Received: 28 December 2022 | Revised: 7 April 2023 | Accepted: 24 April 2023

DOI: 10.1002/ptr.7865

REVIEW

WILEY

Edible mushrooms as potential functional foods in amelioration of hypertension

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Funding information
Universidade de Vigo, Grant/Award Number: CRUE/CSIC

Abstract

Edible mushrooms are popular functional foods attributed to their rich nutritional bioactive constituent profile influencing cardiovascular function. Edible mushrooms are omnipresent in various prescribed Dietary Approaches to Stop Hypertension, Mediterranean diet, and fortified meal plans as they are rich in amino acids, dietary fiber, proteins, sterols, vitamins, and minerals. However, without an understanding of the influence of mushroom bioactive constituents, mechanism of action on heart and allergenicity, it is difficult to fully comprehend the role of mushrooms as dietary interventions in alleviating hypertension and other cardiovascular malfunctions. To accomplish this endeavor, we chose to review edible mushrooms and their bioactive constituents in ameliorating hypertension. Hypertension and cardiovascular diseases are interrelated and if the former is managed by dietary changes, it is postulated that overall heart health could also be improved. With a concise note on different edible varieties of mushrooms, a particular focus is presented on the antihypertensive potential of mushroom bioactive constituents, mode of action, absorption kinetics and bioavailability. Ergosterol, lovastatin, cordycepin, tocopherols, chitosan, ergothioneine, γ-aminobutyric acid, quercetin, and eritadenine are described as essential bioactives with hypotensive effects. Finally, safety concerns on allergens and limitations of consuming edible mushrooms with special reference to chemical toxins and their postulated metabolites are highlighted. It is opined that the present review will redirect toxicologists to further investigate mushroom bioactives and allergens, thereby influencing dietary interventions for heart health.

KEYWORDS
absorption kinetics, bioactive constituents, cardiovascular, edible mushrooms, functional foods, hypertension

Abbreviations: AHA, American Heart Association; AMPKα, activated protein kinase α; CVDs, cardiovascular diseases; CytochromeP450scc, cytochrome P450 side-chain cleavage enzyme; CYP7A1, cytochrome P450 7A1; DASH, Dietary Approaches to Stop Hypertension; DGAT1, diacylglycerol *O*-acyltransferase-1; FAOSTAT, Food and Agriculture Organization Corporate Statistical Database; FFs, functional foods; GABA, γ-amino butyric acid; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IC_{50}, half-maximal inhibitory concentration; LDLR, low-density lipoprotein receptor; MedDiet, Mediterranean diet; PKC, protein kinase C; PWE, pressurized water extraction; SAHH, *S*-adenosylhomocysteine hydrolyze; SQS mRNA, squalene synthase messenger RNA.

1 | INTRODUCTION

Hypertension is one of the major risk factors for heart diseases and an indicator of global health exigency. It is regarded as a chronic, non-communicable, modifiable, and a multifactorial pathophysiological condition associated with increased arterial blood pressure. A normal blood pressure is sustained at an average diastolic blood pressure (80 mmHg) and average systolic blood pressure (120 mmHg). According to National Health and Nutrition Examination Surveys, hypertension is defined as "systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg" (Egan & Zhao, 2013). Hypertension, or systemic arterial hypertension if unchecked, leads to serious pathological conditions namely, stroke, CVDs, heart failure, aortic syndromes, aortic valve stenosis, atrial fibrillation and hypertensive cardiomyopathy (Fuchs, 2018). According to Noncommunicable Diseases Risk Factor Collaboration report, hypertension is asymptomatic and caused a global burden of hypertensive patients (Nguyen & Chow, 2021).

In 2015, an estimated 4.5 million deaths in men and 4.0 million deaths in women were attributed to higher systolic pressure (>115 mmHg), of which 88% were in low-income and middle-income regions (Zhou et al., 2021). Efforts are directed toward either by prescribing antihypertensive drugs or dietary changes that includes functional foods. Functional foods (FFs) have gained considerable attention for managing various chronic ailments including hypertension. In this review, we have focused on edible mushrooms and their role in ameliorating hypertension.

The genesis to review edible mushrooms as functional food ingredient relies on that fact that it has numerous bioactive constituents and its promissory inclusion as healthier meat products (Pérez-Montes et al., 2021). Table 1 depicts the production of edible mushrooms in 2021. Venkatakrishnan et al. (2020) performed meta-analysis describing influence of FFs and nutraceuticals and their pathophysiological impact on hypertension. Sporadic reports claim variety of food stuffs or dietary changes to determine the efficacy for various pathological conditions of the heart. Recently, growing interest on edible mushrooms for its functional ingredients in food industries and as dietary supplements is palpable (You et al., 2022). With abundance of bioactive constituents, mushrooms are explored for novel compounds that could potentially act as therapeutics. Edible mushrooms have demonstrated their efficacy as therapeutics in ailments such as diabetes, obesity, cancer, and CVDs leading to human wellness (Singh et al., 2022). Since long, mushrooms are explored for novel compounds that may have pharmacological relevance. At times, it can be posed that mushrooms are rich with numerous bioactives that it may seem rather indistinguishable as edible or medicinal by terminology. The expanse of edible mushrooms is so vast that it was realized to reexamine the classification system of the fungus (Li et al., 2021). Herein, we ventured to describe various edible mushrooms with potency toward ameliorating hypertension.

The present review is structured as: first, we describe the literature review on edible mushrooms focusing on heart health. Next, we discuss functional foods as substitutes for synthetic drugs with mushrooms under purview. Different types of edible mushrooms and their bioactive constituents are discussed in detail along with some patent literature. An insight on correlating structure of bioactive constituents and their hypotensive effects are postulated with a concise note on mushroom toxins. Furthermore, discussion on absorption kinetics and bioavailability of mushroom bioactives is provided. Of all the functional foods (FFs), it is argued that edible mushrooms exert hypocholesterolemia, yet with certain limitations. Taking cues from the review by Izzo et al. (2016), we explored current efforts undertaken to determine food (mushroom)-function (hypotension) relationship that is not a straightforward endeavor. A concise note on the limitations of edible mushrooms as a dietary functional food is presented to avoid overclaiming its benefits per se. It is advised that health practitioners must suggest edible mushrooms in diet with caution as it is also a potential allergen.

TABLE 1 Production of edible mushrooms (FAOSTAT, 2021).

Country	Production (in tons)
China, Mainland	41,117,736.71
Japan	469,046.11
Poland	378,800
United States of America	343,820
Netherlands	260,000
India	243,000
Spain	163,800
Canada	137,796
Russian Federation	110,976.96
France	99,110
Indonesia	90,420.22
United Kingdom	85,754.04
Germany	83,800
Italy	67,770
Australia	42,526

1.1 | Literature review

In the quest to unravel the relationship of food (mushroom)-disease (hypertension), a literature search was performed using PubMed, Science Direct, and Google Scholar. We also included articles that were cross-referenced from bibliographic references from the collected papers. Due to the premise of the review, selected patents and pertinent books on hypertension and edible mushrooms are cited, wherever necessary, to provide an expanse to the readers.

