Therapeutic potential of mushrooms in preventing and ameliorating hypertension

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Hypertension is a multi-aetiological, chronic pathophysiology that leads to multi-organ dysfunctions like cardiovascular diseases, strokes, and renal complications. Synthetic anti-hypertensive drugs have been blamed for side effects of various sorts. Thus, the search for natural, safe, and food-based anti-hypertensive agents has gained momentum. Mushrooms, abundant in bio-active components, had been recognized for its use as therapeutics in alternative and complementary medicine as well as functional food. In the present article, the potential of both culinary and edible-turned-medicinal mushrooms is reviewed with respect to their anti-hypertensive effects along with the respective bio-component’s mode of action.

Introduction

Hypertension is a multifactorial and chronic pathophysiological condition characterised by elevated arterial blood pressure (Fig. 1). Normal blood pressure is maintained at an average systolic blood pressure (SBP) of 120 mmHg and an average diastolic blood pressure (DBP) of 80 mmHg. National Health and Nutrition Examination Surveys (NHANES) defined hypertension as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg (Egan & Zhao, 2013). Hypertension is known as the ‘silent killer’ as it raises the risk of cardiovascular diseases (CVDs) and strokes while remaining asymptomatic. Hypertension has become an epidemic and the World Health Organization (WHO) marked it as the third ranked cause of disability-adjusted life-years (Ezzati, Lopez, Rodgers, Hoorn, & Murray, 2002). More than 1 billion people worldwide suffer from hypertension and this number may rise up to 1.56 billion by the year 2025 (Kearny et al., 2005). Hypertension has been purported to cause 13.5% of global premature deaths (Lawes, Hoom, & Rodgers, 2008).

Hypertension is of two types: primary or essential (90–95%) and secondary (5–10%). Although the specific cause of primary hypertension is yet to be elucidated, pathophysiological contributors include: stress-induced hyperactivities of the sympathetic nervous system; overproduction of vasoconstrictors and mineralocorticoids that retain excessive sodium ions; decreased production of vasodilators such as prostacyclin, nitric oxide (NO), and natriuretic peptides; oxidative stress-induced endothelial dysfunction and vascular remodelling; obesity; and diabetes mellitus (Oparil, Zaman & Callhoun, 2003). Secondary hypertension is caused by factors other than those for primary hypertension such as apnoea, drug-induced, neurological, and/or endocrinological abnormality (such as aldosteronism). Secondary hypertension develops more rapidly compared with primary hypertension. It emanates from identifiable, often modifiable causes and if not treated, evokes multi-organ dysfunction such as peripheral arterial diseases, renal failure, retinal haemorrhage, and visual problems (Onusko, 2003).

Factors contributing to prevalence of hypertension worldwide

Hypertension has become a global challenge because of its higher frequency as well as being a progenitor of CVD, stroke, and kidney diseases. The most pronounced factors...
underlying this global threat include changed lifestyles, rapid urbanisation, racial differences, malnutrition, and imbalanced dietary intake, as well as in utero malformation (Mittal & Singh, 2010). Hypertension alone does not pose the threat; rather, along with hypercholesterolaemia and atherosclerosis, it makes a person vulnerable to vascular dysfunctions (Kearney et al., 2005). All these health problems are correlated to each other and frequently diagnosed in most of the patients (Ariyo et al., 2000; Egan & Zhao, 2013). A report produced in 2008 based on a 3-year study indicated that approximately one-third of adults in the United States have hypertension (Amy, 2012). Between 2003 and 2010, the overall prevalence of hypertension among adults aged 18 and above reached 66.9 million or equal to 30.4%. Almost half of them were uncontrolled because they were either unaware or aware but untreated, while others were aware and treated, but still uncontrolled.

In Nepal, the prevalence of hypertension has increased by 30 times in the urban population and 10 times in the rural population (Chataut, Adhikari, & Sinha, 2012). Among 527 volunteers aged 18 and above, 22.4% were detected to have hypertension. Factors identified to be associated with hypertension included sex, age, physical activity, weight, and habits. Among them, the most prevalent factors were weight and habits. Almost 40.5% of the overweight Nepalese involved in the study had hypertension. Besides, people having smoking and drinking habits, were found to be more prone to hypertension compared to those not having such habits.

