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Review

Effects of bioactive compounds from *Pleurotus* mushrooms on COVID-19 risk factors associated with the cardiovascular system

Eduardo Echer dos Reis [a,b], Paulo Cavalheiro Schenkel [a,c], Marli Camassola [b,*]

[a] Department of Physiology, Federal University of Rio Grande do Sul, Campus Centro, 90050-170 Porto Alegre, Brazil
[b] Enzymes and Biomass Laboratory, Institute of Biotechnology, University of Caxias do Sul, 95070-560 Caxias do Sul, Brazil
[c] Department of Physiology and Pharmacology, Federal University of Pelotas, Campus Capão do Leão, 96900-010 Pelotas, Brazil

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ABSTRACT

Mushrooms are a group of fungi with great diversity and ultra-accelerated metabolism. As a consequence, mushrooms have developed a protective mechanism consisting of high concentrations of antioxidants such as selenium, polyphenols, β-glucans, ergothioneine, various vitamins and other bioactive metabolites. The mushrooms of the *Pleurotus* genus have generated scientific interest due to their therapeutic properties, especially related to risk factors connected to the severity of coronavirus disease 2019 (COVID-19). In this report, we highlight the therapeutic properties of *Pleurotus* mushrooms that may be associated with a reduction in the severity of COVID-19: antihypertensive, antihyperlipidemic, antiatherogenic, anticholesterolemic, antioxidant, anti-inflammatory and antihyperglycemic properties. These properties may interact significantly with risk factors for COVID-19 severity, and the therapeutic potential of these mushrooms for the treatment or prevention of this disease is evident. Besides this, studies show that regular consumption of *Pleurotus* species mushrooms or components isolated from their tissues is beneficial for immune health. *Pleurotus* species mushrooms may have a role in the prevention or treatment of infectious diseases either as food supplements or as sources for pharmacological agents.

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* Corresponding author.
E-mail address: mcamassola@gmail.com (M. Camassola).

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1. Introduction

Mushrooms are fungi belonging to the divisions of Ascomycetes and Basidiomycetes, and constitute a group of organisms with a great diversity of forms, colors and sizes. They were among the foods first harvested by pre-historical people and may have become an important food source due to their flavor and their nutritional and medicinal properties [1–3].

The order Agaricales is in the division Basidiomycetes and comprises 300 genera and approximately 5000 species [4]. Among them, the genus *Pleurotus*, defined by Paul Kummer in 1871, is notable. Of the 40 *Pleurotus* species, about 20 are commercially grown for their ability to flourish on agro-industrial waste, which facilitates their low cost of production in a variety of regions [5,6]. In fact, commercial mushrooms of this genus are the second most common among edible mushrooms, surpassed only by *Lentinula* [7]. In addition, *Pleurotus* production is aligned with current regenerative economic practices, as they grow well on regional lignocellulosic waste [8,9].

The genus *Pleurotus* has attractive culinary characteristics, such as high fiber and protein content and low fat content [10]. Unlike other protein-rich foods, such as meats and chicken, mushrooms do not contain the steroid cholesterol, but rather contain ergosterol. Ergosterol has been associated with several biological activities and can be converted by irradiation into vitamin D for dietary supplementation or use as a food additive [10–13].

Besides their high nutritional value, the mushrooms of the genus *Pleurotus* have aroused scientific interest due to their therapeutic properties. In the last decade, the number of patents and scientific articles concerning this genus has increased exponentially. Research has shown that mushrooms in this genus have therapeutic properties, including antihypercholesterolemic, antihypertensive, antidiabetic, antiobesity, antiaging, antimicrobial, antioxidant and hepatoprotective activities [14–19]. This can be an important alternative to changing patients' diet in the prevention of heart disease (Fig. 1) [15]. Considering all of these potential benefits, the potential uses for *Pleurotus* mushrooms are numerous, and it is possible that they could even be used to attenuate risk factors that affect the severity of coronavirus disease 2019 (COVID-19) [20–24].

COVID-19 has affected about 200 territories across the world and is considered by the World Health Organization to be a pandemic disease. At the time of writing, COVID-19 has infected 37,728,386 people and caused the death of 1,078,446 worldwide. The agent behind this disease is a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The concerns about the comorbidities and deaths caused by this virus are of global interest, so it is important to understand the risk factors that can contribute to the severity of the disease [20,25]. As other works suggest, identifying the major risks and how they can be mitigated can be decisive in the treatment of COVID-19 and may be able to help us to understand future treatments for another pandemic disease [19]. One of the largest studies about these risks is the report by the China Center for Disease Control and Prevention, which observed that advanced age, cardiovascular disease, hyperglycemia/diabetes, hypertension, cancer, and chronic respiratory disease were associated with an increased risk of COVID-19-related death [20]. Furthermore, it has been suggested that obesity is also a risk factor for the severity of COVID-19 [21]. Since these factors appear to be the biggest determinants of the severity of coronavirus infection, we conducted a database review based on them.

We searched for scholarly articles and patents published in the PubMed and Google Patent databases from their inception until December 2020. The search terms used in the search were: *Pleurotus* coronavirus, mushroom coronavirus, *Pleurotus* COVID, *Pleurotus* SARS-CoV-2, mushroom COVID, mushroom SARS-CoV-2, *Pleurotus* antihypertensive, *Pleurotus* antihypercholesterolemic, *Pleurotus* antiatherogenic, *Pleurotus* antihyperlipidemic, *Pleurotus* antioxidant, *Pleurotus* anti-inflammatory, *Pleurotus* antihyperglycemic and *Pleurotus* antiviral.