Francia et al. (1999) reviewed on fungal macromycetes that exerted decreased hypertension, hyperchloresterolemia and dyslipoprotenemia. Guillamón et al. (2010) reported the influence of consuming mushrooms on CVD biomarkers and identified bioactive constituents exerting hypotensive effects. Choi et al. (2012) described the therapeutic potential of edible mushrooms on cardiac diseases. This was followed by literature reports on edible mushrooms as health promoting foods (Roupas et al., 2012; Ahmad et al., 2013; Roncero-Ramos & Delgado-Andrade, 2017). A concise review by Mohamed

Yahaya et al. (2014) discussed on correlating edible mushroom consumption for preventing hypertensive symptoms. Tung et al. (2020) reported link between cardiovascular syndrome and consuming mushrooms. However, the review listed various bioactive constituents of mushrooms to heart health with no correlation to structure–activity relationships (SAR). González et al. (2020) reviewed on edible mushrooms fortified in different food products. Wouk et al. (2021) described the carbohydrate chemistry of β-glucans and their role as polysaccharide-protein complex exerting antihypertension. Individual studies on mushrooms are also reported such as *Volvariella volvacea* (Chiu et al., 1995), *Ganoderma lucidum* (Ahmad et al., 2021; Rahman et al., 2018), *Pleurotus* sp. (dos Reis et al., 2022). With growing interest of edible mushrooms, this review attempts to explore relation of mushroom bioactives with anticholesterolemic effects.

2 | METHODS TO MANAGE HYPERTENSION

An increase in the intra-arterial pressure is referred to as hypertension. Often categorized as essential and secondary hypertension, the former one is fairly common and managed by dietary changes and prescription drugs. Secondary hypertension is less predominant type of metabolic disorder caused due to endocrine malfunction. The two common methods of managing hypertension are first, prescribing "antihypertensives" and second, including dietary changes with functional foods. Nevertheless, the chosen method for controlling hypertension is based on age, severity, gender and race of the patient.

2.1 | Antihypertensive drugs

Antihypertensives are synthetic drugs prescribed as a therapeutic intervention for alleviating, preventing, or treating hypertension. These drugs are categorized based on the site or mechanism of action. Some of the most popular classes used as first-line therapy include, targeting renin–angiotensin system, calcium channel blockers, adrenoceptor antagonists and diuretics (Jackson & Bellamy, 2015). *Calcium channel blockers* act by preventing calcium to enter heart and blood vessel muscle cells. Diltiazem, nifedipine and amlodipine tend to enlarge the arteries thereby lowering blood pressure (Savage et al., 2020). Enalapril, lisinopril, and perindopril are examples of *angiotensin-converting enzyme (ACE) inhibitors* that lower blood pressure by relaxing blood vessels. Drugs such as azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, valsartan block the renin-angiotensin system. These drugs reduce blood pressure by dislodging angiotensin II from the angiotensin I receptors (P. Zhang et al., 2020). Amiloride, chlorthalidone, frusemide, and indapamide are common *diuretics*, also referred to as "water pills," which act by excreting extra water and salts from the body via urine (Shah, 2004).

Hypercalcemia, excess fluid loss, heart palpitations, dizziness, fatigue, and swelling are common side effects of antihypertensives. These drugs potentially cross blood–brain barrier and blood cerebrospinal fluid barrier, thereby exerting psychotropic effects (Carnovale et al., 2022; Hollis et al., 2019). There are rising incidences of pregnancy-related hypertension called, gestational hypertension and preeclampsia (Ford et al., 2022). Antihypertensives have adverse impact on either the mother or fetus, or both. Dietary interventions must be prescribed in such cases based on age, patient history and allergenicity (Fogacci et al., 2020; Sun & Niu, 2020).

2.2 | Functional foods as alternative to antihypertensive drugs

Functional foods (FFs) are those that are consumed as a regular diet and offer various bioactive constituents providing nutrition and positive health impacts. Strict adherence to medication is difficult and thus, changes in diet for intervening chronic illness without compromising taste and flavors is plausible. Gebreyohannes et al. (2019) discussed correlation of nonadherence to antihypertensives and poor heart conditions. Thus, FFs are employed to achieve sustainable management of chronic ailments. Most of the literature features terminologies, "functional foods" and "nutraceuticals" interchangeably. These terms have separate definitions. Readers are encouraged to refer (Egbuna & Dable-Tupas, 2020; Cheung, 2009; Pandita & Pandita, 2023) for definitions. Mushrooms are one of the popular FFs and its consumption correlates to incorporating numerous health-promoting compounds. They occupy special place in different cultures as medicine and culinary delicacies. Today, food industries fortify most of their products with edible mushrooms in ready-to-eat noodles, milk powders, breads, biscuits and puddings. Edible and medicinal mushrooms are no different, and the former terminology is used throughout the article for brevity.

3 | EDIBLE MUSHROOMS AS POTENT FUNCTIONAL FOODS

Mushroom are "macrofungus with distinctive fruiting body that can be either epigeous or hypogeous and large enough to be seen with naked eye and to be picked by hand" (Chang & Miles, 1992). Mushrooms are abundantly loaded with essential bioactives such as ergosterol, polyphenols, terpene and terpenoids, polysaccharides and proteins (Gupta et al., 2019). All these fungal bioactives tend to exert positive effects on reducing hypertension (Figure 1). Mushrooms possess a typical "meaty" texture making them an ideal plant-based meat substitute. With varying degrees of success, mushrooms are included in diet plans and fortified in meat-based food stuffs.

3.1 | DASH diet and Mediterranean foods

Enormous studies revealed that nutraceuticals (Borghi et al., 2022), Dietary Approaches to Stop Hypertension (DASH) (Cicero et al., 2021; Farhadnejad et al., 2019; Strilchuk et al., 2020) and Mediterranean diets (Cowell et al., 2021; De Pergola & D'Alessandro, 2018) have a marked influence on hypertensive patients.

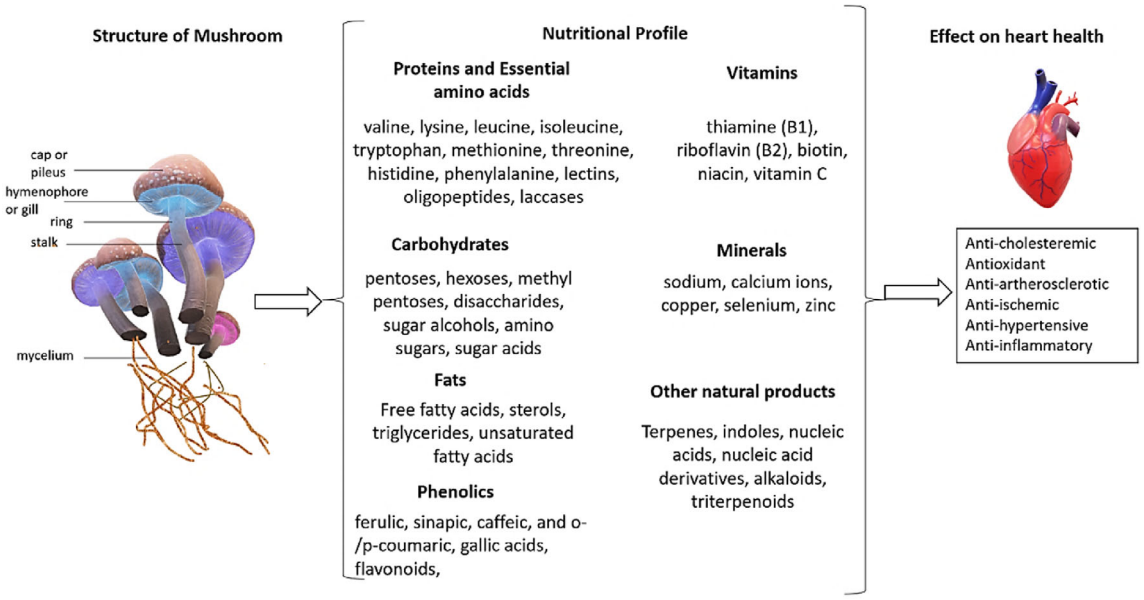


FIGURE 1 Nutritional profile of edible mushrooms.