In Iran, a survey called the Golestan Cohort Study, a population-based study of 8998 men and women aged 35–81 years from both urban and rural areas, was conducted (Malekzadeh et al., 2013). Hypertension-associated risk factors including body weight, gender, and diabetes were studied. The results showed that female gender and diabetes mellitus were the top risk factors. However, body weight did not show a significant association with hypertension.

A community-based cross-sectional study was conducted in Gondar City, Northwest Ethiopia (Awoke, Awoke, Alemu, & Megabiaw, 2012). A total of 679 participants were included in this study. One hundred and ninety-two participants (28.3%) were hypertensive, of whom more than a third (37.0%) did not know they had hypertension. Identified risk factors included age, diabetes status, physical activity, and family history of hypertension.

A study conducted in Kedah, Malaysia, which focused on socioeconomic factors in elderly people (≥60 years), showed a high number of hypertension cases (Rashid & Azizah, 2011). The study concluded that the prevalence of increased pulse pressure contributed to systolic hypertension in elderly people. A previous study conducted in Kuala Lumpur, Malaysia, also reported that both systolic and diastolic hypertension increased with age among the respondents, which were aged 30 and above (Amplavar, Gurpreet, Salmiah, & Odhayakumar, 2010).

Another study conducted in the United States found that employment status was associated with hypertension (Eaker, Sullivan, Kelly-Hayes, D’Agostino, & Benjamin, 2007). People with a good job had better health access, dietary habits, and awareness. Moreover, marriage was also cited to be a protective factor for hypertension, since it affected biological, neuroendocrine, and immune systems.

Studies involving affluent male subjects in north India reported elevated body mass index (BMI), waist-hip ratio, and impaired glucose tolerance (IGT) or diabetes to be the crucial factors of hypertension (Yadav et al., 2008). Other CVD factors such as serum triglycerides and smoking also showed an increment as the population moved from a normotensive to a hypertensive state. In addition, heredity, obesity, high intake of sodium/potassium salts, reduced consumption of fruit and vegetables, and a sedentary lifestyle have been identified as the most prominent causative factors of hypertension in a Chinese population (Zeng et al., 2011).
Strategies for controlling hypertension

Evolution of concepts involving hypertension dates back to mid-19th century when the measurement of blood pressure had been correlated with various diseases (Bakris & Frohlich, 1989; Kotchen, 2011). Thenceforth, numerous strands of strategies for its remedy have been elucidated and updated. Life style changes including appropriate dietary intake stand as the first line of defence against hypertension. However, drug treatment becomes inevitable in addition to or in parallel with life style modifications in severe cases (Appel, 2003). Initiated from the extraction and validation of alkaloids from the plant *Rauwolfia serpentina*, the last half a century has witnessed the research and development of chemically synthesized anti-hypertensive agents (Bakris & Frohlich, 1989; Kotchen, 2011). The evolutionary trends in developing antihypertensive agents have been depicted in Fig. 2.

The seventh report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (Chobanian et al., 2003) recommended the use of diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and/or calcium channel blockers (CCBs) for the treatment of hypertension in patients who are at increased risk for coronary complications or stroke (White, 2005).

Diuretics are used to remove excessive water and salt from the body through urine with a view to reducing blood pressure (Fuchs, 2001). Beta-blockers bind to the beta receptors in heart muscle and reduce the tissue stress stimulated by the hormone adrenaline (Bangalore, Sawhney & Messerli, 2008). ACE inhibitors act by inhibiting the ACE that reduces the activity of the renin-angiotensin-aldosterone system (RAAS). This system is activated when there is a fall in blood pressure (Van der Horst, Voors, & Van Veldhuisen, 2007). The ARBs also interrupt the RAAS and cause vasodilation. However, ARB is prescribed for patients who are intolerant to ACE inhibitors (Nishida, Takahashi, Nakayama, & Asai, 2012). CCBs work by blocking voltage-gated calcium channels (VGCCs) in cardiac muscle and blood vessels. Since calcium is crucial for muscle contraction, the blocking by CCBs relaxes and dilates the artery muscle. In addition, some patients may need combination therapy of these drugs for better healing. The target organ and mode of action of these anti-hypertensive drugs currently prescribed worldwide, has been depicted in Fig. 3.

