

Microplastics and cardiovascular toxicity: Mitigating risks through mushrooms

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Abstract

Microplastics (MPs) are increasingly being detected in drinking water as well as in aquatic ecosystems, posing serious risks to both human health and aquatic life. These particles adversely affect multiple organs, including the gastrointestinal tract, reproductive and endocrine systems, lungs, and heart. Research suggests that MPs accumulate within cell membranes and the cytosol, where they promote the generation of reactive oxygen species (ROS). Recent findings indicate that MPs act as strong contributors to cardiovascular disorders, which remain a major cause of global morbidity and mortality. Exposure to MPs has been linked to endothelial dysfunction, atherosclerosis, irregular cardiac rhythms, cardiac hypertrophy, and fibrosis. However, only limited molecular-level studies have explored the mechanisms underlying MP-induced cardiovascular diseases (CAVDs). Existing research shows that MPs increase the expression of Bax, Wnt, β -catenin, and collagen types I and III, while reducing the activity of antioxidative enzymes in cardiac tissue. Further investigation into the signaling pathways involved in MP-mediated cardiovascular damage is essential to better understand disease progression and to identify potential therapeutic strategies like the efficiency of mushrooms in ameliorating the effects of MPs in our heart by attenuation of ROS generation, suppression of pro-inflammatory mediators and inhibition of collagen deposition.

Keywords: Microplastics; Reactive Oxygen Species; Edible Mushroom; Cardiovascular Disorders; Hypertrophy; Mushroom Derived Extracts

1. Introduction

In today's developing world, cardiovascular disorders (CAVDs) are gradually increasing its penetrance in our life. According to World Heart Report (2023), CAVDs are one of the leading causes of death causing approximately 33% of global deaths (reported till 2019). Studies say that the mortality- incidence ratio remained around 0.35 (till 2017) in Central and South Asia.¹ Factors like diabetes, heavy metals in drinking water, improper food intake habits (excessive sodium intake), kidney disorders seem to play a direct or indirect role in the occurrence of CAVDs. Recent research indicates that microplastics (MPs) can trigger various cardiovascular problems in a dose dependent manner, but the actual pathways behind the fatality still remains a mystery in the field of toxicological research. The main area of interest of this review paper is the cardiovascular effects of MPs in humans. Recent investigations indicate that MPs can contribute to the changes in cardiac rhythm, bradycardia and tachycardia, abnormalities like pericardial edema, myocardial fibrosis by inducing myocardial inflammation.^{2,3} There are not many publications that interest upon the effects of MPs in the cardiovascular system in human. It is expected that the mystery behind the toxicity of MPs and its molecular signaling mechanism in inducing CAVDs will soon be found out, and the information will be effectively spread among common people to build up awareness. Till date regarding complete mitigation of microplastic induced cardiovascular disorders are not reported so we can look for a natural resource to overcome this problem.

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Mushrooms well defined as macrofungi with distinguished and prominent fruiting bodies usually found on overground or subterranean have been used as food and medicine by various mankind cultures since antiquity.⁴ These days both cultivable and wildy grown mushrooms were either straightaway or secondarily utilised as food or food constituent owing to their entrancing texture, palate, savour and dietary values.^{5,6} The nutritive value of mushrooms depends on their high protein content, low fat level, high fiber and considerable amount of vitamins and minerals.⁷ Along with these the amino acid constituents of mushroom proteins are quite proportionate with animal protein which makes it important to counterbalance the extravagant use of protein from animal sources in developed countries.⁸ In addition, medicinal mushrooms characteristically contain variety of distinct bioactive compounds like alkaloids, polyphenols, polysaccharides, polysaccharide glucans, terpenoids and steroids.^{9,10} Experimental studies like *in vitro*, *in vivo* and human study trials have demonstrated that mushroom extract, as well as fresh edible mushrooms, possess an enormous scope of therapeutic applications in human health benefits, entailing antiobesity, anticancer, antiviral, hepatoprotective, anti-diabetic, cardioprotective, immunomodulation and many more.^{11,12} In recent times, mushrooms have gain increasing attention as functional foods for their prospective beneficial effects on human well-being; hence, food industry is exceptionally displaying enthusiasm in cultivated and wild edible mushrooms.¹³ Cardiovascular disorders including heart attacks, stroke and hampering the circulatory system, being most prevalent causes of morbidity and mortality in the developed countries.⁹ Conventionally, edible mushrooms have been stipulated in oriental medicine due to their hypocholesterolemic effects.¹⁴ Relevant nutritional facets of mushrooms including high fiber content, microelement content, a low fat content with low trans isomers of unsaturated fatty acids are chiefly perfect for diets to circumvent cardiovascular disease and lead a healthy lifestyle.^{8,15} Reports explained that occurrence of specific substance and bioactive compounds extracted from mushrooms helps in maintain the levels of total cholesterol, high-density homocysteine, and lipoproteins to halt the occurrence of hypertension, arterial oxidative stress, and cardiovascular disorder.¹⁶ With this approach mushrooms can be contemplate as satisfactory dietary supplements with possible healing value of treating cardiovascular disorder. The aims of this review are to report cardiac toxicity mediated by MPs and explore putative positive effects of mushrooms consumption on cardiovascular diseases risk caused by MPs.

