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RESEARCH ARTICLE

Research on the use of traditional chinese medicine mushrooms in treatment of cardiovasculat diseases

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Abstract

Traditional Chinese Medicine (TCM) is a system of practices that has been developing for over 2,000 years. Unlike in medicine developed in western culture, it is characterized by a holistic approach to treat diseases, taking into account context of given disease (co-occurring diseases, age and sex of the patient). The practices of Traditional Chinese Medicine include acupuncture, acupressure, qigong gymnastics, and the application of herbal medicine and usage of medicinal mushrooms. According to WHO, cardiovascular diseases, such as stroke or heart attack, are one of leading causes of death, accounting for almost 1/3 of all deaths in 2019. Of the many mushrooms with medicinal properties, those that can be used as drugs for the treatment of cardiovascular diseases deserve special attention. This category includes, among others mushrooms from genus Agaricus, Auricularia or Pleurotus. They are rich source of bioactive compounds, such as flavonoids, sterols, polysaccharides and fiber. Among them, some mushrooms act in a direct way, e.g. by reducing atherosclerotic plaque, and some in an indirect manner, e.g. by reducing blood pressure and cholesterol levels. The main issues in the integration of TCM into Western medicine are the lack of sufficient evidence of its effectiveness, the poor quality of clinical trials, as well as the small number of publications available in English. In the case of mushrooms used in TCM, most studies were performed in animal models or cell lines and used only a single substance instead of the whole fungus.

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1. Introduction

Traditional Chinese Medicine (TCM) is a system of healing practices that has been developing for over 2,000 years. This system focuses on treating the body as a whole. TCM is mainly based on the Chinese philosophy of Yin-Yang, Five Elements, Zang-Fu and the vital energy Qi [43][13]. The oldest manuscript on TCM is the Inner Cannon of the Yellow Emperor (Huángdì Nèijīng), dating back to the 1st century BC (figure. 1). It contains the main concepts of TCM [19]. In recent decades, Western countries have started to recognize the potential health benefits of TCM. The first TCM hospital in the Western world was opened in Kötzting, Germany, in 1991 [29], while in the United States, the UCLA Center for Integrative Medicine has been operating since 1993. Also in the US, the National Center as part of the Department of Health was founded in 1998 for Complementary and Alternative Medicine [44] [33]. In 2018, the WHO included TCM in its compendium (International Statistical Classification of Diseases and Related

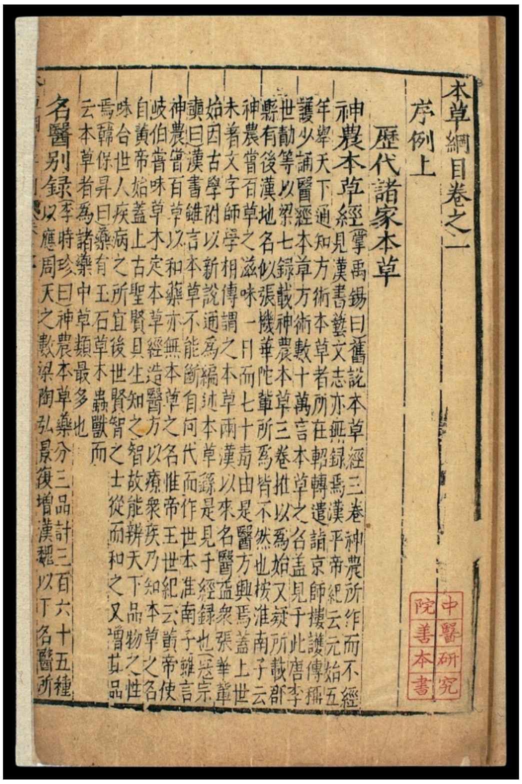

Figure 1. First edition of Bencao Gangmu; Chinese, 1590. source: Wellcome Collection. Public Domain Mark. Source: Wellcome Collection

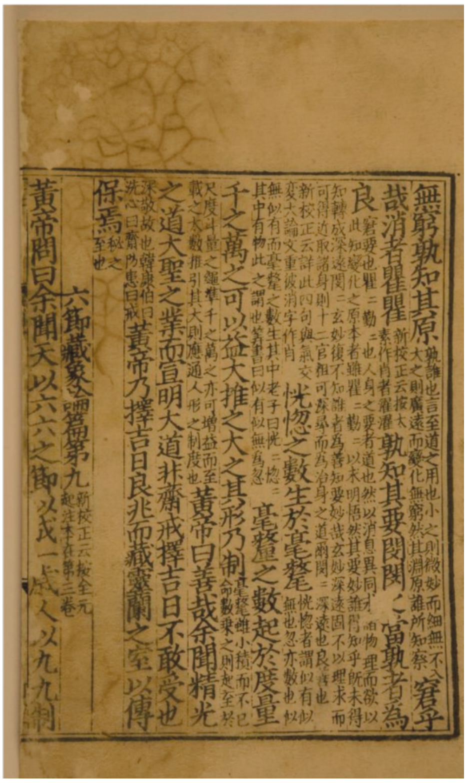

Figure 2. Page from Huang di nei jing; source: https://www.loc.gov/resource/gdcwdl.wdl_03044/?sp=6&r=-0.597,-0.108,2.195,1.857,0, World Digital Library