DASH or Mediterranean foods are typical culinary diet regime that incorporates fruits, vegetables, nuts, legumes, fish, lean meat, mushrooms, low-fat diary products and reduced saturated fats, sodium content/salts, sugars and cholesterol. One key feature is its exclusion of red meats. DASH diet was formulated by AHA that recommends 55% carbohydrates, 18% proteins, 27% fats with minerals and vitamins (Appel et al., 2006). Mushroom-based diet has lower sodium content (about 100 and 400 ppm) and hence, particularly useful for hypertensive patients (Vetter, 2003). Edible mushrooms are considered as a part of this dietary plan.

Such dietary plan is postulated to lower hypertension among patients, though meta-analysis and systematic reviews are inconclusive on this claim (Siervo et al., 2015). Mediterranean diet (or MedDiet) is a typical meal plan for hypertensive patients and mushrooms is considered as a vegetable on USDA's MyPyramid and MedDiet Pyramid. Agarwal and Fulgoni III (2020) assessed the nutritional influence of mushrooms prescribed by USDA's guidelines. They examined mushroom composite (made of white, crimini and portabello) and raw oyster mushrooms. It was revealed that 1 serving of 84 g (one serving ~2000 kcal) raw edible mushrooms increased macronutrients (5%), dietary fiber (2%–6%), riboflavin (~15%), potassium (~11%), niacin (13%–26%), Cu (13%–22%), vitamin D (9%–11%) and choline levels (~14%) post-inclusion of oyster mushrooms. The correlation on edible mushrooms in MedDiet and CVDs is currently trialed by Purdue University and Mushroom council (Campbell, 2022). Today, most meat- or muscle-based foods are fortified with edible mushrooms to take advantage of its bioactive properties (Das et al., 2021).

3.2 | Different types of edible mushrooms

Portobello, oyster, shiitake, maitake, reishi, shimeji, yellow-cap, cauliflower and enoki mushrooms are described. Edibility of mushrooms also comes across as being region-specific, as most wild mushrooms that are poisonous for one particular country may be medicinal for another region or country. Table 2 lists selected patents pertaining to novel mushroom extraction processes for hypotensive compounds. The presence of characteristic bioactive compounds especially, high amount of selenium further adds to lower the chances of chronic diseases (Falandysz, 2008). It is loaded with vitamins (riboflavin, thiamine, cobalamin, ascorbic acid and vitamin D) and minerals (Mn, Ca, Cu, Fe, P, K, Na, Mg, and Se) (Mattila et al., 2001).

3.2.1 | Portobello mushrooms

Agaricus bisporus (or portobello mushroom) is widely consumed mushroom and has a mild taste. It contains glutathione, selenium, β-glucan, and ergothioneine known to exert hypoglycemic and hypolipidemic effects synergistically (Jeong et al., 2010). β-Glucan is a soluble fiber that has the ability to form gel-like substance on digestion. This gel-like substance traps cholesterol and triglycerides to prevent their absorption in GI tract that eventually lowers the blood cholesterol levels (Sima et al., 2018). Ergothioneine reduces triglyceride levels and prevents the formation of arterial plaque—one of the causative factors of heart failure (Martin, 2010).

3.2.2 | Oyster mushrooms

Pleurotus ostreatus (or oyster mushrooms) are widely popular, possess mild anise-type flavors and are either served as raw or cooked forms. Certain bioactive peptides are obtained after digestion of *P. ostreatus* mushrooms inhibit ACE-I that plays a crucial role in reducing blood pressure and glucose levels (Agunloye & Oboh, 2022; Baeva et al., 2019).

TABLE 2 Patents on selected edible mushrooms or their products and their pharmacological claims related to cardiovascular conditions.

Mushroom products/bioactive extraction process	Pharmacological claim	References
Milk powder supplement obtained from *Pleurotus ostreatus*	Hypocholesterolemic	Motte and Wyvekens (2015)
Novel ACE inhibitor from *Lentinula edodes* and *Creolophus cirrhatus* using proteases	Hypotensive action	Ito et al. (2006)
Food supplements prepared from *G. frondosa*, *P. eryngii* and *H. erinaceus*	Antihypertensive, lowers blood lipid levels	Zhiqiang et al. (2008)
Method of eritadenine production in liquid phase fermentation of *Lentinus edodes*	Hypocholesterolemic agent	Berglund et al. (2008)
Novel method to prepare heteroglycans from *Ganoderma lucidum*	Anti-obesity, antihypertensive	Ko et al. (2017)

3.2.3 | Shiitake mushrooms

Lentinula edodes (or shiitake mushrooms) are a staple edible mushroom characterized as large, brown mushrooms with umami flavors. On cooking, shiitake develops a velvety texture. Bioactive compounds such as ergosterol, eritadenine and lentinan exert hypotensive effects (Agunloye & Oboh, 2022). Preclinical studies illustrated that shiitake extracts stimulate removal of excess sodium renally and reduces fluid retention. It also contains calcium and magnesium that play a key role in lowering hypertension (Khatun et al., 2007).

3.2.4 | Maitake mushrooms

Grifola frondosa (or maitake mushrooms) are indispensable to Asian cooking. Their name is derived from Japanese language; meaning dancing mushrooms due to their characteristic ribbon-like appearance. It has deep earthy flavor that makes it an ideal choice for meals with complex flavors. In vivo studies on rat models revealed that maitake mushrooms have potency to enhance insulin sensitivity, reduce inflammation and triglyceride levels especially in age-related hypertensive cases (Preuss et al., 2010).

3.2.5 | Reishi mushrooms

Ganoderma lingzhi (or reishi mushrooms) are characterized by their deep-red colors and bitter taste. It is mostly consumed as as a supplement in powder form and is also used in cooking. Fungal bioactives found in reishi mushrooms play an important role in regulation of ACE; an enzyme responsible for cardiovascular functioning and decreased serum cholesterol levels (El Sheikha, 2022).

3.2.6 | Shimeji/brown mushrooms

Hypsizus marmoreus (or shimeji mushrooms) occur in a variety of shapes and is bitter to taste, when consumed raw. On cooking, shimeji mushrooms elicit a nutty umami flavor. It contains angiotensin ACE inhibitors (oligopeptides) that reduces blood pressure. Several polysaccharides, flavonoids, cytokines and other phenolic content in shimeji mushrooms prevent oxidative stress and inflammation, thereby improving blood pressure dynamics (Chien et al., 2016).

3.2.7 | Yellow cap mushrooms

Cantharellus cibarius (or yellow cap mushrooms) are golden-yellow colored wild edible chanterelle mushrooms with unique fruity-peppery flavors. Niacin, pantothenic acid, vitamin D, copper, phenols and flavanoids helps to lower blood pressure, and is safer for consumption in pregnancy-induced hypertension and preeclampsia (Kozarski et al., 2015).

