The Cardioprotective Properties of Agaricomycetes Mushrooms Growing in the Territory of Armenia: Review

Susanna M. Badalyan,[a,*] Anush Barkhudaryan,[b] & Sylvie Rapior[c]

[a]Laboratory of Fungal Biology and Biotechnology, Institute of Pharmacy, Department of Biomedicine, Yerevan State University, Yerevan, Armenia; [b]Department of Cardiology, Clinic of General and Invasive Cardiology, University Hospital No. 1, Yerevan State Medical University, Yerevan, Armenia; [c]Laboratoire de Botanique, Phytochimie et Mycologie, Faculté de Pharmacie, Centre d'Ecologie Fonctionnelle et Evolutive, Univ Montpellier, CNRS, EPHE, IRD, Montpellier, France

*Address all correspondence to: Susanna M. Badalyan, Laboratory of Fungal Biology and Biotechnology, Institute of Pharmacy, Department of Biomedicine, Yerevan State University, 1 A. Manoogian Street, 0025 Yerevan, Armenia; Tel.: +374 94 242535; Fax: +374 10 554641, E-mail: s.badalyan@ysu.am

ABSTRACT: Several edible and medicinal Agaricomycetes mushrooms possess biologically active compounds with different therapeutic effects, such as antioxidant, anti-inflammatory, hypocholesterolemic, hypoglycemic, anti-hypertensive, fibrinolytic, and thrombolytic, and have potential use as cardioprotective remedies. Previous studies have shown that mushrooms possessing cardioprotective effects (CPEs) contain a high amount of vitamins and minerals and low fat content, which make them applicable as a supplementary dietary and functional food for the prevention and treatment of cardiovascular diseases. The current review evaluates the resource value of 31 edible and nonedible medicinal Agaricomycetes mushrooms with potential CPEs growing in the territory of Armenia and discusses the future perspectives of their usage in biotechnology and biomedicine.

KEY WORDS: Agaricomycetes, anti-hypertensive, anti-obesity, antioxidant, anti-inflammatory, Armenia, cardioprotective, hypoglycemic, hypocholesterolemic, fibrinolytic, medicinal mushrooms

ABBREVIATIONS: ACE, angiotensin-converting enzyme; **AH**, arterial hypertension; **AOA**, antioxidant activity; **CL**, cultural liquid; **CPE**, cardioprotective effect; **CVD**, cardiovascular disease; **FLA**, fibrinolytic activity; **HDL**, high-density lipoprotein; **HMG-CoA**, 3-hydroxyl-3-methylglutaryl coenzyme A; **LDL**, low-density lipoprotein; **MM**, medicinal mushroom; **MS**, metabolic syndrome; **RAAS**, renin-angiotensin-aldosteron system; **TLA**, thrombolytic activity

I. INTRODUCTION

Cardiovascular disease (CVD) affects the heart and circulatory system and is considered the leading cause of mortality worldwide. The main risk factors for CVD include metabolic syndrome (MS), arterial hypertension (AH), and high levels of blood glucose and cholesterol. Several pathological conditions, including diabetes, obesity, drug toxicity, aging, and oxidative stress, have a significant role in the development of CVD. Among the variety of CVDs, AH affects 15%–20% of all adults and may be complicated by atherosclerosis, stroke, and myocardial infarction. The renin-angiotensin-aldosteron system (RAAS) plays an important role in the pathophysiology of AH.[1] Activation of the RAAS leads to increased production of angiotensin II from angiotensin I, facilitated by the angiotensin-converting enzyme (ACE), which is associated with the development of AH and myocardial remodeling. Atherosclerosis is considered a major risk factor for CVD, which may lead to coronary artery disease, coronary artery disease, characterized by accumulation of lipoproteins and fibrous elements in the vessel wall. Inflammation and oxidative stress are associated with atherosclerosis and play a major role in the development of CVD. Furthermore, the development of thrombosis in the coronary artery can lead to myocardial infarction due to fibrin aggregation in the blood.[2] Thromboembolic complications may develop as a result of deep vein thrombosis, surgery, certain medications, and a hypodynamic lifestyle. The thrombotic occlusion leads to cessation of blood flow,

1521-9437/21/$35.00

depriving tissues of normal blood supply and oxygen. The processes of thrombus formation and fibrinolysis (fibrin dissolution by proteolytic enzymes) are balanced in biological systems. Thus, hyperglycemia, hyperlipidemia, insulin resistance, obesity, atherosclerosis, AH, and thrombosis are associated with MS and are considered risk biomarkers contributing to the development of CVD.

The drugs used for the treatment of MS, such as insulin and inhibitors of 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase, aldose reductase, ACE, and α-glucosidase, possess limited therapeutic efficacy and several side effects. Currently, the main areas of biomedical research of ACE inhibitors are directed to the prevention and treatment of CVD, and considerable effort has been made in the pharmacological industry to develop new preparations with natural origin to improve glucose and lipid metabolism without significant side effects.

Mushrooms are considered natural sources of different groups of bioactive compounds (phenolics, terpenoids, polysaccharides, oligopeptides, sterols, etc.) and enzymes (proteases) possessing hypocholesterolemic, hypoglycemic, hypotensive, anti-inflammatory, antioxidative, and fibrino- and thrombolytic effects.[3–26] Furthermore, mushrooms also possess a high content of proteins, unsaturated fatty acids, fiber, vitamins (B complex, C, D, E, H, K, PP), and minerals (iron, potassium, manganese, sodium, selenium, zinc) and a low concentration of sodium.[27–30] The pharmacological and nutritional properties of mushrooms allow them to be considered as a functional food for the prevention and treatment of various diseases, including CVD.[31–36] Previous studies suggest that regular consumption of edible mushrooms may potentially reduce the risk of CVD.[37–42] The focus of the current review is to assess the resource value of edible and nonedible Agaricomycetes medicinal mushrooms (MMs) with potential cardioprotective effects (CPEs) growing in the territory of Armenia and evaluate the perspective of their usage in biotechnology and biomedicine.