However, anti-hypertensive drugs have been reported as having various adverse effects. Diuretics cause frequent urination, arrhythmia, muscle cramps, nausea, and vomiting. Beta-blockers can worsen asthma and diabetes and cause stomach cramps, blurred vision, confusion, dizziness, depression, and nightmares (Ko et al., 2004). ACE inhibitors such as captopril and enalapril cause dry cough, skin rashes, hyperkalaemia, renal failure, foetal anomalies, angioedema and allergic reactions (Brown & Douglas, 1998). The side effects of ARBs and CCBs also coincide with each other (Alomar, 2014). In addition, adverse drug reactions (ADRs) are always encountered with multiple diseases and the use of many drugs. If hypertension is accompanied by other diseases, these diseases may have an impact on the response of the body to anti-hypertensive drugs and the metabolic processes of the body may be affected negatively. Later on, increased dosages may be required, which in turn would only worsen the ADRs.

Mushrooms as medicinal-functional food against hypertension

The conflict between the merits and demerits of synthetic anti-hypertensive drugs demands the search for safe, efficacious, and novel therapeutic agents of a natural source. The term ‘functional food’ has been coined in this context and is defined as “a natural or processed food that contains known biologically-active compounds which when in defined quantitative and qualitative amounts provides a clinically proven and documented health benefit, and thus, an important source in the prevention, management and treatment of chronic diseases of the modern age” (Martirosyan, 2011). Mushrooms (macrofungi), mostly members of the Basidiomycetes class of macrofungi, fulfill the requirement of functional foods. The terminology can be extended to ‘medicinal-functional foods’ and/or expressed as ‘functional-medicinal foods’, due to the fact that some culinary/edible mushrooms possess immense medicinal values while several medicinally...
important species are of high culinary demand (Abdulla, Noor, Wong, & Ali, 2008; Abdullah, Ismail, Aminudin, Shuib, & Lau, 2012; Paterson, 2006).

A plethora of bioactive compounds present in mushrooms confer antioxidant, antitumor/anticancer, antimicrobial, immunomodulatory, antiatherogenic, and hypoglycemic properties (Wasser, 2002, 2011). The hypocholesterolaemic effect of mushrooms has been attributed to their inhibitory effect on cholesterol biosynthesis and absorption and stimulatory effect on faecal excretion (Guillamón et al., 2010). The dietary fibres present in mushrooms further reinforce their suitability as hypolipidaemic agents (Fukushima et al., 2000; Hsing-Hsien, Wen-Chi, & Mei-Ling, 2002). They have also been highly regarded for possessing natural free radical scavengers of various sorts including polysaccharides (e.g., β-D-glucan), polyphenols (e.g., phenolic acids and flavonoids), vitamins (e.g., tocopherol, ascorbic acid, and niacin), ergosterol, and carotenoids (Guillamón et al., 2010). From as early as 100 B.C., culinary-medicinal usage of mushrooms has ranged from simple and common diseases to present-day complex and pandemics like AIDS (Paterson, 2006).

Mushrooms, as alternative and complementary medicinal foods, stand out as being excellent for treating hypertension. Hong et al. (2008) demonstrated that ACE inhibitory peptides present in mushrooms lowered blood pressure with no adverse effect. This finding was supported by further research upon both culinary and medicinal mushrooms of different categories (Abdullah et al., 2012). Jao, Huang, and Hsu (2012) elucidated the mode of action of these hypertension-ameliorating bioactive peptides along with their bioavailability. Numerous studies and findings on the anti-hypertensive properties of both edible and medicinal mushrooms have attracted scientists all over the world to further their studies on these ‘gifts from God’. Among the highly studied species are *Tricholoma giganteum* (giant mushroom), *Marasmius androsaceus* (horsehair parachute mushroom), *Grifola frondosa* (maitake mushroom), *Pleurotus* species (oyster mushroom), *Lentinula edodes* (shiitake mushroom), *Sparassis crispa* (cauliflower mushroom), *Pholiota adiposa* (black tiger’s paw mushroom) and *Hypsizygus marmoreus* (shimeji/buna shimeji mushroom), *Flammulina velutipes* (enoki mushroom), *Hericium erinaceus* (lion’s mane mushroom), and *Agaricus bisporus* (button mushroom).