3.2.8 | Cauliflower mushrooms

As the name suggests, *Sparasis crispa* (or cauliflower mushrooms) resembles to cauliflower in shape and are combined with red meat, soups and noodle broths. Sparassol (methyl-2-hydroxy-4-methoxy-6-methylbenzoate) is an antimicrobial agent (Sharma et al., 2022). *S. crispa* was determined as an antihypertensive food and prevented stroke on experimentation in spontaneously hypertensive rats. An increase in NO production served as the main mechanism behind decreased blood pressure dynamics. It improved endothelial dysfunction by activating Akt/eNOS pathway on the cerebral cortex in hypertensive rats (Yoshitomi et al., 2011).

3.2.9 | Enoki (Golden needle) mushrooms

Flammulina velutipes (or enoki/enokitake mushrooms) are lighter in color with log stems while the wild variety tends to be darker with shorter stems. Mycosterol is a major bioactive constituent found in enoki mushrooms that is postulated to lower blood pressure dynamics and decrease the concentration of total cholesterol levels in blood and liver (Yeh et al., 2014).

4 | MECHANISM OF ACTION

The consumption of mushrooms is related to various biomarkers to determine their influence on heart health and blood pressure

dynamics. Biomarkers which are used to determine the causal food-hypertension link are cholesterol, total LDL, HDL, fasting triacylglycerol, homocysteine, homeostasis, antiplatelet aggregation, and inflammation.

Cholesterol is an essential sterol found in all mammalian cells and is a vital component that influences phospholipid layers, cell membrane functionalities, cell cycles, protein regulation and most importantly, initiates production of steroidal hormones and bile acids (Rozman & Gebhardt, 2020).

As seen in Figure 2, cholesterol biosynthesis is an enzymatic biochemical pathway called *mevalonate pathway* occurring through hepatic system and involves 20 reactions cascading through various enzymes. The transformation of HGA-CoA to mevalonic acid is a rate-limiting step. Any changes in HGA-CoA enzyme activity will immediately influence changes in cholesterol biosynthesis. Hence, this transformation step is a therapeutic target for alleviating hypertension especially using statins.

Statins found in mushrooms can inhibit the activity of a key enzyme in cholesterol synthesis, called the HMG-CoA reductase. Other modes of action are vasorelaxation by flavanols and reduced platelet aggregation due to fibrinolytic enzymes (Figure 2b,c) that plays similar role of plasmin in fibrinolytic system. Both flavanols, particularly quercetin and fibrinolytic enzymes are found abundantly in mushrooms and are known to exert vasorelaxation and inhibit vascular plaque within the arteries.

Efforts to unravel the mode of action of different bioactive constituents are reported (see Table 3). It is postulated that the synergistic effects of mediating cholesterol biosynthesis, fibrinolytic systems and vasorelaxation via Ca-channels prevents hypertension. A detailed account on effect of mushroom bioactives on cholesterol homeostasis and gut absorption is described in Section 5.1. It was recently postulated that severity of COVID-19 infection and underlying hypertension is due to ACE-II enzyme activity and immunocompromised or disordered renin-angiotensin-aldosterone system (Peng et al., 2021). However, this claim is beyond the scope of our present discussion. Proceeding with the next section, discussion on structural moieties of bioactives and their influence on hypertension is presented.

5 | MUSHROOM BIOACTIVES AND CARDIOVASCULAR FUNCTION

Natural products obtained from mushrooms are well-established as lead compounds for developing novel medicines. Lovastatin, ergosterol, cordycepin, polysaccharides such as mannitols, chitosan, eritadenine, indoles, tocopherols, β-glucans, GABA, ergothioneine are chosen bioactive constituents (Scheme 1) that exert positive effects on heart function.

An attempt is made to examine the structural features and correlate them to their effects on lowering hypertension or other cardiovascular conditions. Chemical structures are redrawn using ACD/ChemSketch version 2020.1.2 (Advanced Chemistry Development Inc., Canada, http://www.acdlabs.com).

Ergosterol, a fungal phytosterol is structurally similar to cholesterol. If ergosterol assimilates in the alimentary tract, it gets accumulated in the adrenal glands. It metabolizes in vivo to generate a bioactive constituent, 17α,24-dihydroxyergosterol (Slominski et al., 2005) (see Scheme 2).

Ergosterol undergoes photolysis to generate various metabolites of vitamin D that has the potential to regulate calcium levels in the

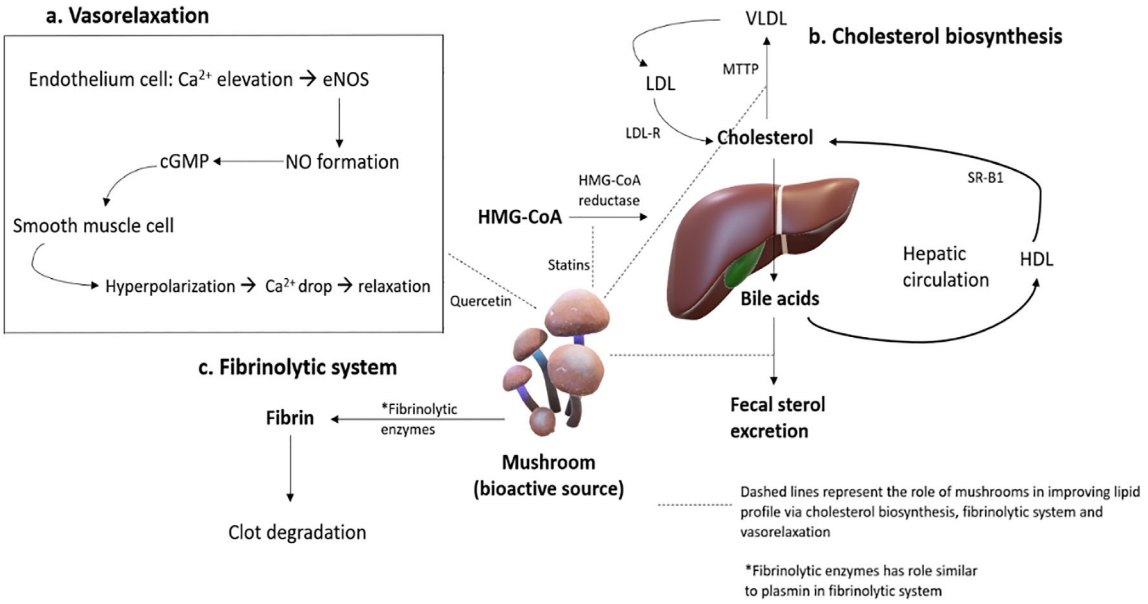
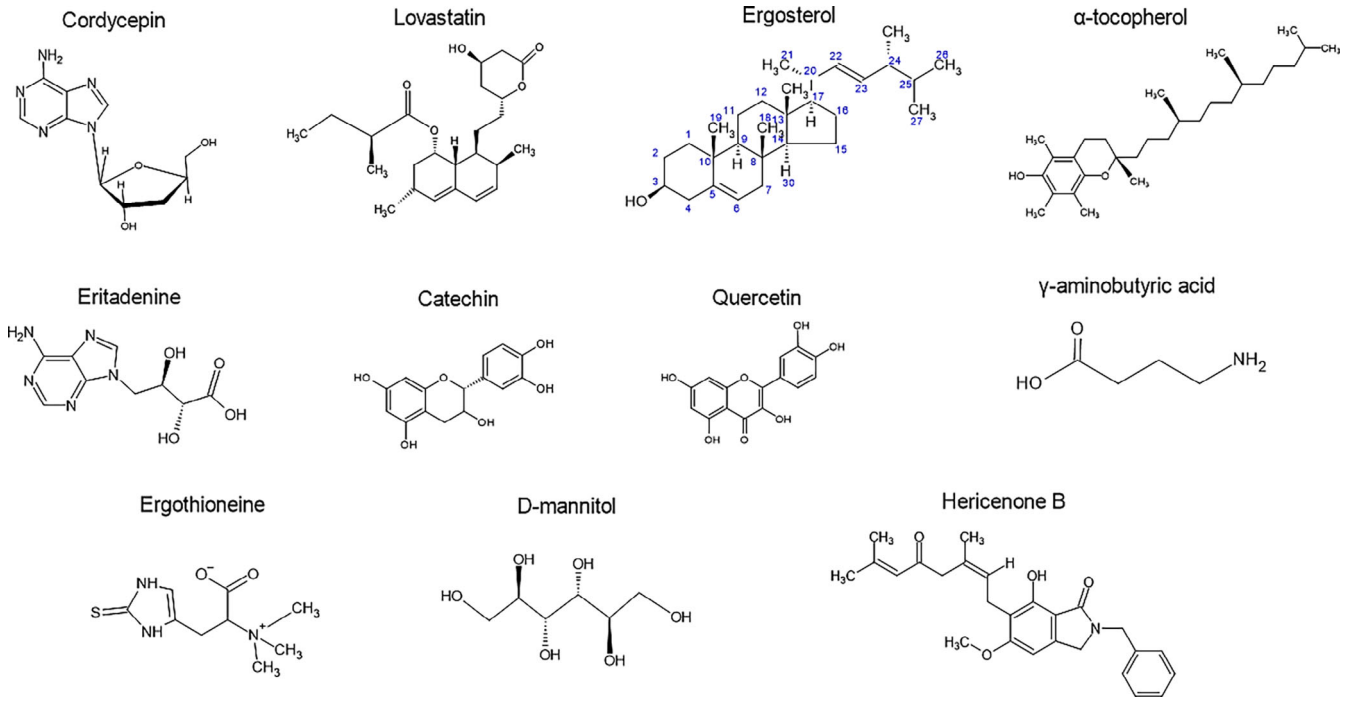


