as IL-1, 1L-2 and lymphokines.

In their review, Suwannarach, et al. [13] identified several bioactive substances from *Ganoderma*, which exhibited various immunological effects including immunomodulatory proteins (regulates cytokines such IL-2, IL-3, IL-4, IFN- γ, TNF- α), polysaccharides such as α & β-glucans (inducing synthesis of IFN-γ) and Polysaccharide G (activates macrophages & T lymphocytes), and various triterpenoids such as exo-biopolymers (activates NK cell) and Ganolucidoid A & B (exhibits NO production and anti-inflammatory activities).

In a mouse model, Cai, et al. [50] demonstrated the anti-inflammatory effects of *Ganoderma*-based supplements for the treatment of systemic lupus erythematosus, which is an autoimmune disorder characterized by antibodies attacking the body's own tissues and organs, which can affect the joints, skin, kidneys, blood cells, brain, heart and lungs causing multisystem inflammation similar to COVID-19. Given that the main symptoms of systemic lupus erythematosus include

inflammation of the joints, joint pain, edema and palpitations of the heart, it was envisaged that the supplement could be used as potential treatments for this autoimmune disease and to possibly address some age-related and COVID-19 complications [50]. Their result show that *Ganoderma*-based supplement resulted in significant increases in the percentages of $CD4^+CD25^+Foxp3^+$ Treg and $IL\text{-}10^+$ Breg cells, coupled with a reduction in the plasma concentrations of several inflammatory cytokines including IL-21, IL-10 and IL-17A, which therefore have the capacity to mitigate the cytokine storm syndrome associated with severe COVID-19.

The immunomodulatory effects of the mushroom are phenomenal. The mushroom is able to either boost the immune system when it is weakened by poor nutrition, lifestyle (smoking, alcohol), HIV infection or reduce immune system activity when the system is overstimulated by the release of pro-inflammatory cytokines from coronavirus infection. Bulam, et al. [12] listed the immunomodulatory effect including activation of cytotoxic T or B lymphocytes, macrophages, natural killer cells, dendritic cells, and other immune cells along with their secretory products like TNF-α, reactive nitrogen, oxygen intermediates, and interleukins particularly IL-1, IL-2, IL-3, IL-6.

The combined effects of the anti-inflammatory and immune boosting effects of *Ganoderma* extracts could prevent or address the multiorgan damaging effects of the CRS occasioned by coronavirus infection. Thus, potentially leading to multiorgan protection including the lungs, heart, kidney, liver, heart and brain [51]. Subjected 14 patients with persistent proteinuria to *G. lucidum* treatment and found that the mushroom extract suppressed endothelial cell cytotoxicity, restored immunocirculatory balance and successfully suppressed proteinuria in all the patients. Hence, extracts from this mushroom have the potential of repairing damaged kidney associated with severe COVID-19.

Cardioprotective and Antihypertension

Ganoderma lucidum has been used extensively in oriental countries for centuries, and is becoming increasingly popular in western countries as a complementary medicine for cardiovascular health [35]. *Ganoderma lucidum* can possibly have beneficial effects on blood pressure, plasma lipids and glucose levels [52].

Ganoderic acids, which are a triterpene compound lower blood pressure, reduce platelet stickiness and could decrease LDL-cholesterol [37], all of which will have a positive effect on the cardiovascular system. Tran, et al. [33] used Ganoderma's own proteases to hydrolyze its protein and obtained auto-digested extract, which was administered to spontaneous hypertensive rats (SHRs) in order to determine its potential as a hypotensive medication. They found out that four out the eleven peptides identified, showed potent inhibition against Angiotensin-Converting Enzyme (ACE) and concluded that the mushroom could be a good source of hypotensive substances for antihypertensive medication. This inhibitory effect could address the effect of coronavirus on ACE2 and blood pressure.

Wen, et al. [53] developed and tested an antiasthma herbal medicine intervention, which consists of the extract of *G. lucidum*, and two herbs viz. Ku-Shen (Radix *Sophora flavescentis*), and Gan-Cao (Radix *Glycyrrhiza uralensis*) and found that the herbal mixture was safe and effective in the treatment of asthma, in contrast to prednisone, it did not have adverse effect on adrenal function, and had a beneficial effect on T(H)1 and T(H)2 cytokine balance.

Anti-Coagulant/Antithrombotic

Blood coagulation plays major roles in the incidences of cardiovascular problems including ischemic stroke, acute myocardial infarction, unstable angina, pulmonary embolism, and deep vein thrombosis, which are major causes of death globally [34]. Some of these diseases are also associated with severe COVID-19. Elkhateeb, et al. [34] listed some of the profound cardioprotective effect of *Ganoderma* extracts, which includes the prevention of atherosclerosis and lowering of blood cholesterol, triglyceride level and blood pressure.

Elkhateeb, et al. [34] reviewed the anticoagulant capacities of certain species of mushrooms including *Ganoderma* as promising sources of anticoagulant compounds. They found that the mushroom shows a great usefulness for the treatment of various cardiovascular disorders. They reported that *G. lucidum* produces metalloprotease that exhibits both antithrombotic and fibrinolytic activities, which have been demonstrated in human plasma. Choi, et al. [54] isolated and characterized a metalloprotease from the mycelium of *Ganoderma lucidum* that displayed an anticoagulant activity in human plasma. This protease hydrolyzed A and B chains of human fibrinogen, but did not cleave thrombin, albumin, hemoglobin and immunoglobulin under the same condition. They observed that *Ganoderma* protease behaved as a competitive inhibitor of thrombin-catalyzed fibrin formation and therefore have the potential to overcome the blood clotting associated with severe COVID-19.

Antioxidants

Ganoderma lucidum has antioxidant effects [52]. Their polysaccharides have a protective effect against free radicals and reduce cell damage caused by mutagens [55]. Sargowo, et al. [56] demonstrated that *G. lucidum* polysaccharide

peptide is a potent antioxidant against pathogenesis of atherosclerosis in angina and high-risk patients. This effect could be relevant in the management of blood system complications in severe COVID-19 cases. In a randomized, double-blind placebo-control clinical trial, Chiu, et al. [57] demonstrated that triterpenoids and polysaccharide peptides from *G. lucidum* exhibited antioxidation, antiaging and hepatoprotective activity in healthy volunteers, which can effectively curb oxidative stress.