2. Microplastics and its exposure on human health

MPs are fragmented polymers of plastics measuring <5mm. This fragmentation may be induced by weather conditions, mechanical abrasions and photooxidation.¹⁷ Due to their small structure, they can involve themselves with the various components of the ecosystem, like soil, air and water. The major source of exposure in the water ecosystem is the uncontrolled disposal of plastics in the coastal beaches.¹⁸ MPs adversely affect the aquatic ecosystem by accumulation inside the physiological system of fishes and other aquatic fauna and show its toxicity.¹⁹ Terrestrial MP pollution can be formed due to dumping mechanisms and their subsequent release to the environment after their biodegradation.²⁰ MPs can be divided in two types: Primary MPs and Secondary MPs. Primary MPs are those types of microplastics that are intentionally used for commercial purposes like in case of cosmetic detergents, synthetic paints, insecticides etc. Secondary MPs are formed unintentionally because of biodegradation of disposed plastic things in the environment which are made up of large polymeric chains.²¹

MPs' penetrance in the human physiological system is initiated with contact, inhalation and ingestion.²² Experiments on rats reveal that these MPs exposure may result in accumulation in the cell membrane and in the cytosol of neonatal rat ventricular myocytes (NVRM).²³ Air borne particulate plastics get accumulated in the respiratory organ causing interstitial lung diseases.²⁴ MPs induce ROS generation leading to cytotoxicity and damage of the zonula occludens proteins resulting in obstructive pulmonary disease.²⁵ MPs ingestion affect the intestinal microbiome causing metabolic disorders and gut barrier dysfunction eventually resulting in abdominal pain, bloating and sudden changes in feeding habits.²⁶ MPs cause damage in mitochondria by penetrating the mitochondrial membrane inducing a change in the mitochondrial membrane potential thereby causing a down regulation of mitochondrial activity, as seen in Chronic Obstructive Pulmonary Diseases (COPDs).²⁷ In this review, we will emphasize on the various CAVDs that MPs induce along their underlying molecular mechanism. Moreover, we will also discuss about potent natural agent that can help in the process of amelioration from MPs induced CAVDs.

3. Cardiac toxicity mediated by MPs

The chronic and acute exposure of MPs is diverse. Recent research has shed light on how MPs can affect the vascular system in mammals. As most mammals are terrestrial organisms, they inhale the MPs present in air. This might lead to diseases like cardiac fibrosis, coronary arteriolar endothelial damage, myocardial damage. It may also induce hypoxia, significant arterial hypotension and permanent pulmonary obstruction (Fig.1).²⁸ It has been seen that one of the major

molecules involved in cardiac injury is the N6-methyladenosine (m6A) modifications of in the ncRNA. High concentrations of MPs elevate the expression of methylated m6A in ncRNA that raises the risk of cardiotoxicity.²⁹