Thus, this review explores the properties (based mainly on *in vitro* and *in vivo* investigations) of *Pleurotus* mushrooms that

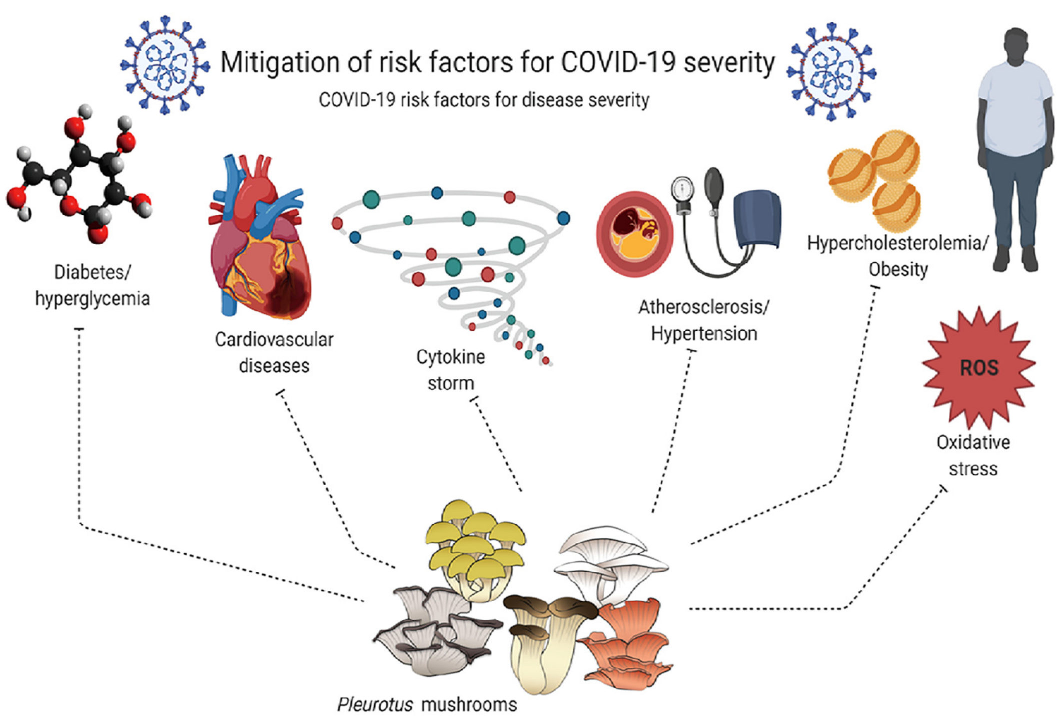

Fig. 1. Areas of *Pleurotus* mushroom bioactivity that could help to reduce risk factors for COVID-19. COVID-19: coronavirus disease 2019; ROS: reactive oxygen species.

may be associated with the mitigation of poor prognosis in COVID-19 (Fig. 1). Mechanisms of protection from extracts and preparations of these mushrooms are shown in Fig. 2.

2. Properties of *Pleurotus* mushrooms

2.1. Antihypertensive effects

Systemic arterial hypertension is among the most important risk factors for cardiovascular diseases and affects 25%–30% of the world's adult population [22]. Since cardiovascular disease has been consistently identified as a major risk factor for COVID-19 severity, it is important to control blood pressure [19].

Factors that contribute to the development of systemic arterial hypertension include lifestyle, rapid urbanization, racial differences, malnutrition, and diet imbalances [23]. Non-pharmaceutical antihypertensive treatments are based on exercise and diet, while the most commonly used classes of drugs are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and diuretics [24]. A strong connection has been found between eating habits (such as high sodium intake), lifestyle and hypertension [25].