Lee, et al. [58] investigated the cytoprotective effect of ethanol extract of *G. lucidum* against oxidative stress, and demonstrated inhibition of hydrogen peroxide-induced generation of reactive oxygen species and DNA damage. They also demonstrated that the extract effectively induced the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), as well as heme oxygenase-1 (HO-1). They concluded that the ethanol extract of *Ganoderma* augments the cellular anti-oxidant defense capacity through activation of Nrf2/HO-1, thereby protecting C2C12 myoblasts from hydrogen peroxide-induced oxidative cytotoxicity.

In rats, Deepalakshmi, et al. [59] evaluated the antioxidant potential of the ethanolic extract of the fruiting bodies of *G. lucidum* and found that the mushroom exhibited antioxidant and radical scavenging activities both in vitro and in vivo. Based on their study, they recommended that *G. lucidum* extract could be a potential source of natural antioxidants.

Oluba, et al. [60] demonstrated that the crude aqueous extract of *G. lucidum* fruiting bodies possesses potent antioxidant activity that protects hemoglobin against *Plasmodium*-induced oxidative damage, which seemed to justify the use of the plant in traditional medicine as antioxidant and anti-inflammatory agent.

Antiviral and Antimicrobial Activities

One of the promising activities of *Ganoderma* extract is its antiviral and antimicrobial properties, which could be relevant in the management of coronavirus and opportunistic infections. Antiviral properties of the mushroom have been demonstrated against dengue virus, influenza virus, HIV, and enterovirus.

Ellan, et al. [61] demonstrated that the various extracts (water, ethanol, hexane and ethyl acetate) of mushrooms including *Lignosus rhinocerotis*, *Pleurotus giganteus*, *Hericium erinaceus, Schizophyllum commune* and *G. lucidium* exhibited anti-dengue virus serotype 2 (DENV-2) activities in-vitro. From *in silico* analysis of twenty-two triterpenoids of *G. lucidum*, Bharadwaj, et al. [9] found four triterpenoids that possess viral protease inhibitors viz. Ganodermanontriol, Lucidumol A, Ganoderic acid C2 and Ganosporeric acid A, of which Ganodermanontriol exhibited antiviral activity against dengue virus.

Zhang, et al. [62] demonstrated the antiviral activities of two *G. lucidum* triterpenoids, Lanosta-7,9(11),24-trien-3-one,15;26-dihydroxy and Ganoderic acid Y, against Enterovirus 71 infection. Their results show that these triterpenoids work through interaction with the viral particles to block the adsorption of virus to the cells. Their study shows that the triterpenoids can bind viral capsid protein at a hydrophobic moiety, which could block uncoating, entering and ultimately replication of the virus.

Eo, et al. [63] isolated two water soluble substances and eight methanol soluble substances from the carpophores of *G. lucidum* that displayed antiviral activity against five strains of pathogenic viruses namely herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), influenza A virus (Flu A) and vesicular stomatitis virus (VSV) Indiana and New Jersey strains in vitro. Based on their study, they recommended the development of antiviral agents from the mushroom.

Reports on the specific mechanisms of actions of bioactive compounds against viruses are not common in literature. Riikka, et al. [64] reviewed the diversity, mechanisms and potential applications of several antiviral agents obtained from fungi. However, there is the possibility that the bioactive substances from mushrooms act at one or more of the different stages of virus life cycle. The two antiviral mechanisms exhibited by *Ganoderma* act to prevent virus entry into the cell and inhibition of virus replication. Zhang, et al. [65] demonstrated that *Ganoderma* triterpenoids particularly ganoderic acid significantly inhibit the replication of the viral RNA of EV71 through binding to the viral capsid protein at a hydrophobic site that prevented EV71 from uncoating. Other studies have shown that *Ganoderma* triterpenoids can also be inhibitory to virus protein synthesis. For instance, Sato, et al. [66] isolated characterized and demonstrated that *Ganoderma* triterpenoids particularly ganoderic acid inhibited human immunodeficiency virus-1 protease, which will affect the replication of the virus. Suwannarach, et al. [13] reviewed literatures on fungi as producers of protease inhibitors and bioactive compounds that can offer immunomodulatory activities as potential therapeutic agents of coronaviruses. El-Mekkawy, et al. [67] and Min et al [68] isolated and characterized some triterpenes called ganoderic acids from *G. lucidum* that were inhibitory to HIV-1. Protease inhibitors play an important role in viral replication by selectively binding to viral proteases and blocking proteolytic cleavage of the protein precursors that are necessary for the production of infectious viral particles [13]. The inhibition of viral protease is an important target in

antiviral drug discovery and development. Protease inhibitor drugs, especially HIV-1 protease inhibitors, are potentially available for the treatment of coronaviruses [13].

Kumar, et al. [69] demonstrated the antifungal activity of ethanol and methanol extracts of *G. lucidum* against five fungal species, namely, *Candida albicans*, *Aspergillus niger*, *A. flavus*, *A. fumigatus* and *Cryptococcus neoformans*. The crude n-hexane:diethyl ether, chloroform:acetone and methanol extracts of four species of *Ganoderma* (*G. colossum, G. resinaceum, G. lucidum* and *G. boninense*), exhibited antimicrobial activity against *Pseudomonas syringae* and *Bacillus subtilis*, but not against *Cladosporium herbarum* [70].

The antibacterial activities of water, acetone, ethanol and methanol extracts of *G. lucidum* were demonstrated against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [71]. Quereshi, et al. [72] demonstrated the water, acetone, ethanol and methanol extracts of *G. lucidum* exhibited antimicrobial activity against six species of bacteria: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Bacillus subtilis, Salmonella typhi* and *Pseudomonas aeruginosa*.