II. THE CARDIOPROTECTIVE EFFECT OF MUSHROOMS

Mushrooms have been prescribed in traditional medicine due to their diverse bioactivity to reduce the risk of CVD (Table 1). The reported therapeutic properties of MMs (e.g., antioxidant, anti-inflammatory, anti-atherosclerotic, hypotensive, anti-obesity, hypoglycemic, hypolipidemic, and fibrinolytic effects) may have clinical relevance in the prevention and treatment of cardiac diseases.[3,4,11,14,15,37–43]

The maintenance of balance between free radical production and antioxidant defense is an essential condition for normal functioning of biological organisms. Free radicals may damage cellular lipids, proteins, and DNA, thus affecting their normal function and potentially leading to the development of various diseases. Natural products with antioxidant activity (AOA) are considered potential protective agents against oxidative damage. The development of CVD may also be prevented by dietary intake of natural antioxidants, including mushrooms. They neutralize free radicals by enhancing catalase and superoxide dismutase activity and stabilize glutathione and malondialdehyde levels.[12] In this regard, *Agaricus brasiliensis*, *Agrocybe aegerita*, *Boletus edulis*, *Flammulina velutipes*, *Hericium erinaceus*, *Lentinus edodes*, *Trametes versicolor*, and *Volvariella volvacea*, as well as species from genera *Pleurotus* and *Ganoderma* are considered a natural source of biomolecules (fatty acids, phenolics, polysaccharides, steroids, terpenoids, tocopherols, etc.) with anti-atherosclerotic, anti-inflammatory, antioxidant, cardioprotective, hypocholesterolemic, hypoglycemic, and hypotensive effects.[3,4,11–16,27,30,35,39,40] The lanostane type triterpenoids isolated from *G. lucidum* were suggested as promising bioactive agents for the treatment of MS.[6] *In vitro* studies and animal assays as well as several human trials suggest that *A. bisporus*, *G. lucidum*, *H. erinaceus*, *Phellinus linteus*, and *Pleurotus* species may normalize blood glucose and lipid levels.[4,16–18,20,21] Eritadenine extracted from *L. edodes* has been identified as an anti-atherogenic compound that not only improves lipid metabolism but also inhibits *in vitro* activity of ACE.[10] *In vitro* anti-atherogenic, ACE, and HMG-CoA reductase inhibitory effects as well as protection of endothelium against oxidative stress were evaluated in *P. pulmonarius*.[20] Several edible MMs possess anti-atherosclerotic effects due to their high content of unsaturated fatty acids,

TABLE 1: Taxonomy, bioactive compounds, and cardioprotective effects of Agaricomycetes mushrooms growing in Armenia

No.	Mushroom species[a]	Floristic regions[b]	Bioactive compound	Medicinal effect	Refs.
1	*Agaricus bisporus* (J.E. Lange) Imbach*	GG, YE	Polysaccharides, ergothioneine, polyphenols, vitamins	Antioxidant, anti-inflammatory, hypoglycemic, pancreas protective, hypocholesterolemic, hypotensive, cardioprotective	5,17, 42,58
2	*Agrocybe* (= *Cyclocybe*) *aegerita* (V. Brig.) Vizzini*	YE	Polysaccharides, phenolics	Antioxidant, anti-atherosclerotic, anti-atherosclerotic, hypoglycemic	37,39, 62
3	*Armillariella mellea* (Vahl) P. Kumm.*	YE, AP, IJ, LR, SE, ZG	Polysaccharides, proteases	Fibrinolytic, hypotensive, spasmolytic	5,45
4	*Auricularia auricula-judae* (Bull.) J. Schröt.*	IJ	Polysaccharides, phenolics	Antioxidant, anti-coagulant, cardiovascular, hypolipidemic, hypoglycemic, fibrinolytic	4,5, 39,61, 67
5	*Boletus edulis* Bull.*	AP, IJ, LR, ZG	Polysaccharides, oligopeptides, polyphenols, vitamins	Antioxidant, anti-inflammatory, anti-atherosclerotic, ACE inhibitory	3,36, 37,39
6	*Cantharellus cibarius* Fr.*	IJ, LR	Polysaccharides, phenolics	Antioxidant, anti-inflammatory, cardioprotective, hypolipidemic, anti-obesity, hypoglycemic	3,5
7	*Coprinus comatus* (O.F. Müll.) Pers.*	YE, IJ, LR, SV, ZG	Polysaccharides, tocopherols, phenolics, fatty acids, proteases	Anti-inflammatory, anti-obesity, antioxidant, cardiovascular, hypoglycemic, fibrinolytic, thrombolytic	5,46, 49
8	*Coprinellus micaceus* (Bull.) Vilgalys, Hopple & Jacq. Johnson	YE, IJ, LR	Polysaccharides, fatty acids, proteases	Hypoglycemic, thrombolytic	5,46, 49
9	*Coprinopsis strossmayeri* (Schulzer) Redhead, Vilgalys & Moncalvo	YE	Terpenoids, linoleic, palmitic, stearic, oleic acids	Antioxidant, caseinolytic, fibrinolytic	5,46, 49
10	*Flammulina velutipes* (Curtis) Singer*	YE, IJ, LR, AP	Polysaccharides, fatty acids, steroids, tocopherols, proteases	Antioxidant, anti-atherosclerotic, anti-inflammatory, hypocholesterolemic, hypotensive, fibrinolytic, thrombolytic	4,37, 39,51
11	*Fomes fomentarius* (L.) Fr.	All	Phenolics, flavonoids, exopolysaccharides, triterpenoids, ketones, proteases	Antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic, fibrinolytic, thrombolytic	4,47, 48,67