Health Problems, ICD) for the first time [50]. In 2022 foundation stone was laid of WHO Global Centre for Traditional Medicine in India, which goal is to advance traditional medicine's contribution to global health and sustainable development [51]. The TCM therapeutic strategies include acupuncture, acupressure, cupping, qigong gymnastics, and herbal medicine. Herbal medicine has attracted increased interest on a global level. In 2016, value of export of TCM products from China was $ 1.174 billion [25] and according to Fortune Business Insights herbal medicine market is expected to be worth USD 216.40 billion in 2023 [15]. Herbal medicine used in TCM accounted for 20-50% of the total herbal medicine used around the world in 2009 [55]. Substances used in TMC include both plants and mushrooms. The use of mushrooms or their extracts as health-promoting agents is called mycotherapy or fungotherapy [34]. Mycotherapy is a popular form of therapy in the traditional medicine of the Far East [37]. The use of fungi of the genus Ganoderma can be dated back to 4800 BC [60]. Particularly noteworthy is the work entitled Bencao Gangmu (Materia Medica), which is a pharmacopoeia from the Ming Dynasty. It was created by Li Shizhen in the years 1552-1587, and its first edition dates back to 1596 (figure. 2). It is one of the most important works of TCM and describes over 11,000 recipes and treatment methods as well as 1,892 pharmaceutical substances, of which 1,094 are of plant or mushroom origin. The list of mushrooms with medical properties is constantly growing. In 2009, Dai et al. published a list of 936 edible mushrooms found in China [9]. In 2019 this list consisted of 1,020 species species, of which 277 are considered edible with medical properties and no known toxicity. These are the so-called "golden mushrooms" [52]. Many of these mushrooms are commercially cultivated. In 2017, five genus were responsible for approximately 85% of worldwide mushroom production. These five genus being Lentinula, Pleurotus, Auricularia, Agaricus, and Flammulina, accounting for 22%, 19%, 17%, 15% and 11% of global mushroom production, respectively [10]. Although most of these mushrooms are mainly cultivated in Asia for centuries, Poland is one of the leading mushrooms producers in Europe. Some of medicinal mushrooms can be cultivated commercially on large using simple sawdust-based logs, for example Lentinula or Pleurotus. Others, like Ophiocordyceps requires special conditions and cannot be cultivated on large scale.

Among many potential medical properties, those that can reduce the risk of cardiovascular disease (CVD) or support treatment deserve special attention. CVDs are among leading causes of death in the world, accounting for approximately 32% of all deaths (data for 2019) of which 85% was caused by stroke or heart attack. CVDs include, among others, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, pulmonary embolism, and deep vein thrombosis. The occurrence of many CVDs depends on risk factors such as alcohol consumption, smoking, hypertension, overweight, diabetes, poor diet, and hyperlipidemia (WHO, 2021). To this day, most research regarding treatment of cardiovascular diseases are conducted on cell lines and animal models. Among animal models, Apoe−/− mice deserves special attention. Apoe is ligand for lipoprotein receptors involved in lipoprotein recognition and clearance. Mice with knockout gene responsible for synthesis of Apoe are prone to develop severe atherosclerotic lesions and hypercholesterolemia, when on normal diet. This makes them perfect model for research on CVDs [38]. Aim of this work is to review studies on the most promising mushrooms regarding treating cardiovascular diseases.

Bioactivities of TCM mushrooms used for treating/preventing cardiovascular diseases

Some fungi with the potential to reduce the risk of CVD or to support treatment of CVD and used in TMC are characterized below. These mushrooms were selected based on available research data, as well as their common usage in TCM practices. Among them are mushrooms whose consumption acts directly, e.g., reduces atherosclerotic plaque, as well as indirectly, i.e., reducing risk factors. Most relevant bioactive compounds in context of treating cardiovascular diseases, as well as models used in research are presented in table 1. Systematic position of each mushroom can be found in supplementary tables S1-S16, all systematic names were provided from the index fungorum [17].

Genus *Agaricus*.

Usage of mushrooms from genus Agaricus has been described by Li Shizhen in Bencao Gangmu. Agaricus bisporus reduces the risk of CVDs by regulating blood cholesterol levels. It is rich in plant sterols such as ergosta-7,22-dienol, ergosta-5,7-dienol, and fungisterol [42]. A. bisporus contains lovastatin at a concentration of 565.4 mg/kg, which is commonly used to lower the LDL level in the blood, directly reducing the risk of CVDs [2]. In their study Das et al. [11] reported cholesterol reducing properties of lipophilic fraction extracted from A. bisporus, as well as its potential to reduce level of CRP (2,26-2,33 folds), which is one of predictors of atherosclerosis. They attributed this properties to high concentration of ergosterol and polyunsaturated fatty acids. Another example is A. blazei. In TCM, this mushroom has been used for over 3,000 years, mainly to lower blood pressure and cholesterol levels (by 11%). A. blazei accumulate gamma-aminobutyric acid (GABA) in higher concentrations than other edible mushrooms (e.g., enoki, shitake, maitake). Studies have shown that the regular consumption of A. blazei can significantly reduce blood pressure in patients with mild hypertension due to the presence of high concentration of GABA [48].