Compounds having unique antiviral and antimicrobial properties could be prepared from medicinal mushroom mycelium, spores and fruiting bodies. In many cases, the bioactive compound is chemically modified to increase its antiviral and antimicrobial potency [64]. In 2014, Paul Staments secured a patent (US 8,765,138 B2) for mushroom blends prepared from the mycelium of some medicinal mushrooms including *Ganoderma, Fomitopsis, Piptoporus, Inonotus, Trametes* and *Pleurotus* for their unique antiviral and antibacterial properties. The blend was patented for the prevention and treatment of viruses including Poxyiridae and Orthopox viruses, flu viruses including bird flu (H5N1), SARS and Hepatitis C (HCV), as well as bacterial infections from *Mycobacterium tuberculosis, Staphylococcus aureus* and *Escherichia coli.*

Antidiabetic Properties

Diabetes has emerged as one of the risk factors leading to fatality in coronavirus infections. Among the many biologically active constituents of *Ganoderma*, polysaccharides, proteoglycans, proteins, and triterpenoids have hypoglycemic effects [73,74]. Extracts of *G. lucidum* have long been recognized as an alternative adjuvant treatment for diabetes [74].

Possible mechanisms of the anti-diabetic effect of *Ganoderma* have been reported. Ma, et al. [74] showed that the polysaccharides from the mushroom have hypoglycemic activity by increasing plasma insulin levels and decreasing plasma sugar levels in mice. Liu, et al. [73] reviewed the mechanism of the antidiabetic effect of *Ganoderma* and found that it is mediated by protecting the pancreas islet, inhibiting protein tyrosine phosphatase 1B (PTP1B), decreasing lymphocyte infiltration and increasing the antibody detection of insulin in diabetic mice.

Studies on the antidiabetic potency and mechanism of a proteoglycan extract, from the fruiting bodies of *G. lucidum* using streptozotocin-induced type 2 diabetic mellitus rats and showed that the hypoglycemic effects of the extract are caused by inhibition of the PTP1B expression and activity, hence, resulting in the regulation of the tyrosine phosphorylation level of the IR 13-subunit [75,76]. Other authors have also reported that *Ganoderma* proteoglycan can inhibit *in vitro* the PTP1B, a therapeutic target in diabetes [74]. Seto, et al. [77] evaluated the pharmacological effects of the water-extract of *G. lucidum* at 0.003, 0.03 and 0.3g/kg, 4-week oral gavage consumption using the lean (+db/+m) and the obese/diabetic (+db/+db) mice. They demonstrated that consumption of the mushroom can provide beneficial effects in treating type 2 diabetes mellitus by lowering the serum glucose levels through the suppression of the hepatic PEPCK gene expression. *Ganoderma* triterpenoids have inhibitory activity on aldose reductase and α-glucosidase that can suppress postprandial hyperglycemia [74]. Another protein referred to as Ling Zhi-8 extracted from *G. lucidum* significantly decreased lymphocyte infiltration and increased the antibody detection of insulin in diabetic mice [74].

Pan, et al. [78] demonstrated the antidiabetic effect of *Ganoderma* extract in mice model by enhancing insulin secretion and decreasing hepatic glucose output along with increase of adipose and skeletal muscle glucose disposal in the late stage of diabetes. The mushroom extracts were beneficial against oxidative stress, thereby being helpful in preventing diabetic complications. Wang, et al. [79] demonstrated that the consumption of *Ganoderma* spore powder could provide beneficial effect in terms of lowering the blood glucose levels by promoting glycogen synthesis, inhibiting gluconeogenesis and improvement of blood lipid compositions through the regulation of cholesterol homeostasis in type 2 diabetic rats. Milena, et al. demonstrated the antioxidant and antidiabetic activity of ethanolic and water extracts of *Ganoderma*. They also demonstrated protective effects on pancreatic tissue.

Few clinical studies have been carried out on the use of *Ganoderma* in the management of diabetic patients. In a 12-week randomised, double-blind, cross-over study of 26 patients treated with *Ganoderma* mushroom, Chu, et al. [52] demonstrated that the mushroom has mild antidiabetic effects that could potentially improve the dyslipidaemia of diabetes.

A high sugar and fat diet affect multiple systems and organs [80], just as coronavirus affects many organs of the body. Hence, proper management of diabetes could reduce the risk associated with coronavirus infection. *Ganoderma lucidum* have been traditionally used for the treatment of diabetes in Chinese medicine for centuries [76,81,82]. Wińska, et al. [41] suggested the use of natural substances especially from mushrooms as a promising alternative to conventional therapy of diabetes mellitus. Extracts from *G. lucidum* have been reported to be an alternative adjuvant treatment for diabetes [73]. On the other hand, after extensive literature survey [35], could not find evidence from a small number of randomised controlled trials to support the use of *G. lucidum* for the treatment of cardiovascular risk factors in people with type 2 diabetes mellitus.

Anti-Obesity

Obesity has emerged as one of the risk factors for COVID-19. The use of *Ganoderma* for the treatment of obesity has been demonstrated, which could possibly minimize the severity of COVID-19. Obesity is a worldwide disease associated with low-grade chronic inflammation [81,82].

Amin, et al. [83] investigated the effects of *G. lucidum* on body weight in an obese animal model induced by the administration of a high-fat diet (HFD). They found that 5% powder of *G. lucidum* administration significantly reduced body weight in obese rats and therefore suggested that the mushroom may serve as a new potential natural product for the treatment of obesity.

Recent evidence shows that intestinal dysbiosis contributes to obesity and its comorbidities [81,82] showed that the water extract of *G. lucidum* mycelium reduces body weight, inflammation and insulin resistance in mice fed HFD. Their data indicated that the mushroom reverses HFD-induced gut dysbiosis, maintains intestinal barrier integrity and reduces metabolic endotoxemia. They suggested that especially the polysaccharides of *G. lucidum* can be used as prebiotic agents to prevent gut dysbiosis and obesity-related metabolic disorders in obese individuals.

Guo, et al. [81] examined the effects of water extract of *G. lucidum* spores on gut microbiota, obesity and insulin resistance. The mushroom extracts were administered at different concentrations (100 mg/kg and 300 mg/kg) to HFD-fed mice and low-density lipoprotein (LDL)-fed mice for 12 weeks. The mushroom extract reversed HFD-induced gut dysbiosis and improved the intestinal barrier functions in the HFD-fed mice. They therefore concluded that the mushroom extract can be used as prebiotic agents to prevent obesity-related metabolic disorders.