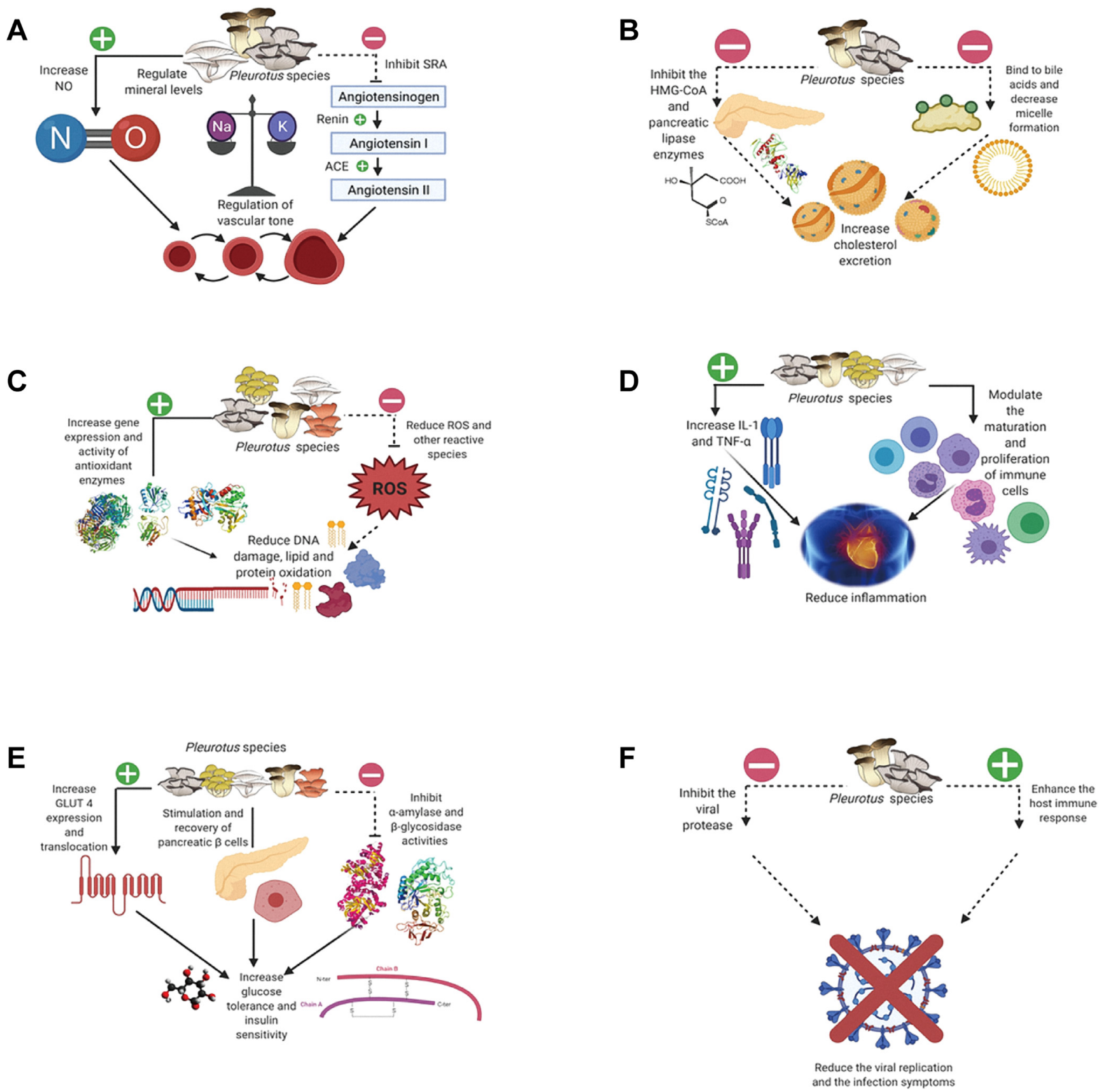

Fig. 2. Mechanistic diagrams of how different extracts or isolates from the tissues of *Pleurotus* reduce risk factors for coronavirus disease 2019. (A) Mechanism associated with regulation of vascular tone; (B) antihypercholesterolemic, antiatherogenic and antihyperlipidemic responses; (C) protection against oxidative stress damage, (D) regulating inflammatory damage, (E) antihyperglycemic effects; (F) antiviral activity. NO: nitric oxide; ACE: angiotensin-converting enzyme; SRA: renin-angiotensin system; HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; ROS: reactive oxygen species; IL: interleukin; TNF: tumor necrosis factor; GLUT 4: glucose transporter type 4.

In this context, edible mushrooms, due to their low sodium content, appear to provide excellent food options for people with high blood pressure. Moreover, mushrooms have a rich nutritional composition, containing a variety of compounds such as polysaccharides, dietary fiber, terpenes, peptides, glycoproteins, alcohols, mineral elements, unsaturated fatty acids, and antioxidants [26].

Edible mushrooms may also act as antihypertensives due to the presence of bioactive compounds capable of inhibiting angiotensin-converting enzyme, blocking calcium channels, and providing antioxidant capacity. In fact, previous studies have shown the hypotensive activity of extracts of *Pleurotus* species in rats, which included vasodilation through the decrease of total peripheral resistance induced by the inhibition of angiotensin-converting enzyme [27,28].

Another report showed that *Pleurotus nebrodensis* (Inzenga) Quél. had a protective effect against hypertension, which may have been linked to the metabolic pathway of blood lipids, renal function or the renin-angiotensin system [29]. The influence of *P. tuber-regium* (Fr.) Singer extract in attenuating systolic blood pressure and mean arterial pressure in rats has also been demonstrated. This hypotensive effect was attributed to the properties of flavonoids and phytosterol [30]. Therefore, edible mushrooms present interesting therapeutic applications for the prevention and treatment of hypertension, contributing to a lower risk of COVID-19 severity.

Table 1 summarizes the protective effects in terms of the antihypertensive response induced by different substances derived from *Pleurotus* fungi. Fig. 2A shows the mechanisms of protection associated with the regulation of vascular tone.

2.2. Antihypercholesterolemic, antiatherogenic and antihyperlipidemic effects

In addition to systemic arterial hypertension, hypercholesterolemia and high plasma concentrations of homocysteine are important risk factors for severity of COVID-19. Low-density lipoprotein (LDL) content and obesity were found to be risk factors for disease severity with moderate consistency [19]. Hypercholesterolemia is associated with increased accumulation of lipids and fibrous elements in the blood vessels and thus accelerates the development of atherosclerotic lesions, especially in the coronary arteries [33]. In addition, LDL-cholesterol may accumulate in the subendothelial space of the arteries to form oxidized LDL, which is highly atherogenic and toxic to vascular cells [34]. Therefore, properties that reduce these risk factors are considered important to the prevention of many diseases.

Mushrooms can attenuate these risk factors, possibly reducing the severity of infection. Bobek et al. [35] found that long-term dietary supplementation with 5% basidioma of dry *P. ostreatus* (Jacq.) P. Kumm. was able to effectively suppress diet-induced hypercholesterolemia in rats by inhibiting cholesterol absorption and very low-density lipoprotein biosynthesis. Such influences on cholesterol levels were associated, respectively, with the ability to inhibit the formation of mixed micelles in the intestinal lumen by binding to bile acids and by inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) enzyme [36].