*T. giganteum* (giant mushroom)

*T. giganteum* is found mainly in Japan, Korea, and tropical areas of Asia and Africa. Hyoung Lee, Ho Kim, Sik Park, Jun Choi, and Soo Lee (2004) reported the ACE inhibitory effect of 61.03% at 1 mg concentration of the hot water extract of *T. giganteum* with IC50 value of 0.74 mg. They then extracted a novel ACE inhibitor (ACEI) peptide from *T. giganteum*, purified it, and tested its efficacy on spontaneously hypertensive rats (SHRs). The peptide competitively inhibited ACE and showed a potent anti-hypertensive effect in the SHRs at the dosage of 1 mg/kg body weight. The blood pressure reduction potential was similar to that of captopril, one of the most common anti-hypertensive drugs (Fig. 4).

The ACEI peptide derived from *T. giganteum* is a unique tripeptide consisting of the amino acids proline (40%), glutamic acid (30%), and glycine (30%), and the sequence was deduced as Gly-Glu-Pro (Hyoung Lee et al., 2004). It shows very low sequence homology with other ACEIs and its molecular weight is small enough (301 Da) for absorption through the intestine. It demonstrated an anti-hypertensive effect without any adverse side effects. The
ACE inhibitory pattern was similar to that of other anti-hypertensive agents derived from mushrooms such as *G. fondosa* and non-mushroom origins such as fibrinogen pentapeptides, milk protein casein fragment, tuna muscle octapeptide, and porcine plasma tripeptides (Ariyosh, 1993). The purified ACEI peptide from *T. giganteum* maintained its inhibitory activity even after incubation with proteases (Hyoung Lee *et al.*, 2004).

*M. androsaceus* (horsehair parachute mushroom)

*M. androsaceus* is a traditional Chinese edible-medicinal mushroom. Zhang *et al.* (2009) extracted the bio-active component 3,3,5,5-tetramethyl-4-piperidone (TMP) from *M. androsaceus* and demonstrated its consistent anti-hypertensive effect. The SBP of spontaneously hypertensive rats (SHR) was significantly lowered in 30 min after TMP administration and lasted for 4 h at the dosages of 2.5, 5 and 10 mg/kg (p.o) body weight (Zhang *et al.*, 2009).

The chemical structure of TMP closely resembles that of mecamylamine, the first available oral anti-hypertensive agent (Table 1). At low dosage (2.5–10 mg, p.o.), mecamylamine can cross the blood brain barrier and TMP’s mode of action was supposed to mimic that of the mecamylamine (Zhang *et al.*, 2009).

In addition, the anti-hypertensive effect of *M. androsaceus* is supposed to be achieved through the partial ganglionic blocking action of TMP, since nictitating membrane contraction was prominently attenuated in 5 min and was totally blocked after TMP administration to the experimental animals (Zhang *et al.*, 2009). Typically, ganglion blockers dilate blood vessels, resulting in reduced blood pressure.

To further substantiate the claim, this group put forward evidence that TMP at the same dosage reduced blood pressure of 2K1C rats in a 2-week study. TMP at 30 mg/kg (intravenously [i.v.]) counteracted preganglionic stimulation-induced nictating membrane responses (Zhang *et al.*, 2009). Haemodynamic studies in dogs confirmed the results and further proved that TMP-mediated blood pressure reduction was independent of any adverse effect. Even the sympathetic-vagal balance was uninterrupted after TMP administration, as revealed by heart rate variability studies.

**G. frondosa** (maitake mushroom)

The anti-hypertensive effect of *G. frondosa* was first demonstrated by Kabir & Kimura, 1989. They fed a diet containing 5% *G. frondosa* powder (w/w) to SHRs and compared their blood pressure pattern with that of normotensive rats. Nine weeks of observation revealed significantly lowered blood pressure. Later on, Talpur *et al.* (2002) reported similar findings while comparing the effect of whole maitake mushroom to that of its two solvent–solvent partitioned fractions (ether and water). They conducted experiments on two rat strains: Zucker fatty rats (ZFRs) and SHRs. After 35 days, they observed that SBP was significantly decreased (mean SBP 176 vs. 197 mmHg, *p* < 0.001) in the SHRs that ingested the ether fraction compared with control SHRs. However, in ZFRs, both the whole maitake powder and water fraction could reduce SBP (120 vs. 138 mm Hg, respectively, *p* < 0.001) (Talpur *et al.* 2002). In the meantime, a peptide with ACE inhibitory activity was isolated from the hot water extract of *G. frondosa* and its amino acid sequence was deciphered to be Val-Ile-Glu-Lys-Tyr-Pro (Choi, Cho, Yang, Ra, & Suh, 2001). The ACEI peptide is supposed to interrupt the RAAS by competitive interaction at the active site of the ACE (Choi *et al.*, 2001; Talpur *et al.* 2002).