TABLE 1: (*continued*)

No.	Mushroom species[a]	Floristic regions[b]	Bioactive compound	Medicinal effect	Refs.
12	*Fomitopsis pinicola* (Sw.) P. Karst.	LR, ZG	Polysaccharides, sterols, triterpenoids, flavonoids, proteases	Anti-inflammatory, antioxidant, anti-obesity, anti-atherosclerotic, thrombolytic, fibrinolytic	47,48, 66,67
13	*Ganoderma lucidum* (Curtis) P. Karst.	IJ, LR, SV, ZG	Polysaccharides, lanostane terpenoids, phenolics, fatty acids, steroids, tocopherols	Antioxidant, antiaggregation, anti-inflammatory, hypotensive, anti-obesity hypoglycemic, hypocholesterolemic, fibrinolytic, thrombolytic	4–7,9, 16,36, 37,39, 47,48, 52,66
14	*G. adspersum* (Schulz.) Donk	YE, IJ	Polysaccharides, terpenoids, phenolics	Antioxidant, hypotensive, hypoglycemic, hypocholesterolemic, fibrinolytic	5,47, 48,67
15	*Hericium erinaceus* (Bull.) Pers.*	IJ, ZG	Meroterpenoids, erinacerins, erinaceolactones, hericenones, herinase	Antioxidant, anti-inflammatory, anti-obesity, hypoglycemic, hypocholesterolemic, fibrinolytic	4,5, 19,53
16	*Hypholoma fasciculare* (Fr.) Kumm.	AP, IJ, LR, YE, ZG	Proteases	Hypoglycemic, fibrinolytic, vasodilator	4,64
17	*Inonotus dryadeus* (Pers.) Murrill	IJ, ZG	Free fatty acids, cerevisterol, sphingosine	Antioxidant	68
18	*I. hispidus* (Bull.) P. Karst.	YE, IJ, LR, MG, ZG	Phenolic compounds, hispidin	Antioxidant, anti-inflammatory, anti-diabetes, cardioprotective	68
19	*I. obliquus* (Ach. ex Pers.) Pilát	IJ, LR	Phenolic compounds, melanin, xylo-galactoglucans, polysaccharides, flavonoids	Anti-obesity, anti-diabetic, antioxidant, anti-inflammatory, cardioprotective	5,68
20	*Laetiporus sulphureus* (Bull.) Murrill*	YE, IJ, LR, ZG	Phenolics, polysaccharides, proteases	Antioxidant, thrombolytic	5,66, 67
21	*Lentinus tigrinus* (Bull.) Fr.*	YE, IJ, LR	Phenolics, sterols, polysaccharides, proteins	Antioxidant, hypoglycemic, hypocholesterolemic	5,67, 72
22	*Phellinus igniarius* (L.) Quél.	All	Phenolic acids, polysaccharides, hispidin	Anti-inflammatory, antioxidant, anti-diabetes	68
23	*Ph. pini* (Brot.) Bondartsev & Singer	IJ, LR	Hispidin, squarrosidine, free phenolic acids, polysaccharides	Antioxidant, hypoglycemic, hypolipidemic	68

TABLE 1: (*continued*)

24	*Ph. ribis* (Schumach.) Quél.	IJ, MG, ZG	Glucans, hispidin	Antioxidant, anti-inflammatory, anti-diabetes	68
25	*Pleurotus cornucopiae* (Paulet) Rolland*	AP, YE, IJ, LR, ZG	Phenolics, fatty acids, mannogalactoglucans, oligopeptides	ACE inhibitory, anti-inflammatory, antioxidant, hypoglycemic, hypocholesterolemic, hypotensive	4,5, 39,67
26	*P. eryngii* (DC.) Quél.*	YE	Phenolics, polysaccharides, fatty acids, proteases	Anti-inflammatory, antioxidant, hypoglycemic, hypocholesterolemic, hypotensive, fibrinolytic	5,37, 39,54, 65,67
27	*P. ostreatus* (Jacq.) P. Kumm.*	YE, IJ, LR	Protocatechuic acid, gallic acids, lovastatin, formononetin, polysaccharides, fatty acids, steroids, tocopherols, vitamins, proteases	Anti-inflammatory, anti-obesity, antioxidant, anti-atherosclerotic, anti-coagulant against ischemia/reperfusion injury, cardioprotective, hypocholesterolemic, hypoglycemic, hypotensive, fibrinolytic, thrombolytic	4,37, 39,59, 60,67, 69
28	*P. pulmonarius* (Fr.) Quél.*	YE, IJ	Phenolics, polysaccharides, fatty acids	Anti-coagulant, anti-diabetes, antioxidant, anti-atherogenic, anti-inflammatory, hypocholesterolemic, hypotensive	4,5, 20
29	*Trametes* (= *Coriolus*) *versicolor* (L.) Lloyd	IJ, LR, YE	Polysaccharides, phenolics, proteases	Antioxidant, anti-obesity, anti-diabetes, cardioprotective, thrombolytic	4,5, 39,66, 67,71
30	*T. hirsuta* (Wulfen) Pilát	YE	Polysaccharides, phenolics, proteases	Antioxidant, thrombolytic	4
31	*Volvariella volvacea* (Bull.) Singer*	YE, IJ	Phenolic compounds, flavonoids, ascorbic acid, β-carotene, lycopene	Antioxidant, hypotensive	4,5, 37,39, 70

[a]Asterisks indicate edible mushroom species.