Other studies reinforce the potential of mushrooms to provide protection through antihypercholesterolemic mechanisms, since dietary supplementation was able to promote an increase in the excretion of steroids and bile acids [37,38]. In fact, Ikewuchi et al. [39] found that treatment with the extract of *P. tuberregium* (Fr.) Singer significantly attenuated the serum levels of triglycerides and total cholesterol. These levels are implicated in the reduction of cardiac risk, thus showing the ability to attenuate the comorbidities of COVID-19.

Another way to use *P. sajor-caju* (Fr.) Singer is in combination with drugs to increase their solubility. Mehra et al. [40] used oyster mushroom (*P. sajor-caju* [Fr.] Singer) to prepare nanoparticles of statins and investigated whether this led to better solubility. Results of the antioxidant assay showed that nanoparticles synthesized from lovastatin and from mushroom had 76.57% and 73.83% inhibition of diphenylpicrylhydrazyl (DPPH) radicals, respectively, while the lovastatin showed only 16.77% inhibition.

Notably, lovastatin, a medication used frequently in the treatment of hypercholesterolemia, due to its competitive inhibition of HMG-CoA activity, is also produced by fungi of the genus *Pleurotus* [41].

This protective activity may also be associated with the presence of coumaric acid, a compound known to have antiatherogenic properties and the ability to increase serum levels of high-density lipoprotein (HDL) [42–46]. Increases in the concentration of HDL are beneficial to the body due to that HDL could absorb cholesterol present in the walls of the arteries and transport it to the liver to be reused or excreted [43]. In addition, it is estimated that with every 1% increase in HDL concentration, the risk of cardiovascular diseases is reduced by 2% [44]. Some authors have demonstrated that *P. ostreatus* (Jacq.) P. Kumm. mushrooms exert an antihyperlipidemic effect by improving antioxidant levels [46]. Therefore, edible mushrooms have therapeutic potential for the prevention and treatment of hypercholesterolemia, contributing to a lower risk of COVID-19 severity.

Table 2 summarizes the literature reports that support the antihypercholesterolemic, antiatherogenic and antihyperlipidemic responses associated with the different substances derived from *Pleurotus* fungi. Fig. 2B shows schematic diagrams of the same responses.

2.3. Antioxidant effects

In addition to their known antihypertensive and antihypercholesterolemic properties, the mushrooms of different *Pleutorus* species also have antioxidant properties. In the literature, many findings highlight the association of oxidative stress with several cardiovascular diseases, such as atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy, and heart failure [48,49]. Since these diseases appear to be related to the severity of COVID-19, we believe that their management is also relevant to combatting COVID-19.

Table 1
Antihypertensive responses to different substances derived from the mycelium and basidiomes of *Pleurotus*.

Research product	Species	Dosage employed	Quantitative data	Reference
Aqueous extract	*P. sajor-caju* (Fr.) Singer	25 mg/kg	Reduction of 36% in the mean systemic blood pressure	[27]
Polysaccharide fraction and protein fraction	*P. nebrodensis* (Inzenga) Quél.	9 g/d in humans	At week 16, reduction of 21% in the SBP	[29]
Aqueous extract	*P. tuber-regium* (Fr.) Singer	200 mg/kg	Reduction of 24.9% in the SBP	[30]
D-mannitol	*P. cornucopiae* (Paulet) Rolland	10 mg/kg	Reduction of 11.4% in the SBP	[31]
Aqueous extract	*P. cornucopiae* (Paulet) Rolland	600 mg/kg	Reduction of 27.7% in the SBP	[32]

SBP: systolic blood pressure.

Table 2
Antihypercholesterolemic, antiatherogenic and antihyperlipidemic responses exerted by different substances derived from the mycelium and basidiomes of *Pleurotus*.

Research product	Species	Dosage employed	Quantitative data	Reference
Aqueous extract	*P. ostreatus* (Jacq.) P. Kumm.	500 mg/kg	53.6% reduction of the cholesterol levels in serum	[34]
Dry powder	*P. ostreatus* (Jacq.) P. Kumm.	10% of the diet	65% reduction of the cholesterol levels in serum	[35]
Dry powder	*P. eryngii* (DC.) Quél.	3% of the diet	30% reduction of the cholesterol levels in serum	[37]
Aqueous extract	*P. tuber-regium* (Fr.) Singer	200 mg/kg	41.7% reduction of the cholesterol levels in serum	[39]
Dry powder	*P. ostreatus* (Jacq.) P. Kumm.	5% of the diet	45.7% reduction of the cholesterol levels in serum	[47]

Many processes in the body can make free radicals and reactive oxygen species (ROS) as by-products [50]. ROS is a group of molecules that contain oxygen and are highly reactive due to their unpaired valence electrons. At physiological levels, ROS has a signaling function and contributes to the maintenance of homeostasis. However, elevated levels of ROS induce cell membrane damage by lipoperoxidation, changes in protein structure and function, and structural damage to DNA [51–53]. As a mechanism of counter-regulation of these oxidative processes, antioxidant systems respond to stabilize the ROS and minimize the damage [53]. An antioxidant can be defined as any substance that is present in low concentrations when compared to the concentration of an oxidizable substrate and slows or inhibits the oxidation of that substrate. They can also be defined as molecules that donate electrons or hydrogen atoms to oxidants, thus stopping chain reactions [54,55]. When antioxidant systems are not effective in stabilizing ROS, these molecules accumulate, and the system can be said to be in a state of oxidative stress. Endogenous defenses maintain the redox balance in normal situations. Among the most important antioxidant defenses are thioredoxin (TRX), glutaredoxin (GRX), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx). TRX can act as an antioxidant enzyme by donating hydrogen to oxidized proteins. GRX can catalyze the reduction of disulfides, regenerating important activities of the cellular molecules. SOD catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide. CAT acts on the decomposition of hydrogen peroxide into water and oxygen, and GPx acts on reduced glutathione, which is oxidized to oxidized glutathione [56]. In addition to the enzymes that are part of the antioxidant reserve, there are also non-enzymatic antioxidants, such as tocopherols, carotenoids, flavonoids, ascorbic acid, and uric acid [57].