Genus *Auricularia*.

Consumption of mushroom from genus Auricularia causes a reduction in total cholesterol and LDL levels and an increase in HDL levels, which is due to the high levels of β-glucan (polysaccharide with hypocholesterolemic properties) and antioxidants, such as flavonoids, which prevent LDL synthesis by blocking VLDL[4,61].

Genus Cordyceps.

Studies have shown that the cordycepin contained in Cordyceps exhibits antithrombotic and antiplatelet properties by inhibiting platelet aggregation. It also inhibits several components of platelet activation, as well as clot formation [22]. It can also inhibit acute pulmonary thromboembolism and thrombus formation in vivo without showing cytotoxicity or an increased risk of major bleeding. This suggests that cordycepin contained in Cordyceps may serve as a therapeutic agent in the treatment of,

Table 1. Bioactive compounds and model used in research on mushrooms used in TCM in context of treating cardiovascular diseases

genus	Research model	Bioactive compound	Citation
Agaricus	mice human in vitro	ergosta-7,22-dienol ergosta-5,7-dienol fungisterol lovastatin gamma-aminobutyric acid (GABA)	[2],[11],[39],[48]
Auricularia	rat	β-glucan flavonoids	[4][61]
Cordyceps	rat in vitro mice	cordycepin polysaccharide CM3II polysaccharide CM1	[22],[26],[40],[58]
Flammulina	hamster In vitro	mycosterol fiber	[59],[35]
Grifola	rat mice in vitro	Ergosterol fiber	[8],[21],[32]
Hypsizygus	mice	fiber	[32]
Lentinus	rat	gamma-aminobutyric acid (GABA)	[12]
Pleurotus	in vitro rat	profilin-like protein GAP dehydrogenase-like protein TP-like protein catalase-like protein tripeptide GVR	[1],[28],[45]
Tricholoma	rat in vitro	peptides	[14]
Wolfiporia	rat in vitro zebrafish, mice	polysaccharides	[23],[53],[57]
Lentinula	in vitro rat	eritadenine α-tocopherol oleic acid linoleic acid ergosterol butyric acid	[31],[39]
Ophiocordyceps	rabbit in vitro rat	adenosine polysaccharide CME-1 polysaccharide CSP1-2	[5],[27],[54],[62]
Ganoderma	hamster minipig in vitro rat mice rabbit	polysaccharide peptide polysaccharides triterpenoids	[3],[20],[30]
Tremella	rat mice	fiber	[6],[7]

among others, thrombosis, atherosclerosis, or myocardial infarction [22]. In their study, Takakura et al. [40] showed that Cordyceps administered in diet improved autophagy and mitochondrial activity in Dahl salt-sensitive hypertensive rats, which extended their life-span due to protection from diastolic heart failure. In another study L. Wang et al. [46] showed that residue polysaccharides (in medium after cultivation of Cordyceps) can lower levels of triglycerides, LDL, V-LDL, total cholesterol and atherogenic index in rats which can lower the risk of cardiovascular diseases. Different study showed, that polysaccharide CM3II, isolated from Cordyceps fruiting body can reduce atherosclerotic lesion/lumen ratio by 17,8 % in apoE−/− mice [58]. Also CM1, different polysaccharide from Cordyceps, can act as anti- atherosclerosis compound. Study showed, that CM1 ameliorate atherosclerosis in a dose-dependent manner via different pathways. CM1 can regulate lipid concentration, oxidoreductase activity and inhibit chemokine activity, therefore reducing inflammatory response in apoE−/− mice [26].

Genus *Flammulina*.

Studies have shown that both the extract and powder from mushrooms from genus Flammulina help lower blood pressure as well as total cholesterol, triglycerides, and LDL levels, which is due to the high contents of mycosterol and fiber [41,59]. These mushrooms is also used to treat atherosclerosis. One of the mechanisms is the inhibition of LDL oxidation by polyphenols contained in mushrooms of genus Flammulina (ox-LDL is one of the key components promoting atherosclerosis). Another mechanism is the inhibition of atherosclerotic plaque formation by protocatechuic acid, which prevents the adhesion of monocytes to endothelial cells (activated by TNF-α) and leads to a decrease in the expression of VCAM-1 and ICAM-1 [35].

Genus *Grifola*.

The consumption of mushrooms from genus Grifola, also known by its Japanese name-maitake, helps reduce blood pressure as well as total cholesterol and VLDL cholesterol levels [21]. Another study, conducted by Mori et al. [32] showed that oral consumption of maitake can reduce total cholesterol and triglycerides levels in apoE−/− mice, although not as much as consumption of mushroom from genus Hypsizygus. It also significantly reduced area of atherosclerotic lesion compared to control group. In different study, hexa-peptide was isolated from cold water extract of Grifola fruiting body. This compound had inhibitory properties towards angiotensin I-converting enzyme, which play an important role in controlling blood pressure [8].

Genus *Hypsizygus*.

Mushrooms of this genus, due to the effects of fiber content, helps draining blood cholesterol levels and reducing the size of the atherosclerotic plaque in apolipoprotein A deficient mice [32]. In another study Xu et al. showed, that mushrooms from genus Hypsizygus are rich source of phenolics: (+)-catechin, gallic acid, and protocatechuic acid. Diet rich in those compounds can reduce risk of occurrence of chronic diseases, including CVDs [56].