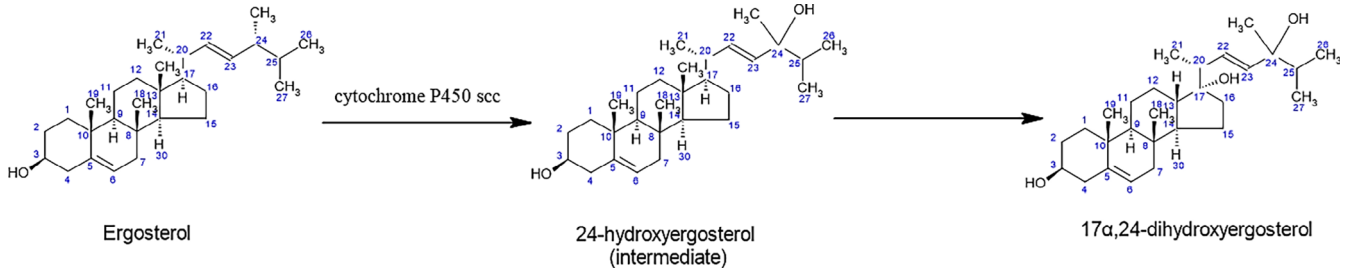
FIGURE 2 Possible mechanism of action of mushrooms on hypertension. cGMP, cyclic guanosine monophosphate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; MTTP, microsomal triglyceride transfer protein; SR-B1, Scavenger Receptor Class B type 1; VLDL, very low-density lipoprotein.

TABLE 3 Mechanism of action to alleviate hypertension and mushroom bioactive constituents (Mohamed Yahaya et al., 2014).

Mushroom species	Bioactive constituents	Mechanism of action
Ganoderma lucidum	Ganoderol A, B; Ganoderal A, Ganoderic acid Y	ACE activity inhibition (Kabir et al., 1988)
Polyporus sclerotium	Ergosta-4-6-8(14), 22-tetraen-3-one	Antialdosteronic, diuretic (Yuan et al., 2004)
Lentinula edodes	Potassium (K^+ form)	Hyperpolarization of smooth muscle cells, stimulating Na–K pumps, dose dependent (Haddy et al., 2006)
	Lentinan, eritadenine	Vasodilation (Bisen et al., 2010)
Sarcodona spratus	L-Piperidine-2-carboxylic acid	Competitive ACE inhibition attributed to stereochemical orientation of —COOH group (Kiyoto et al., 2008)
Marasmius androsaceus	Tripeptide 3,3,5,5-tetramethyl-4-piperidone	Ganglionic blocker (L. Zhang et al., 2009)
Pleurotus cystidiosus and Agaricus bisporus	Oligo peptides and proteins	ACE activity inhibition (Lau et al., 2012)
Antrodia camphorata	Maleic/succinic acid derivatives, triterpenoids, benzenoid, benzoquinone derivatives	Reduces aggregation and phosphorylation of PKC in phorbol-12,13-dibutyrate-activated platelets (Lu et al., 2014)
Cordyceps militaris	Cordycepin	Alleviates cardiac hypertrophy via AMPKα signaling and reduces oxidative stresses (Wang et al., 2019)



SCHEME 1 Selected bioactive constituents in edible mushrooms in ameliorating hypertension.



SCHEME 2 Metabolism of ergosterol.

body. It was predicted by Pilz et al. (2008) that lower levels of vitamin D is associated with increased risk of hypertension and mortality.

Cordycepin is a bioactive constituent obtained from *Cordyceps militaris* and exerts lowering of lipid levels in blood, alleviates accumulation of total cholesterol, LDLs and triglycerides (Gao et al., 2011). The causal link of cordycepin and antihypertensive effects could be attributed to its structural similarity with adenosine moiety.

Lovastatin is a typical bioactive compound found in fruiting portion of *A. bisporus*, *C. cibarius and L. edodes*. It comprises of a lactone ring and conjugated decene ring connected by an ester linkage to 2-methylbutyryl group. Lovastatin can enzymatically transform to hydroxy acid that inhibits transformation of HMG-CoA to mevalonic acid and finally to cholesterol (Kała et al., 2020).

Tocopherols obtained from *Craterellus cornucopioides* is known to exert positive effect on heart function. A systematic review by Rychter et al. (2022) found the correlation of vitamin E and its role in alleviating risk factors of CVDs inconclusive.

Chitosan is a polysaccharide found in *Imerlia badia* that could alleviate LDLs in blood and liver and triglyceride levels in the blood (Ylitalo et al., 2002). The efficacy of chitosan on heart function was explored through an in vivo study (Gallaher et al., 2000) and meta-analysis using murine models (Ahn et al., 2021). Both these studies were inconclusive, but meta-analysis study revealed that gut absorption results in chitosan efficacy on the heart's functionality.

Ergothioneine is a sulfur-containing amino acid with an imidazole moiety postulated to protect heart against myoglobin oxidation to ferryl myoglobin catalyzed by reactive oxygen or nitrogen species. Due to ergothioneine's existence as a tautomer (i.e., between thiol and thione form), its thione form tends to exist as a predominant antioxidant. Smith et al. (2020) reported a direct correlation of five different metabolites, one of which was ergothioneine obtained through diet to enhance cardiovascular function.