[b]Floristic regions of Armenia: AG, Aragats; AP, Aparan; DG, Daralegez; GG, Gegama; IJ, Ijevan; LR, Lori; MG, Meghri; SH, Shirak; SV, Sevan; UA, Upper Akhuryan; YE, Yerevan; ZG, Zangezur.

and their consumption may have a beneficial effect on cellular metabolism in the human body.[29,30] Although the mechanisms of hypocholesterolemic and hypoglycemic effects of mushroom-derived metabolites are unclear, several species (e.g., *A. bisporus*, *Auricularia polytricha*, *F. velutipes*, *G. lucidum*, *Grifola frondosa*, *L. edodes*, *P. pulmonarius*, and *P. ostreatus*) may be recommended in nutraceutical and pharmaceutical industries to develop biotechnology products with hypoglycemic and hypotensive effects.[3,11,12,21,22] The main mechanism of hypotensive effect of mushrooms is considered ACE inhibition.[39]

The fibrinolytic agents, such as tissue-type, urokinase-type, nattokinase, and streptokinase, possess a wide range of clinical applications. However, their uncontrolled use is costly and results in a number of side effects, including internal haemorrhage, allergic reactions, and limitation in specificity toward fibrin.[44] Therefore, the search for natural sources of fibrinolytic agents is in demand. Agaricomycetes mushrooms, belonging to different taxonomic and ecological groups, are considered active producers of extracellular proteolytic (fibrinolytic, thrombolytic, and caseinolytic) enzymes.[24–26,45–50] Previous systematic studies have revealed the presence of fibrinolytic and thrombolytic proteases in *Armillariella mellea*,[45] *A. polytricha*,[26] Coprinoid mushrooms,[46,49] *F. velutipes*,[51] *Fomitopsis pinicola*,[48] *G. lucidum*,[52] *H. erinaceus*,[53] *P. eryngii* var. *ferulae*,[54] and *P. ostreatus*.[55]

The research data provide evidence for the use of mushrooms as a healthy food to decrease the risk of MS and CVD.[4,29,31–33] A mushroom-rich diet decreases the risk factors associated with cardiac diseases, such as levels of total low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, fasting triacylglycerol, homocysteine, and AH, as well as oxidative and inflammatory damage of vessels.[37–39] With this treatment approach for CVD, several agaricoid and polyporoid MMs, such as *Inonotus obliquus*, *H. erinaceus*, *P. ostreatus*, *G. frondosa*, *T.* (=*Coriolus*) *versicolor*, *G. lucidum*, *L. edodes*, and *Laricifomes officinalis*, are considered potential natural products to develop mycopharmaceuticals with CPEs.[4,8,19,23,39,53,56–59] Among these species, *G. frondosa*, *G. lucidum*, *L. edodes*, *P. ostreatus*, and *P. pulmonarius* are considered ideal products along with a low-calorie healthy diet to prevent the development of CVD due to their high content of fiber, proteins, and microelements.[31–33] In particular, *Pleurotus* species decrease the levels of LDL, homocysteine, total cholesterol, and fasting triglycerides; prevent the development of AH, diabetes, and other pathological conditions; and reduce oxidative stress.[3,4,39] A pronounced hypocholesterolemic effect of *P. ostreatus* combined with inhibition of lipid peroxidation has been shown to reduce the incidence and size of atherosclerotic plaques in animals.[59] Furthermore, lovastatin, the leading compound of statins (HMG-CoA reductase inhibitors), has been detected in *P. ostreatus*.[60] The use of *P. cornucopiae*, *A. auricula*, *A. polytricha*, *F. velutipes*, and *A. bisporus* in the hypocholesterolemic, anti-atherosclerotic, anti-coagulant, and antiaggregant diet has been previously reported.[31–33,59,61] Triterpenes derived from *G. lucidum* have been shown to inhibit the biosynthesis of cholesterol and protect against atherosclerosis by inhibition of ACE and platelet aggregation.[7,9] Dried fruiting bodies of *A. aegerita* can significantly reduce the levels of total cholesterol, triacylglycerides, and the atherogenic index in rats and have revealed hypocholesterolemic effects and AOA.[62] Therefore, they have a potential to be used in biomedicine as natural sources of phenolic antioxidants and hypocholesterolemic agents. The steroid, ergosta-4-6-8(14),22-tetraen-3-one, isolated from Chinese MM *Polyporus sclerotium* has been shown to possess aldosterone-antagonizing effects with diuretic properties[63] that could also be of benefit in CVD.

Thus, mushrooms are considered a promising source of naturally derived cardioprotective biomolecules. Further studies of their CPEs for biotechnological and biomedical uses are warranted.

III. BIOLOGICAL RESOURCES OF MUSHROOMS WITH CARDIOPROTECTIVE EFFECTS DISTRIBUTED IN ARMENIA

The analysis of literature and the authors' own data to assess the cardioprotective potential of agaricomycetous mushrooms in Armenia revealed 16 edible and 15 nonedible species of agaricoid, coprinoid, polyporoid,

and hymenochaetoid mushrooms, including *A. bisporus*, *A. auricula-judae*, *A. mellea*, *Coprinus comatus*, *F. pinicola*, *G. lucidum*, *Hypholoma fasciculare*, *P. ostreatus*, and *T. versicolor*, which have been reported in all floristic regions of Armenia (Table 1). Several therapeutic effects, including hypolipidemic, hypoglycemic, antioxidant, anti-inflammatory, anti-obesity, hypotensive, and thrombolytic/fibrinolytic have been previously revealed in these mushrooms (Table 1).[46–49,64–68]