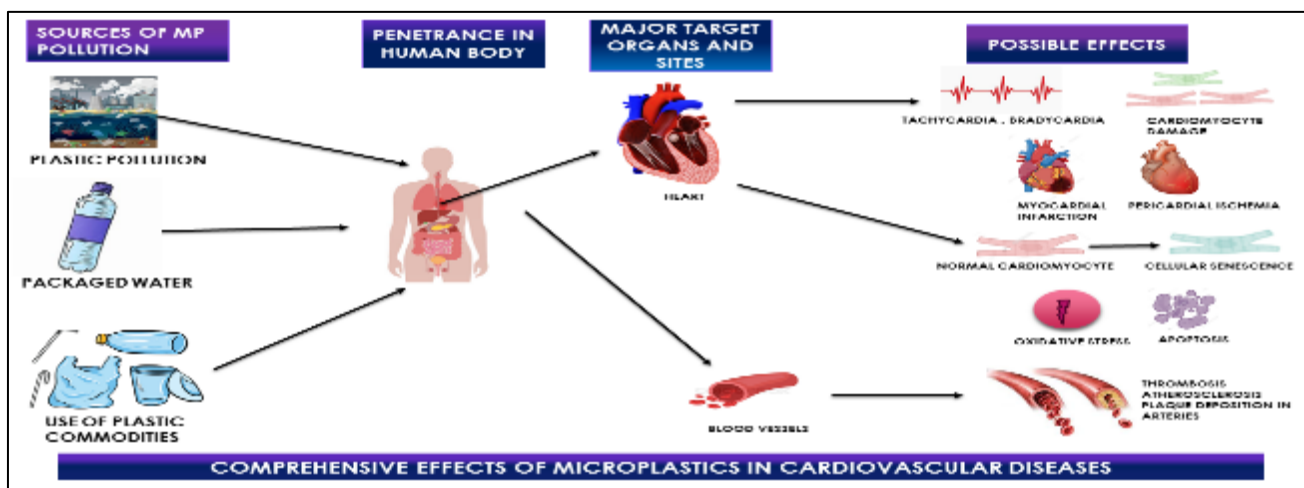


Figure 1 Possible effects of microplastics on heart

3.1. Tachycardia and bradycardia

Previous investigations indicated heart rate to be an efficient indicator for detecting various types of CAVDs. By calculating the heart rate, diseases like MI and heart failure can be easily traced.³⁰ Nanoparticles seem to have a tendency of aggregation on the endothelial cells and deplete their adhesion with the other cells.³¹ In aquatic models, PS-MPs modulate the rate of heart beat which affects the heart, induce inflammatory reactions, suppress immune response and also cause developmental defects in larvae of *O. melastigma*. MPs have been detected to cause both tachycardia as well as bradycardia depending on their concentration and particle size in zebrafish embryos.^{32,33} This may be a result of decrease in the contraction forces of the cardiomyocytes which occurs due to blocking of the L-type calcium channels that interferes with the electrical synchronisation of pulse generation.^{28,34}

3.2. Hypertension and atherosclerosis

Studies have shown that prolonged exposure of MPs have the ability to cause endothelial dysfunctional diseases such as atherosclerosis and hypertension. In murine model, MPs have been shown to induce the expression of vascular cell adhesion molecule (*Vcam*)-1 and intercellular adhesion molecule (*Icam*)-1, indicating activation of endothelial cells.³⁵ Deposition of carotid plaques occurs at the atherosclerotic sites along with minute deposition of MPs. Deposition of higher amount of plaques has an increased expression of cytokine profiles such as IL-18, IL-1 β and TNF- α . Such patients have a higher risk of MI or even death depending upon the severity.³⁶

3.3. Problems in cardiac function

According to previous studies, when zebrafish is exposed to PS MPs (having particle size 3-12 μm), the heart function was observed to decrease significantly with gradual reduction of swimming competence. Due to accumulation of a high amount of MPs in the system of zebra fish, there was a decrease in the heart performance associated with higher frequency of apoptosis and autophagy in the cardiac muscle cells.³ It may be possible that MPs cause disturbance in ventricular signaling and affect cardiac contractility along with significant decrease in the calcium levels in the cell and electrophysiological properties of cardiomyocytes.

3.4. Pericardial edema

Recent research on zebrafish reveals that pericardial edema has been one of the most common indicators of toxic exposure in the cardiovascular system. Studies have revealed that besides intestinal toxicity, nanoplastics may also be responsible for its adverse effects like pericardial toxicity, ROS synthesis, thrombosis and inflammation³⁷. Whether MPs have similar effects on pericardium needs to be investigated.

3.5. Myocardial fibrosis

Ventricular dysfunction and arrhythmia are sensitive indicators of myocardial fibrosis causing cardiomyocyte necrosis³⁸. Studies have shown that MPs can cause cardiac fibrosis by activating the Wnt/ β -catenin signaling pathway. MPs can also trigger myocardial apoptosis by inducing oxidative stress. Studies on Wistar rats have shown that when they were exposed to 0.5 μ m PS MPs at 0.5, 5 and 50 mg/L for 90 days, it caused increased expression of cardiac Troponin I and creatine kinase-MB level in serum leading to myocardial apoptosis³⁹. MPs are the potential stimulants of NOD like receptor protein 3 inflammasomes which lead to apoptosis (by activation of Caspase 1). Studies reveal that treatment of Wistar rats with 0.5 μ m PS MPs at 0.5, 5 and 50 mg/L for 90 days resulted in damage of cardiac membrane structure and decreased mitochondrial integrity⁴⁰. Studies suggest that oxidative stress and inflammation induce an ANP, BNP, MYL2, MYL4 and MYH7B gene expression which leads to cardiac cell death and contractile dysfunction along with induced cardiac fibrosis³⁵.