Recently, Preuss, Eichard, Bagchi, and Perricone (2010) evaluated the protective role of *G. frondosa* active fractions, SX and D, in age-onset hypertensive Sprague–Dawley rats. Data obtained after 4 months of intensive experiments enabled them to opine that *G. frondosa* fractions reduced age-mediated hypertension via the RAAS, along with enhanced insulin sensitivity and reduced inflammatory aspects that ultimately led to a normal blood pressure and longer life span.

**Pleurotus species** (oyster mushrooms)

Oyster mushrooms (*Pleurotus* species) are important both in tropical and temperate countries in respect of their culinary status. The mostly noted species having anti-hypertensive effects include *Pholiota ostreatus*, *Pleurotus cornucopiae*, *Pholiota nebrodensis*, and *Pholiota*...
Table 1. Anti-hypertensive mushroom bio-components and their mode of actions.

<table>
<thead>
<tr>
<th>Anti-hypertensive agent</th>
<th>Structure</th>
<th>Mode of action</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripeptide</td>
<td>Gly-Glu-Pro</td>
<td>Competitive inhibition of ACE</td>
<td><em>Tricholoma giganteum</em></td>
<td>Hyoung Lee et al., 2004</td>
</tr>
<tr>
<td>3,3,5,5-tetramethyl-4-piperidone (TMP)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Partial ganglionic blocking-</td>
<td><em>Marasmius androsaceus</em></td>
<td>Zhang et al., 2009</td>
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<tr>
<td></td>
<td></td>
<td>mediated vasodilation</td>
<td></td>
<td></td>
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<tr>
<td>Hexapeptide</td>
<td>Val-Ile-Glu-Lys-Tyr-Pro</td>
<td>Inhibition of ACE</td>
<td><em>Grifola frondosa</em></td>
<td>Choi et al., 2001</td>
</tr>
<tr>
<td>D-mannitol</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Competitive inhibition of ACE</td>
<td><em>Pleurotus cornucopiae</em></td>
<td>Hagiwara et al., 2005</td>
</tr>
<tr>
<td>Oligo peptides</td>
<td>Arg-Leu-Pro-Ser-Glu-Phe-Asp-Leu-Ser-Ala-Phe-Leu-Arg-Ala</td>
<td>Competitive inhibition of ACE</td>
<td><em>Pleurotus cornucopiae</em></td>
<td>Jang et al., 2011</td>
</tr>
<tr>
<td>Oligo peptides</td>
<td>Arg-Leu-Ser-Gly-Gln-Thr-Ile-Glu-Val-Thr-Ser-Glu-Tyr-Leu-Phe-Arg-His</td>
<td>Competitive inhibition of ACE</td>
<td><em>Pleurotus cornucopiae</em></td>
<td>Jang et al., 2011</td>
</tr>
<tr>
<td>Potassium</td>
<td>K⁺</td>
<td>Hyperpolarization of Na⁺-K⁺ pump</td>
<td><em>Lentinula edodes</em></td>
<td>Haddy, 2006; Julita, 2007</td>
</tr>
<tr>
<td>Lentinan</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Vasodilation</td>
<td><em>Lentinula edodes</em></td>
<td>Bisen et al., 2010</td>
</tr>
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<tr>
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<th>Structure</th>
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<th>Source</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Chitin</td>
<td><img src="image" alt="Chitin Structure" /></td>
<td>Yet to be discovered</td>
<td>Lentinula edodes</td>
<td>Je et al., 2006; Vetter, 2007</td>
</tr>
<tr>
<td>Ganoderics</td>
<td><img src="image" alt="Ganoderics Structures" /></td>
<td>Inhibition of ACE</td>
<td>Ganoderma lucidum</td>
<td>Morigiwa et al., 1986</td>
</tr>
</tbody>
</table>
**cystidiosus** (Hagiwara et al., 2005; Jang et al., 2011). Their ameliorating effect on elevated blood pressure has been attributed to their inhibitory effect on ACE. Hagiwara et al. (2005) reported D-mannitol, a sugar alcohol, as the ACE inhibitory bioactive component of the tamogi-take mushroom, *Pholiota cornucopia*. They compared the ACE inhibitory effect of hot water extract of tamogi-take mushroom (WETM), D-mannitol derived from the hot water extract of tamogi-take mushroom, and pure D-mannitol (authentic D-mannitol) in SHR/Hos male rats. Authentic D-mannitol decreased SBP from 178 to 157 mmHg after 4 h of administration. WETM also significantly decreased SBP from 180 to 165 mm Hg after 4 h. At the concentration of 3 mg/ml, the ACE inhibitory effects of both authentic D-mannitol and D-mannitol derived from tamogi-take mushroom were almost the same. The authors further compared the ACE inhibitory activities of monosaccharides (D-glucose, D-galactose, and D-mannose), monosaccharide-based sugar alcohols (D-mannitol, D-sorbitol, and D dulcitol), and disaccharides (D-maltose and D-lactose). The results showed that the sugar alcohol D-mannitol was the best ACE inhibitor, followed by the monosaccharides containing D-glucose, D-galactose, and D-mannose, whereas the disaccharides had the lowest ACE inhibitory potency.