Genus *Lentinus*.

The consumption of extract from Lentinus fruitbodies reduces blood pressure and heart rate, along with a reduction in triglycerides, blood urea nitrogen, and creatinine. It also increases the levels of total cholesterol and HDL as well as the albumin/globulin ratio, which can prevent the development of hypertension [12].

Genus *Pleurotus*.

Proteins obtained from Pleurotus fruitbodies can potentially be used in the treatment of type 2 diabetes (which is a risk factor of CVDs). There are among others profilin-like, GAP dehydrogenase-like, TP-like, and catalase-like proteins [45]. In another study Manoharan et al. [28] showed, that tripeptide GVR from fraction D6 of Pleurotus exhibit anti-hypertensive properties via competitive inhibition of angiotensin-converting enzyme with IC50 value of 55 μg/mL. Different study shows, that rats fed with high and low doses of Pleurotus extract had significantly lower levels of triglyceride compared to control group (0.41 mmol/L, 0.63 mmol/L and 1.11 mmol/L, respectively). Results were comparable to those after usage of simvastatin [1].

Genus *Tricholoma*.

The consumption of some species belonging to genus helps lower blood pressure due to the inhibition of angiotensin-converting enzyme. This prevents the conversion of angiotensin I into angiotensin II (which is the strongest angiotensin causing muscle contraction of the blood vessels) by cleavage of histidine and leucine at the C-terminus [14].

Genus *Wolfiporia*.

Wolfiporia mushrooms have diuretic properties similar to furosemide but it does not interfere with electrolyte management. The mechanism is based on reducing the expression of aquaporin 2 (regulated, among others, by vasopressin), which is responsible for water resorption in the kidneys. In addition, it inhibits V2R receptor and vasopressin expression. The consumption of these improves cardiovascular and renal parameters after myocardial infarction, and it has been suggested that it may be more effective than furosemide with prolonged intake [53]. In another study H. Yang et al. [57] proved, that water extract of Wolfiporia containing 8 identified compounds exhibit anti-arrhythmia properties in zebrafish model. This is due to regulation of mRNA expression of genes CALM1B, PPP3CA, HTR7 and ADRB1, as well as levels of cAMP in Ca^{2+} signal pathway. It can also regulate synthesis of leucine, isoleucine and valine. Different study shows, that polysaccharides extracted from Wolfiporia significantly reduced atherosclerosis plaque in ApoE−/− mice model treated with high-fat diet. They also inhibit inflammatory mediators such as IL-6, TNF-α and NO as well as LDL, cholesterol and triglycerides increase. Expression of MMP-2 and ICAM-1 proteins as well as TLR4/NF-κB pathway in aorta were also inhibited [23].

Genus *Lentinula*.

Genus Lentinula is rich in a compound called eritadenine [2(R),3(R)-4-(9-adenyl)-butyric acid], which is responsible for lowering cholesterol levels. This mechanism involves inhibition of S-adenosyl-L-homocysteine hydrolase in the liver [31,39]. In another study Rahman et al. [36] proved, that extract of Lentinula, contains among others α-tocopherol, oleic acid, linoleic acid, ergosterol and butyric acid. This extract inhibits biosynthesis of cholesterol interacting with HMG Co-A reductase and lowers LDL oxidation. These actions contributed to anti-atherosclerotic properties of extract of genus Lentinula.

Genus *Ophiocordyceps*.

Mycelia and fruiting bodies of Ophiocordyceps are rich in adenosine, which means it exhibits mild hypotensive properties [47]. An ethanolic extract of Ophiocordyceps counteracts arrhythmia induced by aconitine or BaCl2. The ethanolic extract of Ophiocordyceps mycelium inhibits thrombus formation in the abdominal aorta in rabbits, reducing the platelet number of the injured abdominal aorta. This suggests that Ophiocordyceps inhibits thrombus formation at the de-endothelialized surface of the aorta [62]. In their respective works, Lu et al. [27] and Chang et al. [5] both proved, that CME-1, a polysaccharide extracted from Ophiocordyceps can inhibit platelet activation, acting on PLCγ2-PKC-p47 cascade. It also inhibit PI3-kinase/Akt and MAPK phosphorylation as well as intracellular Ca2+ mobilization. Additionally, another study showed, that polysaccharide CSP1-2 (composed of glucose, mannose and galactose in 2:2:1 ratio) has the ability to decrease blood pressure in hypertensive rats. It is due to inhibition of production of angiotensin-II, TGF-β1, adrenaline, noradrenaline, CRP and endothelin-1, while increasing production of NO [54]. Hiraishi et al. [16] suggests extract from Ophiocordyceps as an alternative therapy for pulmonary hypertension. Study showed vasorelaxation properties of Ophiocordyceps due to inhibition of transient receptor potential melastatin subfamily member 7 (TRPM7) expression in pulmonary artery smooth muscle cells.

Genus *Ganoderma*.