3.6. Other cardiovascular damages

MPs can induce cardiotoxicity via ROS associated NF- κ B-NLRP3 - GSDMD and AMPK-PGC-1 α axes inducing oxidative stress, pyroptosis, inflammation, mitochondrial damage and impairment of energy metabolism thereby triggering myocardial inflammation as demonstrated in chick model^{41,42}. Inflammation is the key factor for major varieties of CAVDs which may lead to angiotensin II induced hypertension along with upregulation of cerebral sphingosine 1 phosphate levels (Fig.2). This may enhance inflammation leading to aortic wall dilation⁴³. Atherosclerosis is a major outcome of pyroptosis which is caused due to death of smooth muscle cells and subsequent inflammation along with decreased regulation of metalloproteinases and release of growth factors, cytokines, proteases which induce CAVDs^{42,44}. Thickening of cardiac structure has been persistent with increased exposure to MPs causing cardiac hypertrophy. Increased accumulation of MPs also induced the increase in concentration of cardiac organoids collagen accumulation, disruption of cellular arrangements and change in mitochondrial membrane potential, along with fibrin overexpression⁴³. Experiments in rats reveal that intravenous injection of PS-MP causes arterial hypotension and increased arterial lactate concentration indicating significant hypoxia⁴⁵. All these studies make the analysis of molecular mechanism on MPs induced cardiovascular damages much necessary in order to find out therapeutic strategies.

4. Molecular mechanism of cardiovascular damage induced by MPs

MPs can induce various CAVDs like atherosclerosis, problems in cardiac rhythmicity, hypertension. It has been seen that MPs when exposed to apolipoprotein knockout mice (ApoE -/-) caused increase in expression of atherosclerotic markers.⁴⁶ MPs may accumulate toxic environmental chemicals that may trigger inflammation, endothelial dysfunction, apoptosis and thereby affect proper cardiac functioning. Oxidative stress, reduced cell proliferation and altered gene expression is induced by MPs in other cells apart from cells of the heart, like human kidney and liver. MPs induced weight gain, increased blood glucose and insulin resistance to mice all of which may add to the risk of inducing CAVD by MPs⁴⁷. Recent investigations on effects of MPs in cardiotoxicity have shown that mice exposed to MPs administered intratracheally for 4 weeks (twice a week) had altered myocardial structure and myocardial hypertrophy. MPs were detected in myocardial cells of the MP exposed groups of mice. MPs induce alteration in the arrangement of myocardial fibres, causes ventricular hypertrophy and cardiac fibrosis in the MP treated mice. MPs also cause oxidative stress in the heart as indicated by reduced expression of antioxidative enzymes like SOD. Overall, previous studies indicate that MPs have the potential to induce CAVDs by mediating oxidative stress, cardiac fibrosis, cardiac hypertrophy and cardiotoxicity⁴¹.

Experiments carried on Wistar rats revealed that prolonged exposure of PS-MPs resulted in vascular congestion and myocardial damage⁴⁸. Studies also indicated that MPs induced collagen deposition and increased fibronectin expression in rat heart as detected by Masson's Trichrome, Sirius Red staining and immunohistochemical analyses. Bax expression increased whereas the expression of Bcl-2 decreased in MP treated rat heart compared to control, indicating that MPs have the potency to induce cardiac apoptosis. Western blot analyses showed increased expression of Wnt, β -catenin, p- β -catenin, TGF- β , fibronectin, collagen I and III in a dose dependent manner in MP exposed rats compared to control. All these results indicate that MPs induce oxidative stress and cardiac fibrosis involving Wnt/ β -catenin pathway⁴⁹. Thus, it is necessary for detailed studies on the therapeutic strategies like any potent natural agent that can attenuate the MP induced cardiotoxicity with very less side effects. The mode of action mediated by microplastics to induce cardiovascular damage has been briefly depicted in Fig. 2.