Jang et al. (2011) isolated and purified two ACEI peptides from the fruiting bodies of *P. cornucopiae* and reported their anti-hypertensive effects in SHR at a dosage of 600 mg/kg body weight. The molecular mass of these two oligo peptides were 1.62 and 2.03 kDa, respectively, with the respective amino acid sequence of Arg-Leu-Pro-Serine-Glu-Phe-Asp-Leu-Ser-Ala-Phe-Leu-Arg-Ala and Arg-Leu-Ser-Gly-Gln-Thr-Ile-Glu-Val-Thr-Ser-Glu-Tyr-Leu-Phe-Arg-His. Their mode of inhibition was non-competitive, unlike the ACEIs of *T. giganteum* and *G. frondosa*. Besides, simultaneous treatment of gastric and intestinal fluids with the ACEI peptide increased its ACE inhibitory potential, indicating its easy absorption under physiological conditions.

Research findings of comparative ACE inhibitory studies of culinary-medicinal mushrooms have received appreciable attention. Based on the IC50 values (mg/ml) of in vitro ACE inhibitory activities, Abdullah et al. (2012) reported the following order of potency as ACE inhibitors for *Pleurotus* species: *Pholiota eryngii* (IC50 0.067 mg/ml) > *Pholiota flabellatus* (IC50 0.058 mg/ml) > *Pholiota sajor-caju* (IC50 0.056 mg/ml) > *P. cystidiosus* (IC50 0.054 mg/ml) > *Pholiota florida* (IC50 0.050 mg/ml). The probability of the presence of a similar type of bioactive components with a similar structure and mode of action was suggested as the basis of the very close proximate IC50 values, which are indicative of the respective ACE inhibitory effects (Abdullah et al., 2012). However, experimental conditions such as the separation technique, solvents used and time and temperature applied might have had a considerable effect on the ACE inhibition pattern of the mushrooms.
**L. edodes (shiitake mushroom)**

*L. edodes* is the second most popular edible-medicinal mushroom worldwide (Bisen, Baghel, Sanodiya, Thakur, & Prasad, 2010). Blood pressure reduction studies involving *L. edodes* date back to as early as 1989 when Kabir and Kimura, through comparative studies of anti-hypertensive and plasma lipid-lowering effects of shiitake and maitake mushrooms upon SHR, reported the ameliorating effects of both the mushrooms (Fig. 5). However, the anti-hypertensive agent and mechanism of blood pressure reduction were not investigated in that study.

The pathogenesis of hypertension includes an intricate relationship among physiological levels of sodium and potassium ions and aldosterone (Büssemaker, Hillebrand, Hausberg, Pavenstädt, & Oberleithner, 2010). Increased plasma sodium levels worsen, while higher potassium levels ameliorate the hypertensive state. Excessive sodium ions impair the endothelial vasculature by reducing production of the vasodilator NO. Thus, to overcome hypertension, it is important to maintain plasma sodium ions and aldosterone at lower levels and potassium ions at higher levels (Büssemaker, et al., 2010).