Studies conducted by Berger et al. show, that species from genus Ganoderma have potential to lower cholesterol level in animal models [3]. The aqueous extract of Ganoderma has significant hypotensive properties. The powdered mycelium of G. lucidum, known as Reishi (most well-known representative of the genus Ganoderma), administered at 5% of the diet of spontaneously hypertensive rats for 4 weeks, caused a decrease in systolic blood pressure without impacting the heart rate [20]. In another study Meng et al. [30] showed, that polysaccharide peptide (150 mg/kg/day) extracted from Ganoderma can improve cardiac function as well as ameliorate cardiac fibrosis following myocardial infraction. It was due to inhibited expression of α-smooth muscle actin, collagen I, collagen III and fibronectin. Additionally, relieves oxidative stress. Different study showed, that polysaccharides and triterpenoids extracted from Ganoderma ameliorates atherosclerosis plaque, promoting apoptosis of foam cells, mitigating inflammatory polarization of macrophages and inhibiting oxidative dysfunction of endothelium in high-fat diet rabbits [24].

Genus *Tremella*.

Fungi belonging to this genus are known for their antioxidant and cosmetic properties, Tremella can influence lipids serum levels [18]. Tremella significantly lower the concentration of serum LDL and cholesterol levels. This is caused by high amount of dietary fiber, which helps to reduce cholesterol absorption. [6]. Tremella also increase the blood insulin concentration. It is caused by enhancing the PPAR-ɣ expression (83% to control) [7].

SUMMARY

Various mushrooms found in China are a rich source of medicinal substances. Mushrooms with potential medicinal properties include both common mushrooms, such as A. bisporus, as well as rare and expensive mushrooms, such as Tricholoma matsutake, which can cost up to $ 1,000 per pound. Many of the species valued by Traditional Chinese Medicine can be found all over the world and are mentioned in various folklore medicine guides. For example, mushrooms belonging to genera: Agaricus, Pleurotus and Auricularia can also be found in Poland. Knowledge and interest in fungi with medicinal potential is constantly growing, as there is great potential in them that has not yet been fully discovered. TCM contains various therapeutic strategies and uses numerous healing substances in the treatment of many diseases. Among mechanisms of action in aforementioned research most common is reducing LDL,VLDL and cholesterol levels, which prevents atherosclerotic plaque formation. Another mechanism worth mentioning is reduction of atherosclerosis plaque after its formation. Also, some compounds can lower blood pressure by inhibiting angiotensin-converting enzyme.

However, there are several factors that inhibit the integration of TCM into Western medicine. The first problem is insufficient evidence of the effectiveness of TCM from the perspective of Western medicine. Although there are many clinical trials focusing on TCM, the level is lower than that of trials on Western medicine. In such studies, a group treated with
a different TCM technique is often used as a reference, and therefore, the treatment of a given disease with TCM and Western medicine cannot be directly compared. Other issues are the small number of publications in English and the fact that TCM treats humans holistically, not focusing on a single disease. Despite many attempts, there is still no evidence of the existence of Qi life energy or meridians, which are essentially Qi's channels and which are crucial from the TCM point of view. Another problem with herbal medicine is the creation of a placebo for multi-herbal decoctions that would be indistinguishable from the test substance. It is worth mentioning, that some studies focus on the high fiber content as the reason for the health-beneficial effects of a given mushroom, yet high amounts of fiber can be found in most if not all edible mushroom species.

So far most studies regarding mushrooms used in TCM were conducted using only single component extracted from given mushroom. In traditional medicine however, mixtures, drugs and decoctions containing whole mushroom are typically used. In addition, most of these studies were conducted on cell lines or animals such as rats, mice, rabbits and zebrafish. Due to this fact question about effectiveness of given treatment in humans remains mostly unanswered. In conclusion, although there is tremendous potential in medicinal mushrooms, to fully benefit from this rich source of bioactive components, quality and number of research (both in laboratory and clinical trials) in the future must improve.

Conflict of interest

Declaration of interest: none.

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REFERENCES

1. Amirullah, N.A., Zainal Abidin, N., Abdullah, N., Manickam, S., The ultrasound extract of Pleurotus pulmonarius (Fr.) Quél alleviates metabolic syndromes in hyperlipidaemic Wistar-Kyoto rats fed with a high-fat diet, Biocatal. Agric. Biotechnol. 2021, 34, 102019.