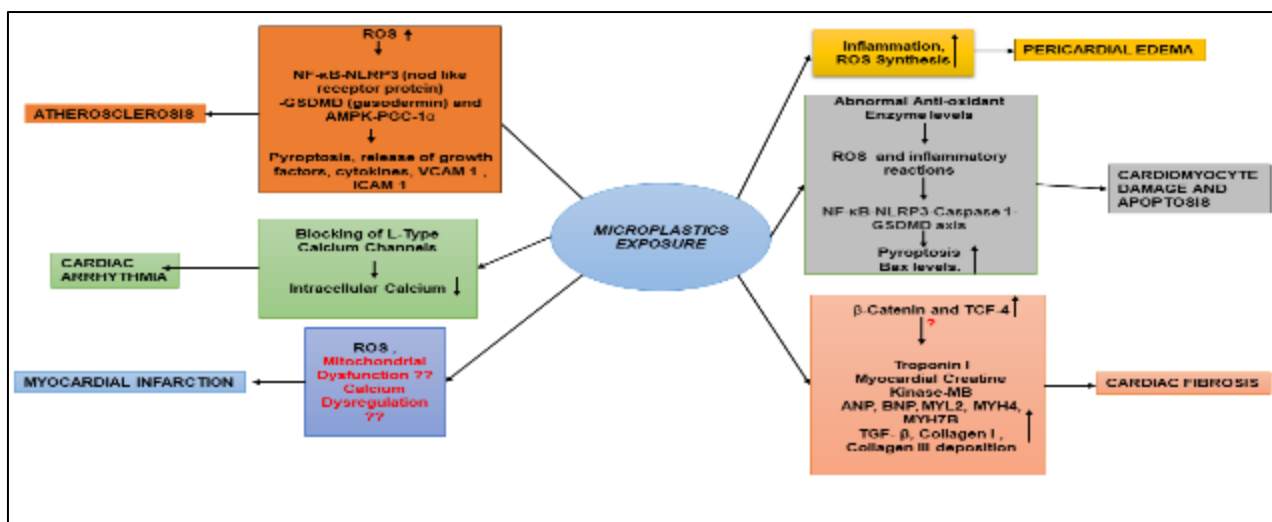


Figure 2 Molecular mechanism of cardiovascular damage mediated by MPs. ↑ -Upregulated, ↓ -Downregulated

5. Cardioprotective role of mushrooms:

Mushrooms considered as nutraceutical with a plethora of favourable bioactive metabolites providing diverse physiological effects⁵⁰. Over the years, amalgamation of mushrooms like *Agaricus bisporus*, *Lentinus edodes*, and *Pleurotus sp.*, in the meal has turned out to be prevalent globally^{51,52}. Mushrooms known to contribute heavy nutritional value to the diet and convey proven favourable effects over hypocholesterolemia, obesity, antihypertensive, diabetes, and cardiovascular diseases^{53,54}. Consuming antioxidants through the diet is a practical approach to help prevent the development of various cardiovascular diseases⁵⁵. Studies explained that polysaccharides and phenolic compounds extracted from mushrooms possess powerful antioxidative properties as they functionally neutralize radical elements by amplifying oxidative enzymes (like glutathione peroxidase, superoxide dismutase and catalase) activity and by stabilizing the levels of glutathione and malondialdehyde⁵⁶. Hypertension, or high blood pressure, places significant strain on the heart and can lead to detrimental changes in its function. Mushrooms, being low in sodium and rich in potassium, serve as beneficial dietary components for managing blood pressure. Studies have demonstrated the antihypertensive properties of various mushrooms, including *Lentinula edodes*, *Ganoderma lucidum*, *Pleurotus nebrodensis*, and *Grifola frondosa*⁵⁷⁻⁶¹. While mushrooms exhibit multiple mechanisms to combat hypertension, one of the most recognized is their ability to inhibit angiotensin-converting enzyme (ACE), thereby offering cardioprotective effects⁶² and in this regard extracts of different mushrooms like *Boletus edulis*⁶³, *Leucopaxillus tricolor*⁶⁴, *Tricholoma matsutake*⁶⁵ and *Pleurotus pulmonarius*⁶⁶ has potentially exhibited the ACE inhibitory effect. The cardioprotective role of some important mushrooms has been discussed below:

5.1. *Lentinus edodes*

Lentinus edodes, commonly known as shiitake, is a macrofungus traditionally used in Korea, Japan, and China for its cholesterol-lowering properties. Elevated cholesterol levels are a major risk factor for cardiovascular diseases, with a strong link between hyperlipidemia and increased CVD-related mortality⁶⁷. According to a Study showed that for 10 weeks rats fed with a dietary supplement comprising of 5% *L. edodes* fruiting bodies has exhibited a prominent reduction in their plasma cholesterol levels⁶⁸. In another *in vivo* study, administration of *L. edodes* caused depletion in the lipidemia-related factors such as serum triglyceride, cholesterol, HDL cholesterol and non-HDL cholesterol⁶⁹. Beyond its therapeutic effects in animal models, *L. edodes* has also demonstrated significant cholesterol-lowering properties in humans. Intake of fresh, dried, or UV-irradiated dried forms of this mushroom has led to a reduction in serum cholesterol levels within seven days in both younger and adult women⁷⁰. Lentinacin, a hypocholesterolemic compound extracted from *L. edodes*, has significantly lowers the level of both HDL and LDL lipoproteins⁷¹.

5.2. *Clitocybe nuda*

The macrofungus well known as wood blewit or blue stalk and occupied in Europe, North America, Asia, and Australia⁷². The ethanol extracts of *C. nuda* depicted an efficient free radical scavenging property, terminating the radical chain reactions occurring during the oxidation of triglyceride and accounts for the antioxidant properties⁷³. Treatment with extracts of *C. nuda* has demonstrated efficient anti-obesity effects by significantly increasing GLUT4 levels and phospho-

AMP-activated protein kinase (AMPK) in the skeletal muscle, adipose, and liver tissues as observed from streptozotocin-induced diabetic mice models⁷⁴.

5.3. *Boletus aestivalis*

Boletus aestivalis (Porcini mushrooms) is a highly valued mushroom in Europe, renowned for its distinctive aroma and commonly used in traditional medicine. An *in vivo* study demonstrated that hot water extracts of porcini mushroom helped to improve hypertension, along with elevated heart rate and the metabolic disturbances associated with the condition. The hot water extract obtained from the mushroom has emerged as a natural nutritional source for alleviating hypertension-related cardiac effects by significantly reducing the creatinine, triglyceride, blood urea nitrogen levels and increasing the high-density lipoprotein-cholesterol levels in blood⁷⁵. In another study presence of phenolics and flavonoids in methanol extracts of *B. aestivalis*, contributes the potent antioxidant effect of the extracts, which may play a key role in their cardioprotective effects⁷⁶.

5.4. *Ganoderma lucidum*

Ganoderma lucidum, long been known as Reishi a medicinal fungus belongs to the family Polyporaceae included as vital constituent in diverse traditional chinese medicine formulations⁷⁷. Over 300 bioactive compounds, like triterpenes, polysaccharides, ganoderic acids, proteins, peptides, steroids, and sterols, were found from *G. lucidum*. These constituents exhibit notable pharmacological activities such as antioxidant, hypolipidemic, hepatoprotective, antiatherosclerotic, and anti-inflammatory effects⁷⁸. A diverse biologically active triterpenoids were isolated from *G. lucidum* including ganoderol A, ganoderol B, ganoderic acid S, and ganoderic acid K which exhibit potent inhibitory effects on angiotensin-converting enzyme⁷⁹. An *in vivo* study with extracts of *G. lucidum* has remarkably controlled the levels of total serum cholesterol, low density lipoproteins, triglyceride concentration, hepatic triglycerides and hepatic cholesterol. Along with these effects mice fed with mushroom extracts depicted a reduction in the expression of lipogenic genes as well as genes involved in reverse cholesterol transport thereby emerging as successful hypocholesterolemic agent⁸⁰. 26-oxygenosterols ganoderol A, ganoderol B, ganoderol A, and ganoderic acid Y isolated from *G. lucidum* observed to inhibit the biosynthesis of cholesterol pathway via conversion of acetate or mevalonate as a precursor of cholesterol leading to new therapeutic agent by lowering levels of blood cholesterol⁸¹.

5.5. *Pleurotus eryngii*

Pleurotus eryngii, an edible and medicinal mushroom belonging to the Pleurotaceae family has demonstrated a range of biological activities, including antioxidant effects and liver-protective properties. The *in vivo* experiments with acidic and alkali-extractable mycelia zinc polysaccharides of *P. eryngii* exhibited reduced levels of LDL cholesterol VLDL cholesterol, total cholesterol, triglyceride levels along with high levels of serum HDL cholesterol confirming *P. eryngii* as potent functional food and nature's drug in combating non-alcoholic fatty liver, hyperglycemia and hyperlipidemia⁸². In another *in vivo* study, mice fed a normal diet containing 3% dried eryngii, mushroom powder exerts positive effects on hyperlipidemic conditions by reducing the serum total cholesterol concentration as well as depleting the atherosclerotic lesion area⁸³.