In an obese mouse model, Diling, et al. [80] showed that alcohol extracts of the *G. lucidum* fruit body could reduce body weight; change the serum levels of lipid; ameliorate the damage to the gut microbiota, colon, liver, brain and other organs induced by the high sugar and fat diet; and activate the leptin regulatory pathways in the hypothalamus to improve metabolism. They concluded that the administration of the alcohol extracts of *G. lucidum* fruit body has beneficial effects on the microbiome-gut-liver and microbiome-gut-brain axes, and activates leptin-mediated signaling to improve metabolic regulation.

Anticancer

Ganoderma has been commonly suggested in Asia as a potential candidate for prevention and treatment of different forms of cancer. The popularity of taking *G. lucidum* as an alternative therapy is increasing among cancer patients [49]. Besides, cancer has also been identified as a possible risk factor for COVID-19. Because of the action of *Ganoderma* in control of pro-inflammatory cytokines, these mushrooms could play a major role in the management of various forms of cancers and provide an alternative treatment option for cancer patient suffering from COVID-19.

Ganoderma has been cited several times for its activities against breast cancers [59,84,] prostate cancer [85] and other forms of cancer [86,87]. Yue, et al. [84] showed that the aqueous extracts (12.5-400 microg/mL) of different parts of the fruiting body (whole fruiting body, pileus, and stipe) of three *Ganoderma* species (*G. lucidum, G. sinense* and *G. tsugae*) displayed antitumor effects in human breast cancer cells and immunomodulatory activities in mouse splenic lymphocytes in vitro. Martinez-Montemayor, et al. [86] isolated and characterized seven bioactive substances including ergosterol from *G. lucidum* extract that demonstrates significant selective efficacy against triple negative and inflammatory breast cancers and other human cancer cell types. Wong, et al. [87] reported several bioactive compounds in *Ganoderma* that played various roles in the suppression of breast cancer including polysaccharides, ergosterol, ergosterol peroxide, Ganodermanontriol, Ganoderic acid and Ganoderiol A. They reported several mechanisms leading to suppression of cancer by *Ganoderma* including antiproliferative and apoptosis-inducing activity, suppression of the migration and growth of cancer cells, reduced pulmonary metastases and attenuated expression of invasiveness-associated genes.

The anti-inflammatory properties of *Ganoderma* play a major role in the anticancer effects of the mushroom. Evidence from in vitro and in vivo studies has demonstrated that *Ganoderma* polysaccharides possess potential anticancer

activity through immunomodulatory, anti-proliferative, pro-apoptotic, anti-metastatic and anti-angiogenic effects [88]. Guggenheim, et al. [89] reviewed the immunological roles of 5 major mushrooms in cancer therapy including *G. lucidum*, *Agaricus blazei*, *Cordyceps sinensis*, *Grifola frondosa*, and *Trametes versicolor* and focused on how the mushrooms modify cytokines to suppress cancer.

Loperena-Alvarez, et al. [90] reported that IL-6 enhances while *Ganoderma* reduces inflammatory breast cancer progression via modulation of the JAK-2/STAT-3 pathway both in vitro and in vivo in mice models. Their results suggest that the mushroom has anti-inflammatory and immunomodulatory roles, demonstrated by its ability to reduce the phosphorylation of the IL-6/JAK-2/STAT-3 pathway. Bulam, et al. [12] reported that among the anticancer and antimetastatic activities of *Ganoderma*, NF-κB and MAPK, which are the most studied major pathways for cancers, were shown to be activated and the released cytokines subsequently inhibit the growth of tumor cells. Jiang, et al. [91] demonstrated that *G. lucidum* suppresses the invasive behavior of breast cancer cells by inhibiting the transcription factor NF-kappa B. They show that *G. lucidum* inhibits proliferation of breast cancer MDA-MB-231 cells by downregulating Akt/NF-kappaB signaling. They also showed that *G. lucidum* suppresses phosphorylation of Akt on Ser473 and downregulates the expression of Akt, which results in the inhibition of NF-kappaB activity in MDA-MB-231 cells and concluded that the mushroom has potential therapeutic use for the treatment of breast cancer. Barbieri, et al. [92] demonstrated how *G. lucidum* extracts significantly inhibited the release of IL-6, IL-8, MMP-2 and MMP-9 in cancer cells under pro-inflammatory conditions. They also demonstrated a significantly decrease in the viability of cancer cells in a time- and concentration-dependent manner, with abilities to reduce cell migration over time, which correlated with a lower release of matrix metalloproteases. They concluded that their results indicated the possibility of using *G. lucidum* extract for the therapeutic management of melanoma and human breast cancer. The findings from this study are relevant in the management of cytokines secreted by cancer cells, which could possibly tackle cytokine storm among cancer patients infected with severe COVID-19.

Studies have also shown that *Ganoderma* modulate many components of the immune system such as the antigen-presenting cells, NK cells, T and B lymphocytes (Lin and Zhang, 2004). The polysaccharides and triterpene of *Ganoderma* exhibit significant anti-tumor effect through its immunoenhancing activity [93]. Laboratory data show that triterpenoids exhibit a broad spectrum of anticancer properties, including anti-proliferative, anti-metastatic and anti-angiogenic activities [94]. Joseph, et al. [95] isolated polysaccharides from *G. lucidum* and investigated their antitumor and anti-inflammatory activities in vivo. They found that antitumor activity was exhibited by *Ganoderma* polysaccharides at 100 mg/kg body mass and showed 80.8 and 77.6% reduction in tumor volume and mass respectively, when administered 24 h after tumor implantation. Wu, et al. [85] demonstrated that *Ganoderma* polysaccharides significantly inhibited human prostate cancer cell viability in a time- and dose-dependent manner, which may serve important role in cancer prevention. They showed that *Ganoderma* polysaccharides induced late apoptosis, which was accompanied by poly (ADP-ribose) polymerase 1 (PARP) cleavage, and inhibition of pro-caspase-3, -6 and -9 protein expression. They further demonstrated that *Ganoderma* polysaccharides inhibited the phosphorylation of protein kinase B and mitogen-activated protein kinase/extracellular signal-regulated kinase signaling in prostate cancer cells.