2. Atila, F., Owaid, M.N., Shariati, M.A., The nutritional and medical benefits of Agaricus Bisporus: A review, J. Microbiol. Biotechnol. Food Sci. 2017, 7, 281-286.
3. Berger, A., Rein, D., Kratky, E., Monnard, I., Hajjaj, H., Meirim, I., Piguet-Welch, C., Hasuer, J., Mace, K., Niederberger, P., Cholesterol-lowering properties of Ganoderma lucidum in vitro, ex vivo, and in hamsters and minipigs, Lipids Health Dis. 2004, 3.
4. Budinastiti, R., Sunoko, H.R., Widiastiti, N.S., The Effect of Cloud Ear Fungus (Auricularia polytricha) on Serum Total Cholesterol, LDL and HDL Levels on Wistar Rats Induced by Reused Cooking Oil, E3S Web Conf. 2018, 31.
5. Chang, Y., Hsu, W.-H., Lu, W.-J., Jayakumar, T., Liao, J.-C., Lin, M.-J., Wang, S.-H., Geraldine, P., Lin, K.-H., Sheu, J.-R., Inhibitory mechanisms of CME-1, a novel polysaccharide from the mycelia of Cordyceps sinensis, in platelet activation., Curr. Pharm. Biotechnol. 2015, 16, 451–461.
6. Cheung, P.C.K., The hypocholesterolemic effect of two edible mushrooms: Auricularia auricula (Tree-ear) and Tremella fuciformis (White jelly-leaf) in hypercholesterolemic rats, Nutr. Res. 1996, 16, 1721–1725.
7. Cho, E.J., Hwang, H.J., Kim, S.W., Oh, J.Y., Baek, Y.M., Choi, J.W., Bae, S.H., Yun, J.W., Hypoglycemic effects of exopolysaccharides produced by mycelial cultures of two different mushrooms Tremella fuciformis and Phellinus baumii in ob/ob mice, Appl. Microbiol. Biotechnol. 2007, 75, 1257–1265.
8. Choi, H.S., Cho, H.Y., Yang, H.C., Ra, K.S., Suh, H.J., Angiotensin I-converting enzyme inhibitor from Grifola frondosa, Food Res. Int. 2001, 34, 177–182.
9. Dai, Y.C., Yang, Z.L., Cui, B.K., Yu, C.J., Zhou, L.W., Species diversity and utilization of medicinal mushrooms and fungi in China (review), Int. J. Med. Mushrooms. 2009, 11, 287–302.
10. Daniel J. R., Baars, J., Tan, Q., Curr. Overv. Mushroom Prod. World. 2017, 2010, 5–13.
11. Das, M., V, G., Zarei, M., Harohally, N. V., Kumar G, S., Modulation of obesity associated metabolic dysfunction by novel lipophilic fraction obtained from Agaricus bisporus, Life Sci. 2022, 305, 120779.
12. Eguchi, F., Milton R. Dulay, R., Kalaw, S.P., Yoshimoto, H., Antihypertensive activities of a Philippine wild edible white rot fungus (Lentinus sajor-caju) in spontaneously hypertensive rats as models, Adv Env. Biol 2014, 8, 74–81.
13. Fung, F.Y., Linn, Y.C., Developing traditional Chinese medicine in the era of evidence-based medicine: Current evidences and challenges, Evidence-Based Complement. Altern. Med. 2015, 2015.
14. Geng, X., Tian, G., Zhang, W., Zhao, Y.,. Zhao, L, Wang, H., Ng, T.B., A Tricholoma matsutake Peptide with Angiotensin Converting Enzyme Inhibitory and Antioxidative Activities and Antihypertensive Effects in Spontaneously Hypertensive Rats, Sci. Rep. 2016, 6, 1–9.
15. Herbal Medicine Market Size to Reach USD 371.45 Billion by 2030 | Exclusive Report by Fortune Business Insights, URL (https://finance.yahoo.com/news/herbal-medicine-market-size-reach-135300402.html) (date of access: december 2023).
16. Hiraishi, K., Kurahara, L.H., Feng, J., Yamamura, A., Cui, Y., Yahiro, E., Yokomise, H., Go, T., Ishikawa, K., Yokota, N., Fujiwara, A., Onitsuka, M., Abe, K., Ohga, S., Satoh, T., Okada, Y., Yue, L., Inoue, R., Hirano, K., Substantial involvement of TRPM7 inhibition in the therapeutic effect of Ophiocordyceps sinensis on pulmonary hypertension, Transl. Res. 2021, 233, 127–143.