5.6. *Grifola frondosa*

Grifola frondosa (Maitake) is a widely recognized and commonly consumed medicinal mushroom, native to Japan, parts of Europe, and the northeastern regions of the United States. Powder of *G. frondosa* when fed to atherosclerosis-susceptible, apolipoprotein E-deficient mice it inhibits the development of atherosclerotic lesion area along with other two medicinal mushroom⁸³. Aqueous methanol extracts of fruit body of *G. frondosa* along with seeds of *Momordica charantia* (bitter gourd) demonstrated to counter diabetes and levels of high blood sugar due to its inhibitory effects on α -glucosidase⁸⁴. Evidences from *in vivo* study with alpha-glucan from basidiocarp of maitake mushrooms exhibit antidiabetic effect by decreasing the body weight of mice, reducing the levels of fasting plasma glucose, serum insulin, triglycerides, cholesterol and free fatty acid. These effects are primarily due to their effects on insulin receptors, which cause enhanced insulin sensitivity⁸⁵.

5.7. *Hypsizygus marmoreus*

Hypsizygus marmoreus, an edible mushroom commonly consumed in China, Japan, Korea, Northern Europe, and East Asia. Dietary supplementation with powder of *H. marmoreus* has been shown to reduce total serum cholesterol and exert a potent antiatherosclerotic effect in mice⁸³. A purified novel oligo peptide ACE inhibitor was extracted from water extracts of brown-cultivar-fruiting-body exhibits a lucid antihypertensive action in spontaneously hypertensive rat models⁸⁶.

5.8. *Pleurotus ostreatus*

Pleurotus ostreatus (oyster mushroom), the most popular and effective medicinal mushroom usually investigated for cardioprotection. An *in vivo* study was conducted on STZ-induced diabetic rats with polysaccharides of oyster mushroom. The polysaccharide reduces the levels of hyperglycemia and hyperlipidemia levels while improved insulin resistance and elevated glycogen storage in STZ-induced diabetic rats, which clearly stated that oyster mushroom exerts antidiabetic effect⁸⁷. Similarly another study was conducted with polysaccharides of *P. ostreatus* to evaluate the dyslipidemia effect of oyster mushroom on fat-emulsion-induced hyperlipidemia rats⁸⁸. Study demonstrated that whole fruiting body of *P. ostreatus* has effectively decreased the content of all lipids in lipoproteins⁸⁹ as well as the cholesterol and triacylglycerol levels in both serum and liver of rats^{89,90}. Though in some studies dried form of *P. ostreatus* has employed cholesterol-lowering effects by amplifying the fractional turnover rate of very-low-density lipoproteins^{90,91,92}, by inhibiting the activity of 3-hydroxy-3-methylglutaryl CoA reductase⁹³ and declining the absorption level of cholesterol in animal model^{94,95}. Report from clinical study demonstrated that supplementing patients having dyslipidemia with lyophilized powder of *P. ostreatus* proceed in the elevated activity of the antioxidant glutathione peroxidase exemplifying the potent antioxidant effect of dietary intake of mushrooms⁹⁶.

5.9. *Agaricus brasiliensis*

Agaricus brasiliensis (formerly known as *A. blazei*), a basidiomycete native to Brazil, is extensively cultivated in Japan due to its notable medicinal properties. It is commonly consumed both as an edible mushroom and in extract form for over-the-counter therapeutic use. Traditionally, *A. brasiliensis* has been employed in the prevention of various conditions such as cancer, hepatitis, atherosclerosis, high cholesterol, diabetes, and dermatitis⁹⁷. Polysaccharides from *A. brasiliensis* have been recognized as the key components responsible for its cardioprotective effects against ischemia-reperfusion injury. Pharmacological studies have demonstrated that administration of mushroom polysaccharides significantly increases myocardial SOD activity and decreases MDA levels in rats subjected to ischemia-reperfusion injury⁹⁸. In another study, STZ-induced diabetic rats were orally administered with *A. brasiliensis* and the treatment has showed potent increase in their pain threshold, body weight, and paw withdrawal threshold with significant reduction in serum glucose as compared to non-treated diabetic animals, this could be a potential therapeutic value in the clinical management of diabetic neuropathy⁹⁷.