Based on the analysis of more than 270 patents and literature, Boh, et al. [96] presented the possible mechanisms of the anticancer activity of *G. lucidum* in five groups: (1) activation/modulation of the immune response of the host, (2) direct cytotoxicity to cancer cells, (3) inhibition of tumor-induced angiogenesis, (4) inhibition of cancer cells proliferation and invasive metastasis behavior, and (5) carcinogens deactivation with protection of cells. Wu, et al. [94] listed the anticancer activities of *Ganoderma* triterpenoids to include cell cycle arrest, induction of apoptosis and autophagy, and suppression of metastasis and angiogenesis.

Ganoderma provides options for the management of cancers including as a prophylactic agent to boost immunity, therapeutic agent for patients with compromised immunity or as a means of reducing the side effects associated with chemotherapy and/or radiotherapy and possibly counters the inflammatory processes in cancer patients [31].

Zhao, et al. [97] revealed that *Ganoderma* extracts can prolong the survival rate of cancer patients while also improving the patient's quality of life. Clinical studies have shown beneficial effects of *G. lucidum* as an alternative adjuvant therapy in cancer patients without obvious toxicity [88], unlike most anticancer therapies. *Ganoderma* is listed China's pharmacopoeia, primarily for its ability to modulate immune function and for its anticancer and hepatoprotective properties [31].

On the other hand, Jin, et al. [49] via extensive search of databases, evaluated the clinical effects of *G. lucidum* on long-term survival, tumor response, host immune functions and quality of life in cancer patients, but did not find sufficient evidence to justify the use of the mushroom as a first-line

treatment for cancer. They are also uncertain whether the mushroom help to prolong long-term cancer survival. They suggested that the mushroom could be administered as an alternative adjunct to conventional treatment in consideration of its potential of enhancing tumor response and stimulating host immunity.

Neuroprotective

SARS-CoV-2 attack neuronal tissues and causes brain damage and possibly compounds sicknesses among the elderly. Traumatic injury to the spinal cord results in the delayed dysfunction and neuronal death [98]. Several properties of *Ganoderma* make them useful therapeutic agents for neuroprotection including anti-inflammatory, immune boosting and antioxidant. *Ganoderma lucidum* has shown potential neuroprotective effects in clinical trials [66]. Zhang, et al. [65] showed that *G. lucidum* have both anti-oxidative and anti-inflammatory effects, and decreases both the infarct area and neuronal apoptosis of the ischemic cortex. Authors have identified various bioactive substances of *Ganoderma* that confers neuroprotective effects. Lu, et al. [10] isolated and identified an aromatic compound called lucidimine that showed remarkable neuroprotection with EC_{50} value of 2.49 ± 0.12 μM. Sun, et al. [99] show that the polysaccharides from *G. lucidum* have protective effects against apoptosis in neurons exposed to ischemia/ reperfusion injury. Because of their effects on inflammation, it is also possible that triterpenes could play some roles in neuroprotection.

Oxidative stress, which induced brain damage have been implicated in many neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and stroke [99]. Impaired mitochondrial function, generation of reactive oxygen species (ROS), and lipid peroxidation occur soon after traumatic spinal cord injury [98]. Hence, neuroprotection targeting mitochondrial dysfunction has been proposed as an important therapeutic strategy for Parkinson's disease and *G. lucidum* has emerged as a potent agent that protects neurons from oxidative stress [100]. Zhou, et al. [101] investigated and reported the pre-administration of *G lucidum* spores in alleviating oxidative stress and mitochondrial dysfunction, conferring neuroprotection from apoptosis, and improvement in cognitive dysfunction in rats.

Evidence suggests that neuroinflammation participates in the pathogenesis of Parkinson's disease [66]. Sun, et al. [99] investigated the underlying mechanisms of the effects of G. *lucidum* polysaccharides against oxidative stress-induced neuronal apoptosis. Their findings suggest that *G. lucidum* polysaccharides regulate expression of apoptosis-associated proteins, inhibit oxidative stress-induced neuronal apoptosis that had significant neuroprotective effects. Ren, et al. [100] established the mechanisms underlying *Ganoderma*-induced neuroprotection in mice and provided evidence that extracts from the mushroom ameliorates Parkinson's disease pathology via regulating mitochondrial function, autophagy, and apoptosis, involved in the activation of both the AMPK/ mTOR and PINK1/Parkin signaling pathway. Ekinci, et al. [98] study suggests that *G. lucidum* reduces spinal cord injury -induced oxidative stress and exerts neuroprotection by inhibiting lipid peroxidation and glutathione depletion.

Zhang, et al. [66] investigated the potential neuroprotective effect of *Ganoderma* and its possible underlying mechanism. They found that the mushroom extracts significantly prevent the production of microglia-derived proinflammatory and cytotoxic factors including nitric oxide, TNF-α and IL-1β in a dose-dependent manner and down-regulated the TNF-α and IL-1β expressions on mRNA level. They concluded that *Ganoderma* can be a promising agent for the treatment of Parkinson's disease through anti-inflammation. Zhang, et al. [65] investigated the protective effects of pretreatment with *G. lucidum* via intragastric administration in cerebral ischemia/reperfusion injury in rats and showed that pretreatment with *G. lucidum* for 3-7 days reduced neuronal loss and levels of TNF-α and IL-8 in the hippocampus, decreased the content of malondialdehyde and increased the activity of superoxide dismutase in the hippocampus and serum. These results suggest that pretreatment with *G. lucidum* was protective against cerebral ischemia/ reperfusion injury through its antioxidative and anti-inflammatory effects.

Anti-Aging

Aging is related to compromised or weak immunity, oxidative stress, and free radical product [102]. Alzheimer's disease is the most common cause of dementia among elderly persons [103]. Age-related changes in methylation are involved in the occurrence and development of tumors, autoimmune disease, and nervous system disorders, including Alzheimer's disease in elderly individuals; hence, modulation of these methylation changes may be an effective strategy to delay the progression of Alzheimer's disease pathology [104].