Two wild-growing and edible mushrooms are widely cultivated in Armenia, *P. ostreatus* and *A. bisporus*, have been shown to possess AOA and hypoglycemic, hypocholesterolemic, and hypotensive effects and prevent the development of atherosclerosis.[69] Traditionally, *A. bisporus* has been used in the treatment of CVD and stroke due to its anti-diabetic and anti-aging properties[41] (Table 1). Polysaccharides isolated from *P. ostreatus* and *A. bisporus*, as well as from *A. auricula* growing in the Ijevan floristic region, showed antioxidant, hypolipidemic, anti-diabetic, and anti-coagulant properties and may protect the heart from ischemia/reperfusion injury.[43] Polysaccharides derived from *A. auricula* are considered natural antioxidants that safeguard myocardial function by maintaining redox levels in the cardiac muscle, improve left ventricular ejection fraction (LVEF) and fractional shortening (FS) of the left ventricle in experimental models.[43]

The cultural liquid (CL) samples of eight polypores (*Fomes fomentarius*, *Fomitella fraxinea*, *F. pinicola*, *Laetiporus sulphureus*, *T. gibbosa*, *T. hirsuta*, *T. ochracea*, and *T. versicolor*) have been recently screened for thrombolytic activity (TLA) on samples of thrombi obtained from human blood.[47,48] The highest activity was detected in *F. fraxinea* (up to 100%), followed by *F. pinicola* (up to 85%), *F. fomentarius* (up to 83%), and *L. sulphureus* (up to 69%) strains, whereas the activity was weaker (20%–55%) in *Trametes* species. The screening of fibrinolytic activity (FLA) of CL samples of two agaricoid (*F. velutipes*, *P. ostreatus*) and two polyporoid (*F. pinicola*, *G. lucidum*) mushrooms revealed the highest activity in *F. pinicola* (95%), followed by *G. lucidum* (55%), *P. ostreatus* (54%), and *F. velutipes* (51%) (Badalyan et al., unpublished data). Thus, these findings show that mushrooms may be considered alternative natural sources of extracellular proteases to develop novel mycopharmaceuticals with TLA and FLA.

Milk-coagulating activity was detected in CL samples of *F. pinicola* and several coprinoid mushrooms[48,49] (Table 1). Hymenochaetoid fungi (*I. dryadeus*, *I. hispidus*, *I. obliquus*, *Ph. gilvus*, *Ph. igniarius*, *Ph. pini*, *Ph. ribis*, *Ph. robustus*, and *Ph. torulosus*) growing in Armenia possess AOA, whereas hypoglycemic and hypocholesterolemic effects were detected mainly in *Phellinus* species (*Ph. igniarius*, *Ph. linteus*, *Ph. pini*, *Ph. ribis*).[68] Hypoglycemic effects, FLA, and CPEs were reported in *C. comatus*, *Coprinellus micaceus*,[46,49] *V. volvacea*,[70] *T. versicolor*,[71] and *L. tigrinus*[72] distributed widely in Armenia (Table 1). *T. versicolor* is known for its hypoglycemic effect; however, the effect of this species on myocardial function of patients with diabetic cardiomyopathy (DCM) remains unclear. The results of a recent study showed a significant improvement of cardiac dysfunction after fungal extract treatment, which decreased the extent of cardiac fibrosis in rats.[71] This protective effect of *T. versicolor* in patients with DCM is associated with the suppression of transforming growth factor β-1/Smad signaling and attenuation of nucleotide-binding oligomerization domain–like receptor protein NLRP3 activation, suggesting that fungal extract may be a therapeutic agent for treatment of diabetic mice.[71]

Thus, Agaricomycetes MMs distributed in Armenia may be considered a potential source of cardioprotective biomolecules to develop functional foods and mycopharmaceuticals for the prevention and treatment of CVD.

IV. CONCLUSION AND FUTURE PERSPECTIVES

It is known that Agaricomycetes mushrooms are considered as a functional food and remedy due to their nutritional value, bioactive compounds, and enzymes for the prevention and treatment of several diseases, including MS and CVD. The current review discusses the resource value and potential CPEs (hypolipidemic,

hypoglycemic, antioxidant, anti-inflammatory, anti-obesity, hypotensive, and thrombolytic/fibrinolytic effects) of 31 species of edible and nonedible Agaricomycetes MMs (e.g., *A. bisporus*, *Auricularia auricula-judae*, *C. comatus*, *G. lucidum*, *H. erinaceus*, and *P. ostreatus*) distributed in all floristic regions of Armenia. Future mycopharmacological and clinical studies are needed to elucidate the mechanisms of cardioprotective properties of bioactive compounds of mushrooms. The biotechnological cultivation of selected species/strains will assist in the development of cardioprotective mushroom-derived biotechnological products and their biomedical application in Armenia.

ACKNOWLEDGMENT

This research was supported by the SCS RA Thematic Project #18T-1F115.