Over the years, many studies have explored the role of oxidative stress in the pathogenesis of various diseases, including neurodegenerative, pulmonary, inflammatory, renal, ocular, and cardiovascular diseases [58,59].

Experimental and clinical data have shown that oxidative damage, widely studied in neurological diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, memory loss and depression, can trigger neuronal losses and release toxic peptides, thus leading to the progression of neurodegenerative processes [60,61].

In pulmonary diseases, oxidants increase inflammation through the activation of different kinases and redox-sensitive transcription factors, aggravating other conditions, such as asthma [59–69].

In autoimmune diseases such as rheumatoid arthritis, it has been possible to verify the influence of oxidative damage due to the high level of isoprostanes and prostaglandins [65]. In addition, oxidants may play crucial roles in renal diseases such as nephritis and chronic renal failure, with the damage mainly caused by lipoperoxidation in the renal cells [62,70]. In addition, in ocular diseases, oxidative stress can contribute to protein aggregation, cellular structural alterations, and damage to the photoreceptors by lipoperoxidation [71–73].

Therefore, considering that the imbalance between the formation of ROS and the antioxidant capacity is one of the main mechanisms involved in cardiovascular disease, together with the fact that cardiovascular disease is among the leading causes of death in the world, studies that seek to ameliorate oxidative stress are promising. Several studies have been carried out in this field [60,67–76].

Some of these studies have used extracts of mushrooms of the genus *Pleurotus* as a possible treatment or pre-treatment to combat oxidative damage. In *in vitro* studies, extracts from different species of *Pleurotus* demonstrated free radical-scavenging activity and ferric ion reduction power, as well as having a metal-chelating effect and partially inhibiting lipoperoxidation [74–81]. In this way, the treatment with *P. eryngii* (DC.) Quél. extract increased antioxidant defenses *in vitro*, increasing the viability of baby hamster kidney cells (BHK 21) that had been exposed to oxidative stress by 1 mmol/L hydrogen peroxide [76]. Similarly, Khatun et al. [82] showed the nutritional and nutraceutical values of three different species of *Pleurotus* and found that *P. florida* Singer was superior, due to its CAT, phenolics and peroxidase contents.

In *in vivo* studies, rats that received carbon tetrachloride (CCl_4) and treatment with *P. ostreatus* (Jacq.) P. Kumm. mushroom extracts had CAT, SOD and GPx activities significantly higher than rats that did not receive mushroom extract. In addition, the levels of malondialdehyde (MDA) and reduced glutathione (GSH) were restored to normal. The hepatoprotective effect and protective effect against oxidative stress were probably due to the reduction in the generation of free radicals that had been induced by CCl_4 [71–73].

The administration of *Pleurotus* mushroom extract to elderly mice increased their levels of antioxidant defenses, such as CAT, SOD, GPx, vitamin C, vitamin E and glucose-6-phosphate dehydrogenase, to the same levels as found in young rats. In addition, the extract restored the levels of GSH, MDA and glutathione transferase, and reduced the levels of lipoperoxidation, xanthine dehydrogenase and carbonyls. Thus, the extract appears to have a protective effect on oxidative stress, reducing the lipoperoxidation and increasing the levels of enzymatic and non-enzymatic antioxidants [16,50,83–87].

In other studies involving liver diseases, carcinoma, diabetes, hypercholesterolemia and hyperlipidemia, mushroom extracts from the genus *Pleurotus* also showed antioxidant effects, restoring MDA levels, and increasing antioxidant defenses such as GSH, SOD, CAT, GPx, vitamin C and vitamin E. Thus, they protect the tissues against oxidative damage [34,42,88–94].

In a study involving acute myocardial infarction, it was shown that the infarct caused a large increase in the MDA content of the cardiac tissue. However, treatment with 100 mg/kg of an extract from *P. nebrodensis* (Inzenga) Quél., prepared by using dry mushrooms twice degreased with $CHCl_3$ (chloroform)/MeOH (methanol), extracted in distilled water and fractionated by chromatography, was able to significantly decrease the MDA content in the myocardial ischemia–reperfusion model group [70]. In addition, the activity of SOD, CAT and GSH in the cardiac tissue decreased dramatically in the infarcted group, but the treatment was able to prevent this. There was also a potential inhibitory effect of the extract on myocardial apoptosis, as pre-treatment with the extract significantly inhibited the increase in cells showing DNA fragmentation [70].

P. nebrodensis (Inzenga) Quél. extract also efficiently reduced the oxidative damage caused by ischemia–reperfusion in hepatic tissue. In addition, a decrease in the expression levels of pro-apoptotic markers, such as Bax, caspase-3 and cytochrome *c*, was observed in the group treated with the extract. There was also an increase in the expression of the anti-apoptotic marker Bcl-2 in the treated rats compared to the ischemia–reperfusion group [71].

According to the literature, oxidative stress is connected to most of the risk factors for COVID-19 severity. Therefore, we think that antioxidant activity is relevant to the attenuation of the severity of COVID-19.