17. Indexfungorum, URL (http://indexfungorum.org/) (date of access: december 2023).
18. Isokauppila, T., Grzyby Lecznicze, przewodnik po azjatyckich grzybach, które odmładzają ciało, dodają energii i przedłużają życie, VIVANTE, Poland, 2018, 124-125.
19. Jia, Q., Traditional Chinese Medicine Could Make " Health for One " True, URL (http://www.who.int/intellectualproperty/studies/Jia.pdf) (date of access: january 2021).
20. Kabir, Y., Klmura, S., Tamura, T., Dietary Effect of Ganoderma lucidum Mushroom on Blood Pressure and Lipid Levels in Spontaneously Hypertensive Rats (SHR), J. Nutr. Sci. Vitaminol. (Tokyo). 1988, 34, 433–438.
21. Kabir, Y., Yamaguchi, M., Klmura, 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. (Tokyo). 1987, 33, 341–346.
22. Kwon, H.W., Shin, J.H., Lim, D.H., Ok, W.J., Nam, G.S., Kim, M.J., Kwon, H.K., Noh, J.H., Lee, J.Y., Kim, H.H., Kim, J.L., Park, H.J., Antiplatelet and antithrombotic effects of cordycepin-enriched WIB-801CE from Cordyceps militaris ex vivo, in vivo, and in vitro, BMC Complement. Altern. Med. 2016, 16, 1–19.
23. Li, W., Yu, J., Zhao, J., Xiao, X., Li, W., Zang, L., Yu, J., Liu, H., Niu, X., Poria cocos polysaccharides reduces high-fat diet-induced arteriosclerosis in ApoE−/− mice by inhibiting inflammation, Phyther. Res. 2021, 35, 2220–2229.
24. Li, Y., Tang, J., Gao, H., Xu, Y., Han, Y., Shang, H., Lu, Y., Qin, C., Ganoderma lucidum triterpenoids and polysaccharides attenuate atherosclerotic plaque in high-fat diet rabbits, Nutr. Metab. Cardiovasc. Dis. 2021, 31, 1929–1938.
25. Lin, A.X., Chan, G., Hu, Y., Ouyang, D., Ung, C.O.L., Shi, L., Hu, H., Internationalization of traditional Chinese medicine: Current international market, internationalization challenges and prospective suggestions, Chinese Med. (United Kingdom) 2018, 13, 1–6.
26. Lin, P., Yin, F., Shen, N., Liu, N., Zhang, B., Li, Y., Guo, S., Integrated bioinformatics analysis of the anti-atherosclerotic mechanisms of the polysaccharide CM1 from Cordyceps militaris, Int. J. Biol. Macromol. 2021, 193, 1274–1285.
27. Lu, W.J., Chang, N.C., Jayakumar, T., Liao, J.C., Lin, M.J., Wang, S.H., Chou, D.S., Thomas, P.A., Sheu, J.R., Ex vivo and in vivo studies of CME-1, a novel polysaccharide purified from the mycelia of Cordyceps sinensis that inhibits human platelet activation by activating adenylate cyclase/cyclic AMP, Thromb. Res. 2014, 134, 1301–1310.
28. Manoharan, S., Shuib, A.S., Abdullah, N., Bin Mohamad, S., Aminudin, N., Characterisation of novel angiotensin-I-converting enzyme inhibitory tripeptide, Gly-Val-Arg derived from mycelium of Pleurotus pulmonarius, Process Biochem. 2017, 62, 215-222.
29. Melchart, D., Linde, K., Weidenhammer, W., Hager, S., Liao, J., Bauer, R., Wagner, H., Use of traditional drugs in a hospital of Chinese medicine in Germany, Pharmacoepidemiol. Drug Saf. 1999, 8, 115–120.
30. Meng, J., Ma, A., Zhang, S., Lin, D., Lin, S., Li, M., Zhou, H., Yang, B., Ganoderma Lucidum Polysaccharide Peptide attenuates post myocardial infarction fibrosis via down-regulating TGF-β1/SMAD and relieving oxidative stress, Pharmacol. Res. - Mod. Chinese Med.2022, 4, 100152.
31. Morales, D., Piris, A., Ruiz-Rodriguez, A., Extraction of