REFERENCES

1. De Mello WC, Danser AHJ. Angiotensin II and the heart: On the intracrine renin-angiotensin system. Hypertension. 2000;35(6):1183–8.
2. Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. Blood Transfus. 2011;9(2):120–38.
3. Badalyan SM. Medicinal aspects of edible ectomycorrhizal mushrooms. In: Zambonelli A, Bonito G, editors. Edible ectomycorrhizal mushrooms, current knowledge and future prospects. Vol 34. Heidelberg, Germany: Springer; 2012. p. 317–34.
4. Badalyan SM, Barkhudaryan A, Rapior S. Recent progress in research on the pharmacological potential of mushrooms and prospects for their clinical application. In: Agrawal D, Dhanasekaran M, editors. Medicinal mushrooms - recent progress in research and development. Singapore: Springer Nature; 2019. p. 1–70.
5. Wu F, Zhou LW, Yang ZL, Bau T, Li TH, Dai YC. Resource diversity of Chinese macrofungi: Edible, medicinal and poisonous species. Fungal Divers. 2019;98:1–76.
6. Chen B, Tian J, Zhang J, Wang K, Liu L, Yang B, Bao L, Liu H. Triterpenes and meroterpenes from Ganoderma lucidum with inhibitory activity against HMGs reductase, aldose reductase and α-glucosidase. Fitoterapia. 2017;120:6–16.
7. Kim HW, Kim BK. Biomedicinal triterpenoids of Ganoderma lucidum (Curt.: Fr.) P. Karst. (Aphyllophoromycetidae). Int J Med Mushrooms. 1999;1(2):121–38.
8. Sturm S, Gallmetzer K, Friedl A, Waltenberger B, Temml V, Stuppner H. Laricifomes officinalis – a rich source of pharmacologically active triterpenes. Planta Med. 2016;81:S1–381.
9. Morigiwa A, Kitabatake K, Fujimoto Y, Ikekawa N. Angiotensin converting enzyme-inhibitory triterpenes from Ganoderma lucidum. Chem Pharm Bull. 1986;34:3025–8.
10. Afrin S, Rakib MA, Kim BH, Kim JO, Ha YL. Eritadenine from edible mushrooms inhibits activity of angiotensin converting enzyme in vitro. J Agric Food Chem. 2016;64(11):2263–8.
11. Ferreira IC, Barros L, Abreu RM. Antioxidants in wild mushrooms. Curr Med Chem. 2009;16:1543–60.
12. Witkowska AM, Zujko ME, Mironczuk-Chodakowska I. Comparative study of wild edible mushrooms as sources of antioxidants. Int J Med Mushrooms. 2011;13:335–41.
13. Saltarelli R, Ceccaroli P, Buffalini M, Vallorani L, Casadei L, Zambonelli A, Iotti M, Badalyan S, Stocchi V. Biochemical characterization, antioxidant and antiproliferative activities of different Ganoderma collections. J Mol Microbiol Biotechnol. 2015;25(1):16–25.
14. Morel S, Arnould S, Vitou M, Boudard F, Guzman C, Poucheret P, Fons F, Rapior S. Antiproliferative and antioxidant activities of wild Boletales mushrooms from France. Int J Med Mushrooms. 2018;20(1):13–29.
15. De Silva DD, Rapior S, Hyde KD, Bahkali AH. Medicinal mushrooms in prevention and control of diabetes mellitus. Fungal Divers. 2012;56:1–29.
16. Ma HT, Hsieh JF, Chen ST. Anti-diabetic effects of Ganoderma lucidum. Phytochemistry. 2015;114:109–13.
17. Yamac M, Kanbak G, Zeytinoglu M, Zeytİnoglu M, Senturk H, Bayramoglu G, DokumacİoglU A, Van Griensven LJLD. Pancreas protective effect of button mushroom Agaricus bisporus (J.E. Lange) Imbach (Agaricomycetidae) extract on rats with streptozotocin-induced diabetes. Int J Med Mushrooms. 2010;12(4):379–89.
18. Yamac M, Zeytinoglu M, Swenturk H, Kartkaya K, Kanbak G, Bayramoglu G, Oglakci A, Van Griensven LJLD. Effects of black hoof medicinal mushroom, Phellinus linteus (Agaricomycetes), polysaccharide extract in streptozotocin-induced diabetic rats. Int J Med Mushrooms. 2016;18(4):301–11.