Table 3 shows data supporting the antioxidant responses and protective effects of different substances from the mycelium and basidiomes of *Pleurotus*. The mechanisms associated with these protective effects are illustrated in Fig. 2C.

2.4. Anti-inflammatory effects

Systemic inflammation is an important factor in the development and progression of many diseases. Many inflammatory markers are used in clinical studies to demonstrate the risks of cardiovascular diseases, such as hypertension, atherosclerosis and stroke [72]. Studies have demonstrated the role of inflammation in SARS-CoV-2 infection, which can cause a systemic cytokine storm and widespread inflammation, leading to tissue damage [73]. In view of these factors, it has been suggested that anti-inflammatory properties may be of interest in the treatment and prevention of severe COVID-19.

Research has shown that extracts from different species of the genus *Pleurotus* can modulate the synthesis and release of pro-inflammatory mediators and reduce in the migration of total leukocytes. Therefore, it has been suggested that these extracts have anti-inflammatory properties, reducing nociception and oedema [78,83–89].

Other studies have shown that β-glycan extracted from mushrooms of the genus *Pleurotus* exerts an immunostimulatory effect by modulating the activity of neutrophils, macrophages, monocytes, and natural killer cells [80,88]. This compound also stimulates cytokines such as interleukin-1 and tumor necrosis factor-α, resulting in an increased immune response. Another study verified that the ability of *Pleurotus* mushroom extracts to inhibit neutrophil accumulation, operated via a reduction in pro-inflammatory cytokine gene expression [85,88].

Another report showed the anti-inflammatory activity of *P. florida* extract; however, the mechanisms by which this activity occurred are unknown [89]. It is believed that a large number of phenolic compounds present in the extract may have been responsible for its activity [89].

Since the COVID-19 pandemic began, several doctors reported a cytokine storm as one of the stronger factors affecting the outcome of the infection. Since these data show the importance of inflammation in the severity of COVID-19, agents with anti-inflammatory activity may be able to reduce its severity.

Anti-inflammatory data related to *Pleurotus* are shown in Table 4 and in Fig. 2D, alongside the mechanisms associated with these protective effects.

2.5. Antihyperglycemic effects

Diabetes mellitus is an endocrine disorder characterized by hyperglycemia, resulting from a deficiency in insulin secretion, insulin action, or a combination of both [90]. It is estimated that there are 284 million people living with diabetes worldwide [91]. In many studies involving the severity of coronavirus infection,

Table 3
Antioxidant responses to different substances from the mycelium and basidiomes of *Pleurotus*.

Research product	Species	Dosage employed	Quantitative data	Reference
Alcoholic extract	*P. ostreatus* (Jacq.) P. Kumm.	200 mg/kg	33% increase in GSH concentration, 26% increase in SOD concentration, and 24% increase in GPx concentration	[16]
Aqueous extract	*P. ostreatus* (Jacq.) P. Kumm.	500 mg/kg	39% reduction in MDA concentration	[34]
Polysaccharides	*P. eryngii* (DC.) Quél.	500 mg/kg	58% reduction in TBARS concentration	[42]
Alcoholic extract	*P. ostreatus* (Jacq.) P. Kumm.	200 mg/kg	47% reduction in MDA concentration	[47]
Polysaccharide-peptide complex	*P. abalonus* Y.H. Han, K.M. Chen & S. Cheng	30 mg/kg	60% reduction in MDA concentration	[50]
Hydroalcoholic extract	*P. albidus* (Berk.) Pegler	10 mg/mL	51% reduction in TBARS concentration	[58]
Polysaccharide	*P. nebrodensis* (Inzenga) Quél.	400 mg/kg	44% reduction of infarct size	[70]
Polysaccharide	*P. nebrodensis* (Inzenga) Quél.	400 mg/kg	66% reduction in MDA concentration	[71]
Polysaccharides	*P. eryngii* (DC.) Quél.	1 mg/kg	35.1% scavenging ability	[74]
Hydroalcoholic extract	*P. eryngii* (DC.) Quél.	1 mg/mL	20% scavenging ability	[76]
Alcoholic extract	*P. ostreatus* (Jacq.) P. Kumm.	200 mg/kg	23% reduction in MDA concentration	[77]
Alcoholic extract	*P. ostreatus* (Jacq.) P. Kumm.	200 mg/kg	18.6% increase in XDH activity	[80]
Alcoholic extract	*P. pulmonarius* (Fr.) Quél.	2 mg/mL	92.7% scavenging ability	[83]
Polypeptide	*P. eryngii* (DC.) Quél.	1 mg/mL	41.8% scavenging ability	[86]
Polysaccharides	*P. tuber-regium* (Fr.) Singer	20 mg/kg	50% increase in SOD activity	[92]
Polysaccharides	*P. eryngii* (DC.) Quél.	600 mg/kg	54% reduction in MDA concentration	[93]
Alcoholic extract	*P. ostreatus* (Jacq.) P. Kumm.	200 mg/kg	20% increase in GSH concentration	[95]
Polysaccharides	*P. cornucopiae* (Paulet) Rolland	150 mg/kg	66% reduction in MDA concentration	[96]
Extract	*P. florida*	200 μg/mL	60% lipid peroxidation inhibition	[97]
Extract	*P. ostreatus* (Jacq.) P. Kumm.	50 mg/mL	30 μmol Trolox equivalent/g dry extract	[98]
Polysaccharides	*P. abalonus* Y.H. Han, K.M. Chen & S. Cheng	180 μg/mL	75.4% scavenging ability	[99]
Extract	*P. pulmonarius* (Fr.) Quél.	9.3 mg/mL	33% lipid peroxidation inhibition	[100]
Alcoholic extract	*P. ostreatus* (Jacq.) P. Kumm.	600 mg/kg	33% reduction in TBARS concentration	[101]
Acetonitrile extract	*P. djamour* (Rumph. ex Fr.) Boedijn	500 mg/L	33% scavenging ability	[102]
Polysaccharides	*P. geesteranus* Singer	6000 mg/kg	80% reduction in MDA concentration	[103]
Supercritical CO_2 extract	*P. ostreatus* (Jacq.) P. Kumm.	15 mg/mL	80.83% scavenging ability	[104]