The potassium content of *L. edodes* had been found to be as high as 31.55 mg/kg dry weight (Manzi, Gambelli, Marconi, Vivanti, & Pizzoferrato, 1999). Increased potassium ions hyperpolarise vascular smooth muscle cells through the voltage-gated Na\(^+\)-K\(^+\) pump and/or Kir channel that causes vasodilation (Haddy, Vanhoutte, & Feletou, 2006). Thus, *L. edodes* aids in maintaining low blood pressure. Besides, lentinan, a polysaccharide obtained from *L. edodes*, has been reported as having multifactorial effects including vasodilation (Bisen et al., 2010; Chihara, 1992). In addition, Lau, Abdullah, Shuib, and Aminudin (2012) reported *L. edodes* to be the second best ACE inhibitory agent among nine edible mushroom species. The hot water extract of *L. edodes* showed 90.1% ACE inhibition in vitro, second only to *F. velutipes* (95.6% ACE inhibition) at 10 mg/ml concentration.

Moreover, the chitin content of *L. edodes* has been found to be as much as 8.07% of the dried mass (Vetter, 2007). Manzi, Marconi, Aguzzi, and Pizzoferrato (2004) found that the levels of chitin and its derivatives increased during cooking. Chitin derivatives act as potent anti-hypertensive agents (Je, Park, Kim, & Kim, 2006). Chitin derivatives with 50% deacetylation at C-6 showed a dose-dependent SBP-lowering effect through inhibiting ACE (Je et al., 2006). At the cellular level, the anti-hypertensive effects of *L. edodes* might be mediated by one or more of the mechanisms stated so far.

**G. lucidum (reishi or lingzhi mushroom)**

*G. lucidum* has been ascribed as the ‘magic mushroom’ for healing numerous physiological and psychological complications (Paterson, 2006; Wasser, 2002, 2011). Among the myriad of bioactive components present in *G. lucidum*, the triterpenoids and the polysaccharides have been reported to be medicinally most potent (Boh, Berovic, Zhang, & Zhi-Bin, 2007). Morigiwa, Kitabatake, Fujimoto & Ikekawa (1986) observed the ACE inhibitory effect of the methanolic extract of *G. lucidum* and identified five novel triterpenes in the extract: ganoderal A; ganoderols A and B; and ganoderic acids K and S (Table 1).

Time-course required for lowering blood pressure may vary from mushroom species to species. Kabir, Kimura & Tamura (1988), through a 4-week study upon the SHR, described the SBP lowering effect of *G. lucidum* (Fig. 6). Feeding of *G. lucidum* for the first two weeks had no

![Fig. 5](image-url)  
**Fig. 5.** Systolic blood pressure changes in SHRs fed mushroom in the diet. Each point represents the mean ± SE for five rats (SD from control *p < 0.05, **p < 0.01*) (Kabir & Kimura, 1989).

![Fig. 6](image-url)  
**Fig. 6.** Changes in systolic blood pressure (SBP) of spontaneously hypertensive rats fed *Ganoderma lucidum* in the diet in a 4-week study period. During the first 2 weeks, SBP remained almost the same as that of control. However, after 2 weeks of *G. lucidum* intake, SBP was significantly lower in the SHRs compared with control. This represents the time course of action and accumulation of *G. lucidum* bioactive components. Each point represents the mean ± SE for seven rats, **p** means significantly different from control (Kabir, Kimura and Tamura, 1988).
ameliorating effect; however, continued feeding for more two weeks significantly lowered SBP of the treated animals. This plummeting pattern sustained for the rest of the study period. This might also be due to the lower amount of bio-active components accumulation during the first two weeks that afterwards increased in amount capable enough to combat the raised blood pressure (Kabir, Kimura and Tamura, 1988).

Abdullah et al. (2012) reported the best ACE inhibitory effect of the hot water extracts of *G. lucidum* compared to other culinary-medicinal mushrooms. Multitudes of phenolic substances present in *G. lucidum* were supposed to contribute to this inhibitory action. The anti-ACE activity of the hot water extract of *G. lucidum* became more enhanced (57.01% inhibition at 2 mg/ml concentration), when grown on the germinated brown rice (Hasnat, Pervin, & Lim, 2013).

However, Lee and Rhee (1990) proposed an alternative mechanism of *G. lucidum* hot water extract mediated-hypotension. According to them, *G. lucidum* extract inhibited the sympathetic nerve actions in the CNS whose secondary effect was hypotension without any altered heart rate.