bioactive compounds against cardiovascular diseases from Lentinula edodes using a sequential extraction method, Biotechnol. Prog. 2018, 34, 746-755.
32. Mori, K., Kobayashi, C., Tomita, T., Inatomi, S., Ikeda, M., Antiatherosclerotic effect of the edible mushrooms Pleurotus eryngii (Eringi), Grifola frondosa (Maitake), and Hypsizygus marmoreus (Bunashimeji) in apolipoprotein E-deficient mice, Nutr. Res. 2008, 28, 335–342.
33. National Center for Complementary and Alternative Medicine, National Center for Complementary and Alternative Medicine, URL (https://www.nccih.nih.gov/) (date of access: january 2021).
34. Popovic, V., Zivkovic, J., Davidovic, S., Stevanovic, M., Stojkovic, D., Mycotherapy of Cancer: An Update on Cytotoxic and Antitumor Activities of Mushrooms, Bioactive Principles and Molecular Mechanisms of their Action, Curr. Top. Med. Chem. 2013, 13, 2791–2806.
35. Rahman, M.A., Abdullah, N., Aminudin, N., Antioxidative effects and inhibition of human low density lipoprotein oxidation in vitro of polyphenolic compounds in flammulina velutipes (Golden Needle Mushroom), Oxid. Med. Cell. Longev. 2015, 2015.
36. Rahman, M.A., Abdullah, N., Aminudin, N., Lentinula edodes (shiitake mushroom): An assessment of in vitro anti-atherosclerotic bio-functionality, Saudi J. Biol. Sci. 2018, 25, 1515–1523.
37. Reshetnikov, S. V, Wasser, S., Tan, K.-K., Higher Basidiomycota as a Source of Antitumor and Immunostimulating Polysaccharides (Review), Int. J. Med. Mushrooms 2001, 3, 361–394.
38. Lo Sasso, G., Schlage, W.K., Boué, S., Veljkovic, E., Peitsch, M.C., Hoeng, J., The Apoe-/- mouse model: A suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction, J. Transl. Med. 2016, 14, 1-16.
39. Sugiyama, K., Akachi, T., Yamakawa, A., Hypocholesterolemic action of eritadenine is mediated by a modification of hepatic phospholipid metabolism in rats, J. Nutr. 1995, 125, 2134-2144.
40. Takakura, K., Ito, S., Sonoda, J., Tabata, K., Shiozaki, M., Nagai, K., Shibata, M., Koike, M., Uchiyama, Y., Gotow, T., Cordyceps militaris improves the survival of Dahl salt-sensitive hypertensive rats possibly via influences of mitochondria and autophagy functions, Heliyon 2017, 3, e00462.
41. Tang, C., Hoo, P.C.X., Tan, L.T.H., Pusparajah, P., Khan, T.M., Lee, L.H., Goh, B.H., Chan, K.G., Golden needle mushroom: A culinary medicine with evidenced-based biological activities and health promoting properties, Front. Pharmacol. 2016, 7.
42. Teichmann, A., Dutta, P.C., Staffas, A., Jägerstad, M., Sterol and vitamin D2 concentrations in cultivated and wild grown mushrooms: Effects of UV irradiation, LWT - Food Sci. Technol. 2007, 40, 815–822.
43. Traditional Chinese Medicine, Traditional Chinese Medicine: What You Need To Know, URL (https://archive.is/iEyUU) (date of access: january 2021).
44. UCLA, The Collaborative Centers for Integrative Medicine UCLA, URL (http://cewm.med.ucla.edu/resources/ucla-ccim/) (date of access: januaru 2021).
45. Wahab, N.A.A., Abdullah, N., Aminudin, N., Characterisation of Potential Antidiabetic-Related Proteins from Pleurotus pulmonarius (Fr.) Quél. (Grey Oyster Mushroom) by MALDI-TOF/TOF Mass Spectrometry, Biomed Res. Int. 2014, 2014.
46. Wang, L., Xu, N., Zhang, J., Zhao, H., Lin, L., Jia, S., Jia, L., Antihyperlipidemic and hepatoprotective activities of residue polysaccharide from Cordyceps militaris SU-12, Carbohydr. Polym. 2015, 131, 355–362.
47. Wang, S.Y., Shiao, M.S., Pharmacological functions of Chinese medicinal fungus Cordyceps sinensis and related species, J. Food Drug Anal. 2000, 8, 248–257.
48. Watanabe, T., Kawashita, A., Ishi, S., Mazumder, T.K., Nagai, S., Tsuji, K., Dan, T., Antihypertensive Effect of γ-Aminobutyric Acid-Enriched Agaricus blazei on Mild Hypertensive Human Subjects, Nippon Shokuhin Kagaku Kogaku Kaishi, 2003, 50, 167-173.
49. WHO, Cardiovascular diseases (CVDs), URL (https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) (date of access: December 2021).
50. WHO, ICD-11, URL (https://www.who.int/classifications/icd/en/) (access date: december 2022).
51. WHO, WHO Global Centre for Traditional Medicine, URL (https://www.who.int/initiatives/who-global-centre-for-traditional-medicine) (date of access: January 2024).
52. Wu, F., Zhou, L.W., Yang, Z.L., Bau, T., Li, T.H., Dai, Y.C., Resource diversity of Chinese macrofungi: edible, medicinal and poisonous species, Springer Netherlands, 2019, 98, 1-76.
53. Wu, Z.L., Ren, H., Lai, W.Y., Lin, S., Jiang, R.Y., Ye, T.C., Shen, Q.B., Zeng, Q.C., Xu, D.L., Sclederma of Poria cocos exerts its diuretic effect via suppression of renal aquaporin-2 expression in rats with chronic heart failure, J. Ethnopharmacol. 2014, 155, 563–571.
54. Xiang, F., Lin, L., Hu, M., Qi, X., Therapeutic efficacy of a polysaccharide isolated from Cordyceps sinensis on hypertensive rats, Int. J. Biol. Macromol. 2016, 82, 308–314.
55. Xu, J., Yang, Y., Traditional Chinese medicine in the Chinese health care system, Health Policy (New. York). 2009, 90, 133-139.
56. Xu, Q., Wang, H., Li, T., Chen, L., Zheng, B., Liu, R.H., Comparison of phenolics, antioxidant, and antiproliferative activities of two Hypsizygus marmoreus varieties, J. Food Sci. 2020, 85, 2227–2235.
57. Yang, H., Liu, Y.R., Song, Z.X., Tang, Z.S., Jia, A.L., Wang, M.G., Duan, J.A., Study on the underlying mechanism of Poria in intervention of arrhythmia zebrafish by integrating metabolomics and network pharmacology, Phytomedicine 2024, 122, 155143.
58. Yang, X., Lin, P., Wang, J., Liu, N., Yin, F., Shen, N., Guo, S., Purification, characterization and anti-atherosclerotic effects of the polysaccharides from the fruiting body of Cordyceps militaris, Int. J. Biol. Macromol. 2021, 181, 890-904.
59. Yeh, M.Y., Ko, W.C., Lin, L.Y., Hypolipidemic and Antioxidant Activity of Enoki Mushrooms (Flammulina velutipes), Biomed Res. Int. 2014, 2014.
60. Yuan, Y., Wang, Y., Sun, G., Wang, Y., Cao, L., Shen, Y., Yuan, B., Han, D., Huang, L., Archaeological evidence suggests earlier use of Ganoderma in Neolithic China, Kexue Tongbao/Chinese Sci. Bull. 2018, 63, 1180-1188.
61. Zhao, S., Rong, C., Liu, Y., Xu, F., Wang, S., Duan, C., Chen, J., Wu, X., Extraction of a soluble polysaccharide from Auricularia polytricha and evaluation of its anti-hypercholesterolemic effect in rats, Carbohydr. Polym. 2015, 122, 39-45.
62. Zhao, Y., Inhibitory effects of alcoholic extract of Cordyceps sinensis on abdominal aortic thrombus formation in rabbits, Zhonghua Yi Xue Za Zhi, 1991, 71, 612-615.