GPx: glutathione peroxidase; GSH: glutathione; MDA: malondialdehyde; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; XDH: xanthine dehydrogenase.

Table 4
Anti-inflammatory responses to different substances from the mycelium and basidiomes of *Pleurotus*.

Research product	Species	Dosage employed	Quantitative data	Reference
β-Glucan	*P. pulmonarius* (Fr.) Quél.	3 mg/kg	82% inhibition of leukocyte infiltration	[83]
Glucans	*P. pulmonarius* (Fr.) Quél.	20 mg/d	62% reduction in secretion of *TNF-α* mRNA transcript levels	[84]
Glucans	*P. albidus* (Berk.) Pegler	200 μg/mL	85% increase in cell viability	[85]
Glucans	*P. citrinopileatus* Singer	10 μg/mL	Inhibition of the expression of the pro-inflammatory cytokines TNF and IL-6	[88]
Alcoholic extract	*P. florida* Singer	1000 mg/kg	60% reduction in carrageenan-induced acute inflammation	[89]
Aqueous extract	*P. ostreatus* (Jacq.) P. Kumm.	100 μg/mL	61% reduction in TNF-α concentration	[105]
β-Glucan	*P. ostreatus* (Jacq.) P. Kumm.	1 mg/kg	15% reduction in the arthrogram score	[106]
Extract	*P. florida* Singer	500 mg/kg	60% reduction in the carrageenan-induced oedema in Wistar rats	[107]
β-Glucan	*P. sajor-caju* (Fr.) Singer	10 mg/kg	77% reduction in *TNF-α* gene expression	[108]
Mannogalactan	*P. sajor-caju* (Fr.) Singer	30 mg/kg	63% reduction in oedema level	[109]
Aqueous extract	*P. ostreatus* (Jacq.) P. Kumm.	4 mg/ear	94% inhibition of auricular oedema	[110]
Alcoholic extract	*P. giganteus* (Berk.) S.C. Karunarathna & K.D. Hyde	100 μg/mL	75% reduction in nitric oxide production	[111]
Protein	*P. eryngii* (DC.) Quél.	200 μg/mL	81% reduction in IL-6 concentration	[112]

IL: interleukin; TNF: tumor necrosis factor.

diabetes and hyperglycemia were indicated as major risk factors for death or severe symptoms [19]. In fact, in a review based on risk factors for this disease, it was stated that diabetes has been highly consistently shown to be a risk factor for the severity of coronavirus infection [19].

The antihyperglycemic effects of *Pleurotus* mushrooms may be due to the healing of damaged pancreatic β cells, partially restoring their hormonal activity [45,89]. Increased peripheral sensitivity to insulin as well as the modulation of its synthesis and release has also been observed in response to treatment with extracts from different mushrooms of the genus *Pleurotus* [89,90–93,113–117].

Extracts from *P. ostreatus* (Jacq.) P. Kumm. and *P. cystidiosus* O.K. Mill. may also promote an increase in glucose utilization by the muscles, thus reducing serum glucose levels [90]. Rats treated with *Pleurotus* mushroom extracts showed increased glucose tolerance, in addition to an increase in expression and translocation of glucose transporter type 4 (GLUT 4). It has been shown that ergosterol present in the extract of these mushrooms can promote GLUT 4 translocation, increase GLUT 4 expression, and increase uptake of glucose through the phosphoinositide 3-kinase, protein kinase B and protein kinase C pathways [31,32,47,94–111,118–120].

Mushrooms of the genus *Pleurotus* had hypoglycemic activity in mice with drug-induced diabetes. It is believed that this hypoglycemic activity is associated with the antioxidant activity of the extract. The polysaccharides from these mushrooms have beneficial effects on non-insulin-dependent diabetes mellitus, reducing blood glucose, reducing glucose and ketones in urine, and restoring normal levels of antioxidant enzymes. Thus, these compounds reduce the severity of diabetes and correct some biological parameters impacted by diabetes [112,121]. The work of Khatun et al. [122] showed that consumption of *P. florida* Singer in the diet of alloxan-induced diabetic rats had hypoglycemic and hypocholesterolemic effects; thus, mushrooms may provide low-cost prevention for these diseases.

Other studies have shown that the use of extracts of *Pleurotus* mushrooms exerted inhibitory activities on α-amylase and α-glycosidase, resulting in a hypoglycemic effect [92,123]. Diabetes and hyperglycemia have consistently been identified as risk factors for COVID-19 severity; therefore, edible mushrooms with a hypoglycemic effect may attenuate the severity of this disease.

Data describing the antihyperglycemic responses to different substances extracted from the mycelium and basidiomes of *Pleurotus* are summarized in Table 5 and Fig. 2E.