Wang, et al. [105] reviewed literature on the potential mechanisms of antiaging effect of *G. lucidum*, which was linked to the presence of bioactive substances that exhibits antioxidant, immunomodulation, anti-neurodegeneration activities. In a rat model, Lai G, et al. [104] isolated and characterized ganoderic acid and lucidone a obtained from the alcohol extracts of *G. lucidum*, which were involved

in delaying Alzheimer's disease progression. Weng, et al. [106] isolated and characterized two novel ergosterol derivatives, ganodermasides A and B, from the methanol extract of spores of *G. lucidum*, which were showed to extend the replicative life span of *Saccharomyces cerevisiae* strain K6001. The antiaging activity of these substances on yeast was comparable to resveratrol (an antioxidant that protects the body against tissue damage). In a mouse model, Yu, et al. [103] demonstrated that *G. lucidum* triterpenoids improve cognitive impairment, alleviate neuronal damage, and inhibit apoptosis in the hippocampus tissues and cells in Alzheimer's disease through inhibiting the ROCK signaling pathway, thus promoting longevity and could potentially reduce the age-related risk factor of COVID-19. Gurovic, et al. [107] demonstrated that extracts from *G. lucidum* displayed weak DNA damaging potential and since DNA injury promotes aging and cancer, the mushroom is not destructive to the body. Extracts from *Ganoderma* are generally regarded as safe (GRAS).

Multiple uses of Ganoderma

Because coronavirus infection results in multiple organ damage, hence, it is considered that a treatment with multiple activities could be useful for the management of the disease and its complications. Medicinal mushrooms have been essential components of traditional Chinese herbal medicines for thousands of years, and they protect against diverse health-related conditions [47].

Ganoderma lucidum contains over 400 different bioactive substances including polysaccharides, triterpenoids, proteins, enzymes, steroids, sterols, nucleotides, fatty acids, vitamins and minerals which have been proved to have several therapeutical properties to control various diseases [36,44]. The pharmacological effects of *Ganoderma* that have been established are many including immunomodulation, anti-atherosclerotic, anti-inflammatory, analgesic, anti-bronchitis, antiasthma, chemo-preventive, antitumor, chemo- and radio-protective i.e. anticancer drug toxicity prevention, sleep promoting, antibacterial, antiviral, antifungal, hypolipidemic, antifibrotic, antinociceptive, antiarthritic, anti-osteoporotic, hepatoprotective, antidiabetic, antiandrogenic, antiangiogenic, antiherpetic, antioxidative and free radical-scavenging, antiaging, hypoglycemic, anti-hypertensive, hypocholesterolemic and anti-histaminic effects, complement inhibition, estrogenic activity and anti-ulcer properties [36,37,44,55]. As a result, *Ganoderma* has now become recognized as an alternative adjuvant in the treatment of leukemia, carcinoma, hepatitis and diabetes and the mushroom has increasingly playing a significant role in various other therapeutic applications [36]. Because of the numerous therapeutic applications of the mushrooms, it is considered that the mushroom could be used for multiorgan protection to counter the ravaging SARS-CoV-2 pandemic.

Although, *G. lucidum* has been used for thousands of years as medicine, studies revealing its effect on lifespan extension are beginning to emerge [105]. The mushroom is widely used as a tonic for the promotion of longevity and health [74,105] and it is often referred to as the 'mushroom of immortality' [91]. The findings of Gurovic, et al. (2018) [107] substantiated the traditional use of *Ganoderma* to prolong life. Pan, et al. [102] reported that *Ganoderma* exert life span elongation activities by inhibiting ROS production, lipid peroxidation, and advanced oxidation protein products; increasing production of mitochondrial electron transport complexes, and radical scavenger activities; and having immunomodulatory and antioxidant activity and ferric reducing antioxidant power. The presence of polysaccharides [105] and/or triterpenoids [103] has been linked to the health promoting and longevity activity of *G. lucidum*. Hence, they have been used for centuries in Asian countries to treat various diseases and to promote health and longevity [88].

Conclusion

The novel coronavirus (SARS-CoV-2), which emerged in China in December 2019 has caused a pandemic (COVID-19) that have disrupted social and economic activities throughout the world. The disease has manifested with multiorgan damage and has disrupted many systems in the body including pulmonary, cardiovascular, hepatic, renal and neuronal causing nearly one million deaths worldwide as of the end of August 2020. This has promoted the scientific community to intensify research in the development of drugs, vaccines and antibodies to counter the virus. Thus far, there has been no licensed drug, vaccine or antibodies [108-114]. Hence, the disease is being managed through using barriers to prevent the spread of the virus (physical distancing, use of face masks, movement restrictions), repurposing of existing drugs while preclinical and clinical trials are ongoing for convalescent plasma therapy, antibodies cocktails, antiviral drugs and vaccines. Since, no approved or licensed products exists for the management of the disease and the dire urgency to save life, all options should be considered. Meanwhile, Ganoderma is known to be effective as antiviral, anti-inflammatory, antioxidant and immune modulatory properties here, we proposed the use of *Ganoderma* mushroom due to its several bioactive properties that could be relevant in the management of COVID-19, pre-existing conditions and complications including antithrombotic, anti-ischemic and multiorgan protection and repairs.