**S. crispa (cauliflower mushroom)**

Hypertension is one of the prominent causative factors of stroke. Thus, mushrooms capable of maintaining normo-tensive state along with preventing stroke, are of high medicinal-functional values. *S. crispa* has been found to serve the dual benefit. Stroke-prone spontaneously hypertensive rats (SHRsSP) orally administered with diet containing 1.5% *S. crispa* powder, showed significant inhibition of the rise in blood pressure along with stroke-amelioration (Yoshitomi, Iwaoka, Kubo, Shibata, & Gao, 2011). The underlying mechanism of reduced blood pressure involved the improvement of endothelial dysfunction via increment in NO production through activation of the Akt/NOS signalling pathway in the cerebral cortex (Yoshitomi et al., 2011).

**P. adiposa (yellow cap mushroom)**

Koo et al. (2006) described the ACE inhibitory effect of the hot water extract of *P. adiposa*, followed by the extraction and characterization of the inhibitor. The purified ACE inhibitory peptide was a novel penta-peptide with molecular weight of 414 Da (Koo et al., 2006). Its sequence was revealed as Gly-Glu-Gly-Gly-Pro and had very little similarity to other ACE inhibitory peptides (Koo et al., 2006).

**S. aspratus (black Tiger’s paw mushroom)**

The aqueous extract of the edible mushroom *S. aspratus* had been found to possess ACE inhibitory effect. *l*-pipericolic acid (1-piperidine-2-carboxylic acid) was identified to be the main bioactive component of this function (Kiyoto et al., 2008). It inhibited in a stereoselective fashion through competitive mode of inhibition whereas the *d*-isomer was inactive (Kiyoto et al., 2008).

**H. marmoreus (shimeji/buna shimeji/brown beech mushroom)**

Kang et al. (2013) reported the anti-ACE effect of the hot water extract of *H. marmoreus*, followed by the identification of the responsible oligopeptide. Its sequence deduced was Leu-Val-Asn-Asp-Leu-Val-Thr-Pro-Val-Phe-Asp with the molecular weight of 567.3 Da. Administered to the SHR at 800 mg/kg body weight; this ACE inhibitor’s potency was similar to that of the synthetic antihypertensive drug, captopril (Kang et al., 2013).

**A. bisporus, F. velutipes and H. erinaceus**

Comparative ACE inhibitory pattern of mushrooms determines their respective antihypertensive potential. In such a study, Lau et al. (2012) determined the relative antihypertensive strength of three most common edible mushrooms based on percentage ACE inhibition at 1 mg/ml concentration and their gradation was as follows: 

*F. velutipes* (95.65%) > *H. erinaceus* (90.1%) > *A. bisporus* (87.2%)

In a separate study, Lau, Abdullah, Shuib, and Aminudin (2014) identified three separate bio-active peptides from *A. bisporus* having the amino acid sequences Ala-His-Glu-Pro-Val-Lys, Arg-Ile-Gly-Leu-Phe and Pro-Ser-Ser-Asp-Lys. The ACE inhibitory mode of the first two peptides was competitive while that of the last one was non-competitive.

**Conclusion**

Adverse side effects of synthetic anti-hypertensive drugs warrant quick removal from the market giving space to the natural, safe and alternative therapeutic approaches. Nutritional analysis has revealed mushrooms to be rich in high-quality protein, polysaccharides, vitamins and minerals (potassium, calcium, and magnesium), fibre and other bioactive compounds but low in sodium and fat. Such a diet supports the recommendations of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003). Apart from consumption of culinary mushrooms as vegetables, the approach in using mushrooms to alleviate hypertension necessitates the use of composite formulae obtained by a specific method of extraction. Hot water extract of various mushrooms studied so far was deemed most potent identifying several peptides, d-mannitol, d-glucose, d-galactose, d-mannose, triterpenes and potassium as the active constituents. Thus, this composite formulae comprising of several different components together could act in concert to prevent and ameliorate hypertension based on various mechanisms, predominantly via inhibiting the RAAS by interaction at the active site of the ACE enzyme.

The effectiveness of various mushroom species extracts and active compounds has been confirmed by numerous laboratory experiments and animal trials. However, clinical trials are desirable not only for single compounds but also for extracts. The consistency of the “extracts” both in terms...
of the overall chemical composition and in the actual levels of active components between different batches and in each mushroom species used could be standardized on the basis of one or two of the active component(s). This will spur high for better development of dietary supplement or nutraceuticals from mushrooms as remedy of hypertension.

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