19. Thongbai B, Rapior S, Hyde KD, Wittstein K, Stadler M. Hericium erinaceus, an amazing medicinal mushroom. Mycol Progress. 2015;14:91.
20. Abidin MHZ, Abdullah N, Abidin NZ. Anti-atherogenic potential of extracts from the gray oyster medicinal mushroom, Pleurotus pulmonarius (Agaricomycetes), in vitro. Int J Med Mushrooms. 2018;20(3):283–90.
21. Gil-Ramirez A, Morales D, Soler-Rivas C. Molecular actions of hypocholesterolaemic compounds from edible mushrooms. Food Funct. 2017;9(1):53–69.
22. Kabir Y, Yamaguchi M, Kimura S. Effect of shiitake (Lentinus edodes) and Maitake (Grifola frondosa) mushrooms on blood pressure and plasma lipids of spontaneously hypertensive rats. J Nutr Sci Vitaminol. 1987;33:341–6.
23. Chien RC, Lin LM, Chang YH, Lin YC, Wu PH, Asatiani MD, Wasser SG, Krakhmalnyi M, Agbarya A, Wasser SP, Mau JL. Anti-inflammation properties of fruiting bodies and submerged cultured mycelia of culinary-medicinal higher Basidiomycetes mushrooms. Int J Med Mushrooms. 2016;18(11):999–1009.
24. Kudryavtseva OA, Dunaevsky YE, Kamzolkina OV, Belozersky MA. Fungal proteolytic enzymes: Features of the extracellular proteases of xylotrophic Basidiomycetes. Microbiology. 2008;77(6):643–53.
25. Denisova NP. History of the study of thrombolytic and fibrinolytic enzymes of higher Basidiomycetes mushrooms at the VL Komarov Botanical Institute in St Petersburg, Russia. Int J Med Mushrooms. 2010;12(3):317–25.
26. Ali SM, Tan YS, Raman J, Lakshmanan H, Ling TC, Phan CW, Sabaratnam W. Do culinary mushrooms have fibrinolytic activities? Biomed Rev. 2017;28:95–103.
27. Mattila P, Könkö K, Eurola M, Pihlava JM, Astola J, Vahteristo L, Hietaniemi V, Kumpulainen J, Valtonen M, Piironen V. Contents of vitamins, mineral elements, sand some phenolic compounds in cultivated mushrooms. J Agric Food Chem. 2001;49:2343–8.
28. Barros L, Venturini BA, Baptista P, Estevinho LM, Ferreira IC. Chemical composition and biological properties of Portuguese wild mushrooms: A comprehensive study. J Agric Food Chem. 2008;56:3856–62.
29. Kalač P. A review of chemical composition and nutritional value of wild-growing and cultivated mushrooms. J Sci Food Agric. 2013;93:209–18.
30. Badalyan SM. Fatty acid composition of different collections of coprinoid mushrooms (Agaricomycetes) and their nutritional and medicinal values. Int J Med Mushrooms. 2016;8(10):883–93.
31. Cheung PCK, editor. Mushrooms as functional foods. Hoboken, NJ: Wiley; 2008.
32. Cheung PCK. Mini-review on edible mushrooms as source of dietary fiber: Preparation and health benefits. Food Sci Human Wellness. 2013;2:162–6.
33. Khatun S, Islam A, Cakilcioglu U, Chatterjee NC. Research on mushroom as a potential source of nutraceuticals: A review on Indian perspective. Am J Exp Agric. 2012;2(1):47–73.
34. VanderMolen KM, Litlle JG, Sica VP, El-Elimat T, Raja HA, Oberlies NH, Baker TR, Mahony C. Safety assessment of mushrooms in dietary supplements by combining analytical data with in silico toxicology evaluation. Food Chem Toxicol. 2017;103:133–47.
35. Chang ST, Wasser SP. Current and future research trends in agricultural and biomedical applications of medicinal mushrooms and mushroom products (Review). Int J Med Mushrooms. 2018;20(12):1121–33.
36. Badalyan SM, Zambonelli A. Biotechnological exploitation of macrofungi for the production of food, pharmaceuticals and cosmeceuticals. In: Sridhar KR, Deshmukh SK, editors. Advances in macrofungi: Diversity, ecology and biotechnology. Boca Raton, FL: CRC Press; 2019. p. 199–230.
37. Guillamón E, García-Lafuente A, Lozano M, D'Arrigo M, Rostagno MA, Villares A, Martínez JA. Edible mushrooms: Role in the prevention of cardiovascular diseases. Fitoterapia. 2010;81(7):715–23.
38. Choi E, Ham O, Lee SY, Song BW, Cha MJ, Lee CY, Park JH, Lee J, Song H, Hwang KC. Mushrooms and cardiovascular disease. Curr Topics Nutraceut Res. 2012;10(1):43–52.
39. Shibu MA, Agrawal DC, Huang CY. Mushrooms: A Pandora box of cardioprotective phytochemicals. In: Agrawal DC, Tsay HS, Shyur LF, Wu YC, Wang SY, editors. Medicinal and aromatic plants of the world. Vol 4. Medicinal plants and fungi: Recent advances in research and development. Singapore: Springer Nature; 2017. p. 337–62.
40. Morales D, Piris AJ, Ruiz-Rodriguez A, Prodanov M, Soler-Rivas C. Extraction of bioactive compounds against cardiovascular diseases from Lentinula edodes using a sequential extraction method. Biotechnol Progress. 2018;34:746.
41. Bhushan A, Kulshreshtha M. Cardioprotective activity of Agaricus bisporus against isoproterenol-induced myocardial infarction in laboratory animals. Curr Nutri Food Sci. 2019;15(4):401–7.
42. Su HH, Chu YC, Liao JM, Wang YH, Jan MS, Lin CW, Wu CY, Tseng CY, Yen JC, Huang SS. Phellinus linteus mycelium alleviates myocardial ischemia-reperfusion injury through autophagic regulation. Front Pharmacol. 2017;8:175.
43. Wu Q, Tan Z, Liu H, Gao L, Wu S, Luo J, Zhang W, Zhao T, Yu J, Xu X. Chemical characterization of Auricularia auricula polysaccharides and its pharmacological effect on heart antioxidant enzyme activities and left ventricular function in aged mice. Int J Biol Macromol. 2010;46:284–8.