Disease	Effects of *Ganoderma* Extract	References
Anti-Inflammatory	Triterpenes from *Ganoderma* demonstrated anti-inflammatory, heme oxygenase (HO)-1 inducing effects, and suppressed lipopolysaccharide (LPS)-induced nitric oxide (NO) production.	Choi S, et al. [43]
Anti-Inflammatory	In mice model, *Ganoderma*-based supplement resulted in significant increases in the percentages of $CD4^+CD25^+Foxp3^+$ Treg and $IL\text{-}10^+$ Breg cells, coupled with a reduction in the plasma concentrations of several inflammatory cytokines including IL-21, IL-10 and IL-17A	Cai Z, et al. [50]
Anti-Inflammatory	They isolated 33 triterpenoids from *Ganoderma*, of which one of them (Compound 4) exhibited the most potent inhibition on NO production induced by LPS in RAW264.7 macrophage cells.	Wu Y, et al. [38]
Anti-Inflammatory	isolated and identified 5 lanostane triterpenoids from the fruiting bodies of G. lucidum that exhibited anti-inflammatory activities	Su HG, et al. [48]
Anti-Inflammatory	isolated and identified 12 aromatic compounds, called lucidumins A-D (1-8) and lucidimine E (9-12), from *Ganoderma lucidum* that was characterized and exhibited significant anti-inflammatory activities against LPS-induced NO production in RAW264.7 macrophages	Lu SY, et al. [10]
Anti-Inflammatory	investigated the anti-inflammatory activity of n-hexane, chloroform, ethyl acetate, and methanol extracts of five commercially available medicinal mushrooms, of which the chloroform extract *G. lucidum* was most effective	Geng Y, et al. [47]
Anti-Inflammatory	In vivo experiments clearly demonstrated that Ganoderma triterpene inhibited the production of TNF-alpha and IL-6 in LPS-induced endotoxemic mice	Dudhgaonkar S, et al. [30]
Anti-Inflammatory	demonstrated that *Ganoderma* extracts reduces tumors produced by inflammatory mediators such as IL-6, which may act as a growth factor that contribute to cancer progression.	Loperena-Alvarez Y, et al. [90]
Anti-Inflammatory	*Ganoderma* polysaccharides significantly suppressed the secretions of TNF-α, IL-1β, IL-6, IL-17A, and IL-4 in mice	Wei B, et al. [46]
Anticancer	isolated and characterized seven bioactive substances including ergosterol from *G. lucidum* extract that demonstrates significant selective efficacy against various human cancer cell types.	Martinez-Montemayor MM, et al. [86]
Anticancer	Aqueous extracts of three *Ganoderma* mushrooms significantly inhibit cell proliferation in human breast cancer cell lines MCF-7 and MDA-MB-231, with *G. tsugae* being the most potent.	Yue GG, et al. [84]
Anticancer	show that *G. lucidum* inhibits proliferation of breast cancer MDA-MB-231 cells by downregulating Akt/NF-kappaB signaling. *Ganoderma lucidum* suppresses phosphorylation of Akt on Ser473 and downregulates the expression of Akt, which results in the inhibition of NF-kappaB activity in MDA-MB-231 cells.	Jiang J, et al. [91]
Anticancer	They demonstrated that *Ganoderma* polysaccharides significantly inhibited prostate cancer cells viability in a time- and dose-dependent manner.	Wu K, et al. [85]
Anticancer	*Ganoderma lucidum* extracts significantly inhibited the release of IL-6, IL-8, MMP-2 and MMP-9 in cancer cells under pro-inflammatory condition	Barbieri A, et al. [92]
Anticancer	They found that antitumor activity was exhibited by Ganoderma polysaccharides at 100 mg/ kg body mass showed 80.8 and 77.6% reduction in tumor volume and tumor mass respectively, when administered 24 h after tumor implantation.	Joseph S, et al. [95]

Anti-Aging	isolated and characterized two novel ergosterol derivatives, ganodermasides A and B, from the methanol extract of spores of *G. lucidum*, showed to extend the replicative life span of Saccharomyces cerevisiae strain K6001	Weng Y, et al. [106]
Anti-Aging	In mice model, they demonstrated that *G. lucidum* triterpenoids improve cognitive impairment, alleviate neuronal damage, and inhibit apoptosis in the hippocampus tissues and cells in Alzheimer's disease through inhibiting the ROCK signaling pathway.	Yue GG, et al. [84]
Anti-Aging	In rat model, they isolated and characterized ganoderic acid and lucidone A obtained from the alcohol extracts of *G. lucidum*, which were involved in delaying Alzheimer's disease progression.	Lai G, et al. [104]
Anti-Aging	They demonstrated that *G. lucidum* extracts display weak DNA damaging potential and substantiated the traditional use of the mushroom to prolong life.	Gurovic MSV, et al. [107]
Antiviral	Demonstrated the antiviral activity of *G. lucidum* triterpenoids against enterovirus 71	Zhang W, et al. [14]
Antiviral	Demonstrated the antiviral activity of water and water extracts of *G. lucidum* against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), influenza A virus (Flu A) and vesicular stomatitis virus (VSV) Indiana and New Jersey strains in vitro	Eo SK, et al. [63]
Antiviral	Demonstrated the antiviral activity of *G. lucidum* triterpenoids against Dengue virus	Bharadwaj S, et al. [9]
Antiviral	Isolated and characterized Ganoderic acids from *G. lucidum* that was active against HIV-1.	El-Mekkawy S, et al. [67]
Antiviral	Isolated and characterized Ganoderic acids from *G. lucidum* that was active against HIV-1.	Min BS, et al. [68]
Antiviral	isolated, characterized and demonstrated that *Ganoderma* triterpenoids inhibited HIV-1 protease	Sato N, et al. [66]
Antiviral	demonstrated that the various extracts (water, ethanol, hexane and ethyl acetate) of several mushrooms including *G. lucidum* exhibited anti-dengue virus serotype 2 (DENV-2) activities in-vitro.	Ellan K, et al. [61]
Antimicrobial	The extracts of four species of *Ganoderma* exhibited antimicrobial activity against *Pseudomonas syringae* and *Bacillus subtilis*, but not against *Cladosporium herbarum*.	Ofodili LN, et al. [70]
Antimicrobial	demonstrated the antifungal activity of ethanol and methanol extracts of *G. lucidum* against five fungal species, namely, *Candida albicans*, *A. niger*, *A. flavus*, *A. fumigatus* and *Cryptococcus neoformans*.	Naveen Kumar C, et al. [69]
Antimicrobial	The antibacterial activities of water, acetone, ethanol and methanol extracts of *G. lucidum* were demonstrated against *Staphylococcus aureus* and *Pseudomonas aeruginosa*	Djide MN, et al. [71]
Antimicrobial	demonstrated the antimicrobial activity of water, acetone, ethanol and methanol extracts of *G. lucidum* against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Bacillus subtilis, Salmonella typhi* and *Pseudomonas aeruginosa*.	Quereshi S, et al. [72]
Antioxidant	investigated the cytoprotective effect of ethanol extract of *G. lucidum* against oxidative stress, and demonstrated inhibition of hydrogen peroxide -induced generation of reactive oxygen species and DNA damage.	Lee YH, et al. [58]