γ-Aminobutyric acid (GABA) is a bioactive compound and various in vivo and in vitro studies revealed that systemically-injected GABA-agonists caused lowering of blood pressure and bradycardia by activating GABA-receptors in cardiovascular tissues (Kimura et al., 2002; Ma et al., 2015).

Quercetin is a naturally occurring flavanol exerting hypotensive, vasodilator, anti-ischemic, and antiatherosclerosis effects. Hydroxy groups on quercetin donate their hydrogen atoms and quench singlet oxygen or nitrogen species and are potent antioxidants. Similar role is observed for catechin; an antioxidant and vasorelaxant rendering them as potential bioactives for ameliorating hypertension (Serban et al., 2016).

Eritadenine is an alkaloid that is structurally analogous to adenosine moiety. It is an efficient inhibitor of cholesterol absorption within the GI tract thereby maintaining synergistic equilibria between plasma and tissue cholesterol levels (Bisen et al., 2010). Eritadenine exerts faster elimination of blood cholesterol either by stimulated tissue uptake or inhibited tissue release. However, eritadenine's direct effect on cholesterol biosynthesis is unclear. It is postulated that eritadenine can suppress metabolic conversion of linoleic acid to arachidonic acid (Yamada et al., 2002) and slow down homocysteine production—an amino acid that reduces HDL levels in plasma via a mechanism of inhibiting hepatic biosynthesis of main HDL apolipoprotein (Liao et al., 2006). Eritadenine also exerts an inhibitory effect on a key enzyme called *S*-adenosylhomocysteine hydrolyze (SAHH). SAHH enzyme plays an important role in hepatic phospholipid metabolism and hence its inhibition by eritadenine could lower cholesterol levels in the blood serum. Furthermore, it was observed that derivative of eritadenine called 3-deaza eritadenine and its analog compounds also exert hypocholesterolemic activities (Yamada et al., 2007).

Edible mushrooms comprise of higher linoleic/linolenic ratio that also influences cardiac functionalities. PUFAs are 'essential' FAs that get converted to tissue hormones thereby preventing arterial blood clots and hypertension (Sande et al., 2019). Table 4 depicts the amount of important hypotensive bioactives found in selected edible mushrooms. An efficient method to prevent CVDs and thrombosis is antiplatelet therapy (Jennings, 2009; Kiernan et al., 2009). Yoon et al. (2003) isolated acidic polysaccharides from *Auricularia auricula* that exhibited antiplatelet aggregation. Furthermore, nonsulphated polysaccharide catalyzed thrombin inhibition by antithrombin. They observed in ex vivo tests where rats were orally fed with polysaccharide showed an inhibitory effect on platelet aggregation similar to aspirin's antiplatelet activity. Hericenone B is a phenolic bioactive constituent isolated from *Hericinum erinaceus* mushrooms which demonstrated antiplatelet activity in collagen-induced rat and human platelets at $IC_{50} \sim 3\,\mu m$ concentration (Mori et al., 2010). D-Mannitol is another bioactive; structurally a sugar alcohol from *P. cornucopiae* that exerted hypotensive action in hypertensive rats (Hagiwara et al., 2005). Other plethora of compounds with hypotensive effects are, gallic acid (Jin et al., 2017), formononetin (Nestel et al., 2007; Xing et al., 2010), chlorogenic acid (Suzuki et al., 2006) (Akila et al., 2017), biochanin A (Jalaludeen et al., 2015), fomiroid A (Chiba et al., 2014) and hispidin (Kim et al., 2014).

5.1 | Absorption kinetics and metabolic role of mushroom bioactive constituents

The role of mushroom bioactives and their influence on cholesterol biosynthesis have been extensively studied in vitro and in vivo models. In an in vitro digestion model study, Gil-Ramírez et al. (2014) observed that ergosterol-enriched fractions from supercritical fluid extraction technique were superior than β-sitosterol in displacing cholesterol. Moreover, sterol-enriched mushroom extracts inhibited HMG-CoA reductase in vitro, and ergosterol was postulated to act as a competitive inhibitor of C24-reductase due to its double bond at C-22 position of its side chain. Polysaccharide fractions obtained using pressurized water extraction (PWE) technique from three mushroom varieties viz, *A. bisporus*, *L. edodes*, and *P. ostreatus* was postulated to impair cholesterol absorption thereby rendering hypercholesterolemia (Palanisamy et al., 2014). Selenium-enriched mushrooms are postulated to enhance the inhibitory activity of statins. In an in vitro study, *A. bisporus* extracts were obtained via PWE technique and applied to HepG2 (hepatoma) cells for 24 h to evaluate genes responsible for

TABLE 4 Content of important bioactive constituents in selected edible mushrooms.

Species	Bioactive constituents		References
	Name	Content	
Agaricus bisporus	Ergothioneine (mg 100 g^{-1} dry weight)	45.0	Dubost et al. (2007)
	Fatty acids (LA:LLA:OA) %	67.3:1.5:6.1	Öztürk et al. (2011)
	β-Carotene (μg/100 g)	368.01–423.48 (cap) 281.94–754.30 (stalk)	Agboola et al. (2023)
	Lovastatin (mg/kg)	565.4	Chen et al. (2012)
Lentinula edodes	Eritadenine (mg 100 g^{-1} dry weight)	642.8	Afrin et al. (2016)
	GABA (mg 100 g^{-1} dry weight)	62.2	Lo et al. (2012)
	Ergothioneine (mg 100 g^{-1} dry weight)	1.22	Lo et al. (2012)
	Fatty acids (LA:LLA:OA) %	75.8:0.28:3.5	Cohen et al. (2014)
Phellinus linteus	Eritadenine (mg 100 g^{-1} dry weight)	9.4	Afrin et al. (2016)
Flammulina velutipes	GABA (mg 100 g^{-1} dry weight)	26.0	Cohen et al. (2014)
	Fatty acids (LA:LLA:OA) %	51.2:13.0:10.7	Cohen et al. (2014)
	Ergothioneine (mg 100 g^{-1} dry weight)	9.9	Cohen et al. (2014)
Boletus edulis	GABA (mg/kg)	202.1	Chen et al. (2012)
	Fatty acids (LA:LLA:OA) %	33.8:1.7:31.1	Kavishree et al. (2008)
Pleurotus ostreatus	Ergothioneine (mg 100 g^{-1} dry weight)	244.4	Cohen et al. (2014)
	GABA (mg 100 g^{-1} dry weight)	130.5	
Grifola frondosa	Fatty acids (LA: OA) %	35.1:44.1	Cohen et al. (2014)
	Ergothioneine (mg 100 g^{-1} dry weight)	113	Dubost et al. (2007)
Sparassis crispa	Fatty acids (LA:OA) %	31.3:49.0	Kavishree et al. (2008)
Hypsizus marmoreus	GABA (mg 100 g^{-1} dry weight)	11.4	Chen et al. (2012)
	Ergothioneine (mg 100 g^{-1} dry weight)	41.0	
Cantharellus cibarius	Fatty acids (LA:OA) %	17.3:35.4	Kavishree et al. (2008)

Note: LA:LLA:OA refers to linoleic acid:linolenic acid:oleic acid respectively.