2.6. Antiviral effects

Alongside the influences on the risk factors for COVID-19 severity, the literature also reports information about bioactive compounds in mushrooms with antiviral activity. Although few studies have looked at the antiviral effects of mushrooms against SARS-CoV-2, we evaluated the activity of these compounds against other viruses.

Krupodorova et al. [124] tested several mushroom extracts against influenza virus type A (H1N1) and herpes simplex virus type 2. Among the mushrooms tested, *P. ostreatus* (Jacq.) P. Kumm. showed a therapeutic index (maximum tolerated concentration/half maximal effective concentration) of 6 against H1N1 and 80.64 against herpes simplex virus type 2. Other authors, such as Hetland et al. [125], cited antiviral activities of mushrooms against poliovirus, influenza virus, Dengue virus, enterovirus, hepatitis virus B and C, and others.

Table 5
Antihyperglycemic responses to different substances from the mycelium and basidiomes of *Pleurotus*.

Research product	Species	Dosage employed	Quantitative data	Reference
Aqueous extract	*P. ostreatus* (Jacq.) P. Kumm.	1250 mg/kg	39% reduction in blood glucose	[90]
Polysaccharides	*P. sajor-caju* (Fr.) Singer	240 mg/kg	37% reduction in blood glucose	[91]
Polysaccharides	*P. tuber-regium* (Fr.) Singer	20 mg/kg	26% reduction in blood glucose	[92]
Polysaccharides	*P. eryngii* (DC.) Quél.	5 mg/mL	50% reduction in blood glucose	[93]
Polysaccharide-protein complex	*P. abalonus* Y.H. Han, K.M. Chen & S. Cheng	300 μg/mL	16% reduction in blood glucose	[113]
Polysaccharides	*P. ostreatus* (Jacq.) P. Kumm.	400 mg/kg	46% reduction in blood glucose	[114]
Ergosterol	*P. ostreatus* (Jacq.) P. Kumm.	120 mg/kg	40% reduction in blood glucose	[115]
Polysaccharide-peptide complex	*P. abalonus* Y.H. Han, K.M. Chen & S. Cheng	1 mg/kg	16% reduction in blood glucose	[116]
Polysaccharides	*P. florida* Singer	400 mg/kg	57% reduction in blood glucose	[117]
Polysaccharide	*P. citrinopileatus* Singer	400 mg/kg	41% reduction in blood glucose	[121]
Aqueous extract	*P. pulmonarius* (Fr.) Quél.	500 mg/kg	50% reduction in blood glucose	[123]

In research on herpes virus, Urbancikova et al. [126] showed that a β-glucan from *P. ostreatus* (Jacq.) P. Kumm. caused a reduction in the duration of herpes symptoms and also caused a reduction in the duration of the acute respiratory symptoms and intercurrent diseases. This reduction in acute respiratory symptoms may be interesting in the context of COVID-19 treatment. One of the most promising glucans from *P. ostreatus* (Jacq.) P. Kumm. is pleuran, an insoluble polysaccharide isolated from the fruiting bodies of these mushrooms. A dietary supplement called Imunoglukan P4H® has been formulated, consisting of pleuran associated with vitamin C, and has been investigated in several clinical studies involving respiratory tract infections, showing promising results [127].

Another antiviral factor associated with mushrooms is the regulation of the immune response. Several natural derivatives have been described in clinical trials, showing the capacity to enhance the immune response to viruses. Molecules derived from edible mushrooms are expected to be safe and can optimize the host immune function to possibly prevent secondary infections during SARS-CoV-2 infection [128].

The identification of bioactive compounds from natural sources that can act as inhibitors of the SARS-CoV-2 protease is considered a possible approach to combat COVID-19, reducing the viral replication. Mushrooms are excellent candidates for this research, since they are a rich source of bioactive compounds with antiviral activity. These compounds have been shown to inhibit human immunodeficiency virus protease, so they may also act against the proteases of coronaviruses [129]. Evidence suggests that mushrooms may be an alternative treatment that helps to attenuate the severity of COVID-19.

The data on the antiviral response exerted by different substances from the mycelium and basidiomes of *Pleurotus* are summarized in Fig. 2F.

3. Unknown aspects of the research and future research

At the time of preparation of this review, we could not find papers in the literature that described the use of *Pleurotus* mushrooms to attenuate the risk factors for COVID-19 severity. As this disease is a global concern, this review aims to provide a background on the use of *Pleurotus* as a protective agent to reduce the severity of this disease. We think that these mushrooms may have an indirect or direct effect on the risk factors associated with COVID-19. However, clinical research data are required to support this claim.

4. Conclusion

This review shows that mushrooms of the genus *Pleurotus* have antihypertensive, antihypercholesterolemic, antiatherogenic, antihyperlipidemic, antioxidant, anti-inflammatory, antihyperglycemic and antiviral properties. Since these properties interfere significantly in the risk factors for COVID-19 severity, the pharmacological potential of these mushrooms is evident. Because they are edible and widely produced in the world, they are easily accessible and could easily be incorporated into the diet, acting as a food supplement, or be used in the creation of pharmacological agents for direct use in treatment. Among the mushrooms described in this paper, we highlight the potential of *P. ostreatus* (Jacq.) P. Kumm. and its constituents, as they are the most cited in the literature research. This body of work should be developed further for verifying the efficacy of *P. ostreatus* products against diseases like COVID-19. Larger studies will be necessary to verify the efficacy of the treatment, especially in the context of food standards and other treatment patterns.

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Authors' contributions

EEDR: conceptualization, investigation, and writing original manuscript. PCS and MC: conceptualization, supervision, and review of manuscript.

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Declaration of competing interest

There are no conflicts to declare.

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