44. Blann AD, Landray MJ, Lip GYH. ABC of antithrombotic therapy: An overview of antithrombotic therapy. BMJ Clin Res. 2002;325(7367):762–5.
45. Kim JH, Kim YS. A fibrinolytic metalloprotease from the fruiting bodies of an edible mushroom, Armillariella mellea. Biosci Biotechnol Biochem. 1999;63(12):2130–6.
46. Badalyan SM, Melikyan LR, Navarro-González M, Kües U. Fibrinolytic activity of several coprinoid mushrooms. In: The Sixth International Conference on Mushroom Biology and Mushroom Products; 2008 Sep 29–Oct 3; Bonn, Germany. p. 66–7.
47. Badalyan SM, Gharibyan NG. Proteolytic and milk-coagulating activities of mycelia of several polypore mushrooms. In: Dyakov YT, editor. Current mycology in Russia. Proceedings of the III International Mycological Forum. Vol 5. 2015 April 14–15; Moscow, Russia. p. 275–7.
48. Badalyan SM, Gharibyan NG, Shahbazyan TA, Shnyreva AV. Milk coagulating and thrombolytic activity of red-belt conk Fomitopsis pinicola. In: Sergeev YV, editor. Advances in medical mycology. Proceedings of Memorial Conference of Medical Mycology. Vol 16. 2016 April 14–15. Moscow, Russia. p. 239–42.
49. Badalyan SM. Medicinal coprinoid mushrooms (Agaricomycetes) distributed in Armenia (Review). Int J Med Mushrooms. 2020;22(3):257–67.
50. Lu LC, Chen SN. Fibrinolytic enzymes from medicinal mushrooms. In: Faraggi E, editor. Biochemistry, genetics and molecular biology. Protein structure. London, UK: InTech Open; 2012. p. 337–62.
51. Morozova EN, Falina NN, Denisova NP, Barkova LV, Psurtseva NV. Analysis of the component constitution and substrate specificity of a fibrinolytic preparation from the fungus Flammulina velutipes. Biokhimia. 1982;47(7):1181–5.
52. Kumaran S, Palani P, Nishanthi R, Kaviyarasan V. Studies on screening, isolation and purification of a fibrinolytic protease from an isolate (VK12) of Ganoderma lucidum and evaluation of its antithrombotic activity. Med Mycol J. 2011;52(2):153–62.
53. Choi BS, Sapkota K, Choi JH, Shin CH, Kim S, Kim SJ. Herinase: A novel bi-functional fibrinolytic protease from the monkey head mushroom, Hericium erinaceum. Appl Biochem Biotechnol. 2013;170(3):609–22.
54. Choi JH, Kim DW, Kim S, Kim SJ. Purification and partial characterization of a fibrinolytic enzyme from the fruiting body of the medicinal and edible mushroom Pleurotus ferulae. Prep Biochem Biotechnol. 2017;7(6):539–46.
55. Choi HS, Shin HH. Purification and partial characterization of a fibrinolytic protease in Pleurotus ostreatus. Mycologia. 1998;90(4):674–9.
56. Khatun K, Mahtab H, Khanam PA, Sayeed MA, Khan KA. Oyster mushroom reduced blood glucose and cholesterol in diabetic subjects. Mymensingh Med J. 2007;16:94–9.
57. Wang C, Chen Z, Pan Y, Gao X, Chen H. Anti-diabetic effects of Inonotus obliquus polysaccharides-chromium (III) complex in type 2 diabetic mice and its sub-acute toxicity evaluation in normal mice. Food Chem Toxicol. 2017;108(Pt B):498–509.
58. Calvo MS, Mehrotra A, Beelman RB, Nadkarni G, Wang L, Cai W, Goh BC, Kalaras MD, Uribarri J. A retrospective study in adults with metabolic syndrome: Diabetic risk factor response to daily consumption of Agaricus bisporus (white button mushrooms). Plant Foods Hum Nutr. 2016;71:245–51.
59. Bobek P, Galbavý Š. Hypocholesterolemic and anti-atherogenic effect of oyster mushroom (Pleurotus ostreatus) in rabbits. Mol Nutr Food Res. 1999;43(3):339–42.
60. Gunde-Cimmerman N. Medicinal value of the genus Pleurotus (Fr.) P. Karst. (Agaricales s.l., Basidiomycetes). Int J Med Mushrooms. 1999;1:69–80.
61. Chen G, Luo YC, Li BP, Li B, Guo Y, Li Y, Su W, Xiao ZL. Effect of polysaccharide from Auricularia auricula on blood lipid metabolism and lipoprotein lipase activity of ICR mice fed a cholesterol-enriched diet. J Food Sci. 2008;73:H103–8.
62. Ng YF. In vitro and in vivo antioxidant activity and hypocholesterolemic effect in extracts of Agrocybe aegerita [master of philosophy thesis]. Hong Kong: The Chinese University of Hong Kong; 2005.
63. Yuan D, Mori J, Komatsu K, Makino T, Kano Y. An anti-aldosteronic diuretic component (drain dampness) in Polyporus sclerotium. Biol Pharm Bull. 2004;27:867–70.
64. Badalian SM, Serrano JJ. Hypoglycemic activity of the medicinal mushroom Hypholoma fasciculare (Fr.) Kumm. Int J Med Mushrooms. 1999;1(3):245–50.
65. Chen L, Zhang Y, Sha O, Xu W, Wang S. Hypolipidaemic and hypoglycaemic activities of polysaccharide from Pleurotus eryngii in Kunming mice. Int J Biol Macromol. 2016;93:1206–9.
66. Badalyan SM, Gharibyan NG. Diversity of polypore bracket mushrooms, Polyporales (Agaricomycetes) recorded in Armenia and their medicinal properties. Int J Med Mushrooms. 2016;1(4):347–54.
67. Badalyan SM, Gharibyan NG. Characteristics of mycelial structures of different fungal collections. Yerevan, Armenia: Yerevan State University Press; 2017.
68. Badalyan SM, Gharibyan NG. Pharmacological properties and resource value of Hymenochaetoid fungi (Agaricomycetes) distributed in Armenia: Review. Int J Med Mushrooms. 2020;22(12):1135–46.
69. Zhang Y, Wang Z, Jin G, Yang X, Zhou H. Regulating dyslipidemia effect of polysaccharides from Pleurotus ostreatus on fat-emulsion-induced hyperlipidemia rats. Int J Biol Macromol. 2017;101:107–16.

70. Punitha SC, Rajasekaran M. Cardioprotective effect of Volvariella volvacea in streptozotocin administered rats. Bangladesh J Pharmacol. 2016;11(4):903–10.
71. Wang Y, Li H, Li Y, Zhao Y, Xiong F, Liu Y, Xue H, Yang Z, Ni S, Sahil A, Che H, Wang L. Coriolus versicolor alleviates diabetic cardiomyopathy by inhibiting cardiac fibrosis and NLRP3 inflammasome activation. Phytother Res. 2019;33:2737–48.
72. Dulay RM, Arenas MC, Kalaw SP, Reyes RG, Cabrera EC. Proximate composition and functionality of the culinary-medicinal tiger sawgill mushroom, Lentinus tigrinus (higher Basidiomycetes), from the Philippines. Int J Med Mushrooms. 2014;16(1):85–94.