cholesterol homeostasis. They observed downregulation of squalene synthase messenger RNA attributed to lowered cholesterol levels (Gil-Ramirez et al., 2015). Even with the presence of bioactives in edible mushrooms, not much benefit can be derived if they are not assimilated well in the body. A seminal study was reported by Kała et al. (2017) which demonstrated the bioavailability of bioactive constituents from 12 varieties of mushrooms in artificial digestive juices. Artificial digestive juices were prepared that mimicked typical human digestive system (artificial saliva, gastric and intestinal juices). They reported highest extraction of serotonin from oyster mushrooms and phenolic compounds namely protocatechuic acid, *p*-hydroxybenzoic, syringic and gallic acid (Kała et al., 2017). It was realized that zinc (Ozyildirim & Baltaci, 2023) and indole compounds (Tan et al., 2022) present in mushrooms have antihypertensive effects. Kała et al. (2019) reported a seminal study on mushroom bioavailability that revealed zinc and indole compounds could regulate hypertension. Kała et al. (2020) reported extracting lovastatin that possesses cholesterol-lowering effects using in vitro models. Muszyńska et al. (2020) reported bioavailability of copper, zinc, and selenium from shiitake mushrooms by investigating its extraction in artificial stomach juices. All these studies reported good bioavailability of mushroom bioactives into the human body. Next, vitamin D deficiency is a known phenomenon among the global populace. Amrein et al. (2020) reported vitamin D deficiency and the general need for providing it as a synthetic supplement. Over the years, there are collated evidences that vitamin D and heart health are correlated. A population-based cohort study was conducted using Mendelian randomization analyses to evaluate dose–response relationship between vitamin D and heart health (Sofianopoulou et al., 2021). Keegan et al. (2013) examined in vivo study for bioavailability of vitamin D extracted from white button mushrooms. Their team reported that ingesting UV-irradiated mushrooms loaded with D_2 had the potency to maintain or cause increased total D levels in blood serum levels. Similar studies on bioactive hypotensive constituents are also reported for ergothioneine (Weigand-Heller et al., 2012), eritadenine (Morales et al., 2018), cordycepin (J. B. Lee, Radhi, et al., 2019), quercetin (Almeida et al., 2018) and ergosterol along with β-glucans (Morales et al., 2019).

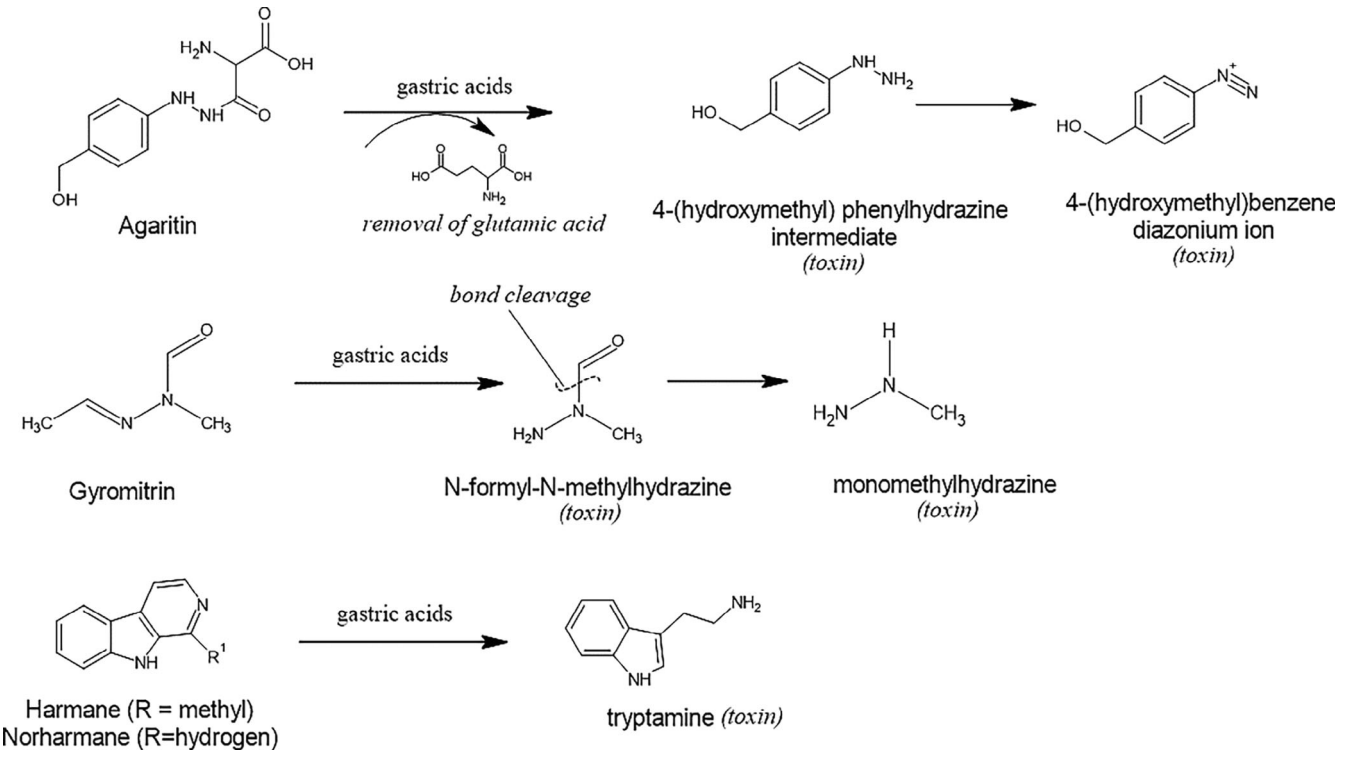
Pertinent in vivo studies are performed that illustrate the specific action of mushroom bioactives on genes that modulate cholesterol biosynthesis. *P. ostreatus* fiber extracts were postulated to modulate transcription of specific genes that played role in cholesterol biosynthesis. On obtaining transcriptomic profiles from C57BL/6J mice fed with hypercholesterolemic diets followed by mushroom supplemented fiber diet, demonstrated reduced triglyceride levels due to DGAT1

downregulation (Caz et al., 2015). The same research group investigated hypocholesterolemic activity of lard functionalized with mushroom extracts. On evaluating mRNA levels of 17 cholesterol-related genes in cecum, jejunum, and liver of high cholesterol-fed mice, they postulated cholesterol-lowering effect was related to post-transcriptional mechanism (Caz et al., 2016). Eritadenine is another important bioactive attributed to exert hypotensive effect due to its role in upregulating CYP7A1 expressions in the liver of hypercholesterolemic mice fed with *L. edodes* (Yang et al., 2013). When *S. crispa* extracts were administered to hypertensive rat models, lipid profiles were significantly improved due to induced upregulation of CYP7A1 mRNA gene expression and HMG-CoA reductase inhibition resulting in cholesterol and bile excretion (Hong et al., 2015). Administering *A. brasiliensis* to hypertensive rats exhibited lower cholesterol levels in blood serum and promoted its excretion attributed to induced activity of LDLR upregulation (de Miranda et al., 2017). We already discussed about eritadenine and ergosterol and their influences on reducing cholesterol in Section 5.

It is evident from in vivo model studies that certain specific gene expression and their pathways are key biochemical features that need detailed investigation. Rather than performing solitary mushroom studies, a comparative study assessing different mushroom varieties and their influence on genes regulating cholesterol metabolism and excretion is yet elusive. Most studies utilized stem extracts, fruit cap extracts, and sometimes whole fruiting body extracts that does not fully substantiate the efficacy. Thus, a fresh assessment is essential to determine bioavailability of mushroom constituents especially those, exerting hypotensive effects with an investigation on particular genes regulating cholesterol homeostasis, transport, and excretion.