5.10. *Auricularia auricula*

The fruiting bodies of *Auricularia auricula* have traditionally been consumed as both food and medicine in China. These mushrooms are notably rich in polysaccharides⁹⁹. Among various mushrooms, the polysaccharides from *Auricularia auricula* are some of the most extensively studied and have been shown to possess potent bioactive properties, including antioxidant, anticoagulant, antihyperlipidemic, and antidiabetic activities¹⁰⁰⁻¹⁰³. Administration of polysaccharides extracted from *A. auricula* has significantly lowered the serum total cholesterol and low-density lipoprotein cholesterol concentration and elevated the antioxidant capacity in experimental animals as well as imparted prevention against hypercholesterolemia¹⁰⁰. In other study the composition and structure of polysaccharide obtained from of *A. auricula* was studied. The polysaccharide of macrofungus was composed of glucose, mannose, xylose and fucose, which when administered in aged mice has elevated the ejection fraction (EF) and shot axis fractional shortening (FS) parameters of their left ventricles. Hence the polysaccharides from *A. auricula* emerge as a potent antioxidant that imparts cardioprotection in aged mice as well as decreased their aging process¹⁰⁴. *A. auricula* has high dietary fiber content so in *in vivo* study 5% dried powder of this mushroom was fed to Sprague-Dawley rats. Feeding dried powder have significantly lowered LDL cholesterol levels in rats with no effect in serum HDL cholesterol, concluding that this mushroom had effective hypocholesterolemic activity¹⁰⁵.

5.11. *Tremella fuciformis*

Tremella fuciformis, commonly known as snow ear, is a member of the family Tremellaceae under the order Tremellales. This widely cultivated and popular mushroom is commonly consumed both as a food item and as a traditional herbal remedy, particularly valued in Chinese medicine for its tonic effects^{106,107}. It contains a variety of bioactive compounds, such as polysaccharides, dietary fiber, and polyphenols and these constituents contribute to the mushroom's diverse health-promoting properties, including immunomodulatory effects¹⁰⁸, antioxidant activity¹⁰⁹, lipid-lowering effects¹¹⁰, and anti-obesity benefits¹⁰⁶. Researchers also studied the anti-atherosclerosis effect of *T. fuciformis* where the extract of this mushroom demonstrated potent decline in the thickness of the aortic root wall and the area of lipid droplets. This mushroom has also regulated the levels of lipid and prevented fat accumulation to enhance aortic root lesions and potentially inhibited the inflammatory response to ameliorate atherosclerosis via downstream signaling¹¹¹. In an *in vivo* study, administration of 5% dried powder of *T. fuciformis* had a distinct decline in serum triacylglycerol as well as LDL cholesterol level, concluding its hypocholesterolemic activity¹⁰⁵.

6. Conclusion

MPs are pervasive in the environment and their effects on human health, especially regarding cardiovascular diseases are emerging as critical areas of concern. Given the growing body of evidence linking MPs to various pathological conditions, there's an urgent need for a deeper understanding of their molecular mechanisms and their role in the etiology of diseases which might help public healthcare to implement policies and strategies to mitigate the effects of MPs. Current research often uses high doses of MPs, which may not reflect typical human exposure levels. There is a pressing need to identify more realistic exposure doses that are likely to cause cardiovascular problems and other health impacts. Detailed exploration of the molecular signaling mechanisms (e.g., NF- κ B, AMPK, ERK, and JNK) triggered by MPs is necessary to better understand the underlying pathogenesis of diseases induced by these particles.

Mushrooms well recognized as a functional food due to their rich nutritional profile and the presence of numerous bioactive compounds that support human health and may aid in the prevention and management of various diseases. In alignment with current dietary guidelines for CAVDs prevention and treatment, edible mushrooms offer valuable nutritional benefits and have been shown to influence several cardiovascular risk markers. Their consumption help prevent the onset of atherosclerosis as well as cholesterol-lowering (hypocholesterolemic) effect which is achieved through mechanisms such as reducing very-low-density lipoprotein (VLDL) levels, enhancing lipid metabolism, and inhibiting HMG-CoA reductase activity. Additionally, the antioxidant and anti-inflammatory properties of compounds found in mushrooms may further contribute to lowering the risk of atherosclerosis. Moreover, in depth research is essential to better understand the mechanisms of macrofungi to combat the MPs associated CAVDs.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflict of interest to disclose.

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