Antioxidant	In rat model, they evaluated the in vitro and in vivo antioxidant potential of the ethanolic extract of the fruiting bodies of *G. lucidum* and found that the mushroom exhibited antioxidant and radical scavenging activities both in vitro and in vivo.	Deepalakshmi K, et al. [59]
Antioxidant	demonstrated that the crude aqueous extract of *G. lucidum* fruiting bodies possesses potent antioxidant activity that protects hemoglobin against *Plasmodium*-induced oxidative damage.	Oluba OM, et al. [60]
Antioxidants	demonstrated that polysaccharide peptide extracted from *G. lucidum* is a potent antioxidant against pathogenesis of atherosclerosis high risk patients	Sargowo D, et al. [56]
Antioxidants	In a randomized, double-blind placebo-control clinical trial, they demonstrated that triterpenoids and polysaccharide peptides from *G. lucidum* exhibited antioxidation, antiaging and hepatoprotective activity in healthy volunteers	Chiu HF, et al. [57]
Anti-Asthma	developed and tested the safety and efficacy of an antiasthma herbal medicine intervention, which consists of the extract of *Ganoderma* and two herbs	Wen MC, et al. [53]
Reno-Protective	subjected 14 patients with persistent proteinuria to *G. lucidum* treatment and found that the mushroom extract suppressed endothelial cell cytotoxicity, restored immunocirculatory balance and successfully suppressed proteinuria in all the patients	Futrakul N, et al. [51]
Antidiabetic	demonstrated that the mushroom has mild antidiabetic effects that could potentially improve the dyslipidaemia of diabetes	Chu TT, et al. [52]
Antidiabetic	Demonstrated the mechanism of type 2 diabetes control by *Ganoderma* extracts	Teng BS, et al. [75]
Antidiabetic	They demonstrate that *G. lucidum* consumption can provide beneficial effects in treating type 2 diabetes mellitus by lowering the serum glucose levels through the suppression of the hepatic PEPCK gene expression.	Seto SW, et al. [77]
Antidiabetic	demonstrated the antioxidant and antidiabetic activity of ethanolic and water extracts of *Ganoderma*. Thy also demonstrated protective effects on pancreatic tissue	Milena, et al.
Antidiabetic	Demonstrated the antidiabetic effect of extract in mice model by enhancing insulin secretion and decreasing hepatic glucose output along with increase of adipose and skeletal muscle glucose disposal in the late stage of diabetes	Pan D, et al. [78]
Antidiabetic	demonstrated that *Ganoderma* spore powder consumption could provide a beneficial effect in terms of lowering the blood glucose levels by promoting glycogen synthesis and inhibiting gluconeogenesis.	Wang F, et al. [79]
Cardioprotective	Through a randomised clinical trial, they could not find evidence supporting the use of *G. lucidum* for the treatment of cardiovascular risk factors in people with diabetes mellitus or metabolic syndrome.	Klupp NL, et al. [35]
Cardioprotective	They found out that four out eleven peptides extracted from *Ganoderma* showed potent inhibition against ACE	Tran HB, et al. [33]
Antithrombotic/ Anticoagulant	isolated and characterized a metalloprotease from the mycelium of *G. lucidum* that displayed an anticoagulant activity in human plasma	Choi S, et al. [43]
Neuroprotective	investigated the pre-administration of *G. lucidum* spore in alleviating oxidative stress and mitochondrial dysfunction, neuroprotection from apoptosis, and improvement in cognitive dysfunction in rats.	Zhou Y, et al. [101]

Neuroprotective	They established the underlying mechanism of neuroprotection by *Ganoderma*. They found that *G. lucidum* polysaccharides regulate expression of apoptosis-associated proteins, inhibit oxidative stress-induced neuronal apoptosis that had significant neuroprotective effects.	Sun XZ, et al. [99]
Neuroprotective	They established the underlying mechanism of neuroprotection by *Ganoderma*.	Ren Z, et al. [100]
Neuroprotective	The study suggests that *G. lucidum*, reduces spinal cord injury -induced oxidative stress and exerts neuroprotection by inhibiting lipid peroxidation, glutathione depletion.	Ekinci A, et al. [98]
Neuroprotective	They found that the mushroom extracts significantly prevent the production of microglia-derived proinflammatory and cytotoxic factors [NO, TNF-α, IL-1β] in a dose-dependent manner and down-regulate the TNF-α and IL-1β expressions on mRNA level	Zhang W, et al. [14]
Neuroprotective	showed that pretreatment with *G. lucidum* for 3 and 7 days reduced neuronal loss and levels of TNF-α and IL-8 in the hippocampus, decreased the content of malondialdehyde and increased the activity of superoxide dismutase in the hippocampus and serum in rats.	Zhang W, et al. [14]
Anti-Obesity	They found that 5% powder of *G. lucidum* administration significantly reduced body weight in obese rats	Amin R, et al. [83]
Anti-Obesity	showed that the water extract of *Ganoderma lucidum* mycelium reduces body weight, inflammation and insulin resistance in mice fed a high-fat diet	Chang C, et al. [82]
Anti-Obesity	They found the down-regulation of pro-inflammatory cytokines (*TNF-α, IL-6, IL-1β*) in tissues and up-regulation of tight junction proteins (*occludin* and *ZO-1*), *Muc2* and *Reg3g* in small intestine after *Ganoderma* treatment	Guo C, et al. [81]
Anti-Obesity	showed that alcohol extracts of the *G. lucidum* fruit body could reduce body weight; change the serum levels of lipid; ameliorate the damage to the gut microbiota, colon, liver, brain and other organs induced by the high sugar and fat diet	Diling C, et al. [80]

Table 1: Possible role of *Ganoderma* extracts for the treatment of COVID-19 chronic risk factors

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Conflict of Interest

I declare no conflict of interest

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