5.2 | Safety, limitations, and other considerations

Agaritin is a poisonous bioactive constituent first isolated from *A. bisporus* and is postulated to be a weak mutagen. Another carcinogenic bioactive compound called gyromitrin was isolated from wild edible *Gyromitra esculenta* mushrooms (Gry & Andersson, 2012). The carcinogenicity of agaritin and gyromitrin is attributed to the presence of N—N bonds either as hydrazine (—NH_2—NH_2—) or diazo functionalities (Scheme 3). Agaritine and gyromitrin can react with stomach acids and transform to toxins leading to vomiting and allergic reactions. *Hygrophorus eburneus* is a white edible mushroom that produces a potential neurotoxin called harmane and norharmane in their fruit caps. They are called β-carbolines and are natural indole alkaloids. Harmane could breakdown into tryptamine, a proven hallucinogen (structurally similar to psilocybin) (Araújo et al., 2015). Some studies are yet elusive to determine safety on consuming mushrooms. One such case is bicyclic hemiacetals, a novel molecule obtained from edible *Ramaria madagascariensis* mushrooms (Liu et al., 2015). The relationship of bicyclic hemiacetal to its toxicology and SAR studies is elusive thereby it can be considered as an antioxidant bioactive due to —OH groups and —CO—NH— linkage. However, this is an inconclusive claim and its metabolite toxicity needs detailed epidemiological investigation.



SCHEME 3 Selected toxins in edible mushrooms and their toxic metabolites.

An attempt to link heart health with mushroom consumption was performed by reviewing clinical studies, meta-analysis, and systematic reviews. The cardioprotective functionalities are understood by unraveling effect of mushroom bioactive constituents on typical biomarkers such as homocysteine and lipid levels. D. H. Lee, Yang, et al. (2019) examined the correlation of consuming mushrooms in their cohort study among US population. They reflected on the direct correlation with reduced hypertension as a flawed correlation; until complete epidemiologic study is performed. Systematic review by Krittanawong et al. (2021) found the interlinking of CVDs to consuming mushrooms to be inconclusive. This could be attributed to the fact that most studies were in vitro models and detailed epidemiologic studies were not covered.

It is also reiterated that epidemiological studies must be performed across different human races and other mediated biomarkers of CVD conditions. A systematic review on randomized controlled clinical trial revealed that consuming mushrooms decreased total triglyceride levels (Uffelman et al., 2022). However, evidences from the report only revealed interlink between plasma triglycerides and mushroom consumption; other lipids and lipoproteins influences were not considered. Even though these clinical studies are inconclusive, it may be a false negative outcome. Most meta-analysis and clinical studies suffered from misclassification of study groups, few biomarkers of CVDs and inefficient window period of mushrooms intake (≥5 times/week is high intake). Hence, it is quite challenging to determine food-disease link especially with scant literature and human volunteer studies. As mushrooms are rich in proteins, allergenicity is another concern which was seminally addressed using in silico technique on shiitake mushrooms (Vashisht et al., 2023). In silico prediction tool is essentially used to determine protein allergens in FFs and crops. Docking studies elucidate protein-ligand/protein–protein interactions that can unravel crucial toxicological information for mushroom proteins as lead drug candidates and therapeutics.

6 | CONCLUSIONS AND FUTURE OUTLOOK

This review described the correlation of bioactive constituents and their influence on ameliorating hypertension. We compared the antihypertensive drugs and the reason to shift toward FFs and dietary changes such as DASH and MedDiet for chronic hypertension. We also found most of the claims to be widely empirical and reliant on the chemistries of different bioactive compounds of mushrooms. We postulated the correlation of structural moieties of mushroom bioactives with hypotensive effects and detailed some toxic allergens and their metabolites. Although, clinical studies are inconclusive, it does not take away the positive effects of consuming mushrooms. Another reason for the inconclusive clinical and cohort study findings is postulated to the synergistic role of bioactive and their metabolites in regulating hypertension. Out of the various mushroom bioactives, cordycepin, lovastatin, eritadenine, and ergosterol are postulated to directly influence gene expressions that induce cardiovascular functionalities due to their structural similarities either with adenosine or cholesterol moieties. These molecules could act as potential drug candidates that reduce hypertension which also necessitates evidences from pharmacology and clinical biochemistry. Thus, an effort in collating SARs of bioactive constituents along with epidemiological studies is essential to unravel the metabolic pathways and cholesterol homeostasis. Dietary interventions with edible mushrooms are supposedly effective only in the early onset of hypertension and thus, cannot be considered therapeutic for chronic hypertensive patients. Hence, one can proclaim dietary interventions with edible mushrooms as prophylactic that does not circumvent antihypertensive drug treatment. As discussed in Section 4, there are multitude of cascading reactions in cholesterol biosynthesis which are influenced by mushroom bioactive statins and other bioactive constituents. Besides cholesterol absorption, in vivo studies revealed that mushroom bioactives exert influence on certain gene expressions that regulate cholesterol transport, metabolism, and bile acid excretion. More clinical trials are required to be conducted, especially about mushroom polysaccharides such as β-glucans and D-mannitol on modulating cholesterol biosynthesis and absorption. Most clinical studies remain inconclusive and require detailed investigation to identify different biomarkers of CVDs and gene expressions. These challenges are responsible for the poor translation of in vivo model studies in clinical trials and in silico docking evaluations. Today, with advances in stem cell engineering, creating in vitro cardiac models called "heart-on-the-chip" may serve as superior templates over traditional rat models and provide better insights to cardiovascular functionalities (Dou et al., 2022). As mushrooms are utilized in fortified foods and meat-substitute diets at an accelerated pace, detailed investigations involving in silico studies for allergenicity seeks immediate attention. No studies have been reported on lactose intolerance and their relation with mushroom consumption that requires fresh assessment by epidemiologists through cohort studies. The causal link of ameliorating hypertension and mushroom consumption has certainly moved leap ahead of mere speculation and is foreseen to be robust with changes in vitro and in vivo models itself. Due to the wide varieties of mushrooms, continued exploration is undertaken to isolate novel compounds. Thus, there is a continuous need to update the chemical literature and elucidate their pharmacological and toxicological investigations of novel mushroom bioactive compounds. Thus, edible mushrooms have a lot of scope in clinical evaluations that necessitates phylogenetic and toxicological analysis of mushroom bioactive constituents. So, next time when you stir up a "mushroom risotto;" appreciate the potential of biologically and nutritionally unique fungus à la "edible mushrooms."

AUTHOR CONTRIBUTIONS

Abdur Rauf: Investigation. **Payal B. Joshi:** Investigation. **Zubair Ahmad:** Investigation. **Hasan A. Hemeg:** Investigation. **Ahmed Olatunde:** Investigation. **Saima Naz:** Investigation. **Nabia Hafeez:** Investigation. **Jesus Simal-Gandara:** Investigation.

ACKNOWLEDGMENT

All the authors express their earnest gratitude to anonymous reviewers for their insightful suggestions that helped to improve the paper significantly.

FUNDING INFORMATION

Open access fee is supported by Universidade de Vigo/CISUG.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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How to cite this article: Rauf, A., Joshi, P. B., Ahmad, Z., Hemeg, H. A., Olatunde, A., Naz, S., Hafeez, N., & Simal-Gandara, J. (2023). Edible mushrooms as potential functional foods in amelioration of hypertension. *Phytotherapy Research*, *37*(6), 2644–2660. https://doi.org/10.1002/ptr.7865