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REVIEW ARTICLE

Interpretation of mushroom as a common therapeutic agent for Alzheimer's disease and cardiovascular diseases

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Abstract

Alzheimer's disease (AD) and cardiovascular diseases (CVD) share common etiology and preventive strategies. As the population of old-aged people is increasing worldwide, AD complications tend to afflict global healthcare budget and economy heavily. CVD is the prime cause of global mortality and remains a grave threat to both the developed and the developing nations. Mushroom bio-components may be promising in controlling both diseases. Based mainly on *in vitro, ex vivo,* cell line and animal studies, this review interprets the polypharmaceutic role of mushrooms treating AD and CVD.

Keywords

Amyloid beta, anti-oxidants, bio-active components, neuro-degeneration, vitamins

History

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Introduction

The unprecedented global rate of increased life span has posed an alarming threat towards the age-onset complications such as Alzheimer's disease (AD), the most common form of dementia. Epidemiological studies indicate global dementia prevalence to be higher than 34 million and this figure would rise to 100 million by 2050 (Reitz et al., 2011). One in every eight males and one in every four females have been predicted to develop AD during their life time. The fastest growing number of the oldest old people (those aged 90 years and above) live mainly in developed countries like the USA, Canada, Australia, Japan and Europe (Reitz et al., 2011). In every year, about 4.6 million new cases of dementia are added, with the highest rate in China and South Asia. If the current growth rate proceeds in the same pattern, by 2040, 71% of 81.1 million dementia cases will be in the developing world (Bullain & Corrada, 2013). Worldwide, cardiovascular diseases (CVD) are the prime cause of mortality (http://www.who.int/cardiovascular_diseases/en/). CVD causes a global annual death toll of about 17 million and according to WHO projection, this figure may rise to 23 million by 2030 (http://www.who.int/cardiovascular_diseases/en/). Modern dietary pattern and life style have been incurred for provoking CVD.

Among the common linking factors between AD and CVD are hypertension, hypercholesterolemia, inflammation, oxidative stress and diabetes. Hypertension affects AD pathogenesis with increased cerebro-vascular oxidative stress, increased amyloid beta (Aβ) production and its decreased clearance (Girouard & Iadecola, 2006; Harrison & Gongora, 2009). Hypertension in mid-life has been linked with reduced cognitive function and 24% increased AD risk in late life. Increased brain cholesterol has been found during AD progression. In the cellular model, decreased cholesterol level has been reported to be inhibitory towards Aβ formation (Buxbaum et al., 2001; Wolozin, 2001). Experimentally induced hypercholesterolemic animals had exhibited significantly increased AD neuropathology (Shie et al., 2002). Autopsy studies of young patients (40–55 years old) showed a correlation between hypercholesterolemia with the presence of neuritic plaques (Pappolla et al., 2003). Hypercholesterolemia is among the major modifiable risk factors of CVD (Backer et al., 2003). Cholesterol lowering drugs, statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been reported to lower the risk of death or cardiovascular events in patients with or without CVD as well as being protective against the risk of developing AD (De Kosky, 2005). Statins have been found effective in reducing the risk of AD from 60% even up to 74% (Wolozin et al., 2000). Statins can directly withstand the production of Aβ and also facilitate their removal from the brain (Fassbender et al., 2001; Hyman et al., 2000). Blood inflammatory markers such as IL-6 and α1-antichymotrypsin have been found at higher levels in AD patients than their controlled counterparts (Federico et al., 2000). Astrocytes in the brain produce pro-inflammatory factors and matrix proteins. Neurons synthesize several mediators of inflammation

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such as amyloid P, complements and C-reactive proteins whose rate of synthesis increases in AD pathology and they co-localise with the senile plaques (Casserly & Topol, 2004; Yasojima et al., 2000).

Oxidative stress has been implicated in being involved in multiple diseases including AD and CVD. Long-term (more than 15 years) usage of antioxidant vitamins C and E has been recommended for optimal neuroprotective effects (Praticò, 2008; Zandi et al., 2004). Vitamin D deficiency has been associated as an independent risk factor of CVD complications (Kendrick et al., 2009). A seven-year long follow-up study has reported lowered risk of AD in women taking vitamin D2 (Annweiler et al., 2012). Saturated fatty acid and trans-unsaturated fatty acids are among the dietary risk factors of CVD (Mozaffarian et al., 2006). However, polyunsaturated fatty acids (PUFA) have been suggested to be involved in reduced CVD complications (Virtanen et al., 2014). Similarly, ω-3 fatty acids have been found protective against AD (Freund-Levi et al., 2006).

Diabetes has multiple physiological complications and AD has been dubbed as ''type 3 diabetes'' as its pathophysiology strongly correlates with diabetes, especially type 2 diabetes (Suzanne, 2014). In this aspect, AD has been described as a manifestation of metabolic disorder emanating from brain insulin resistance and associated signaling derangements (Suzanne, 2014). The 15 years long Hisayama study (2011) found significantly higher rates of AD in diabetic subjects than their normal counterparts (Ohara et al., 2011). The entire brain, especially the hippocampus, the site of memory and learning, contains ample insulin receptors (Zhao & Alkon, 2001). Insulin affects neurotransmission and causes micro- and macrovascular damage to the neurons that link AD with diabetes (Hirvonen et al., 2011). Besides, brain mitochondrial dysfunction generates oxidative stress to the neurons that act as the common etiology of both AD and CVD (Moreira et al., 2007). Adults with diabetes are 4–6 times more prone to suffer from CVD complications and about 65% of diabetics die from heart diseases (Schnell, 2005). Diabetes remains as an independent risk factor for atherosclerosis and CVD (Dokken, 2008).

Mushrooms possess immense nutritional and medicinal bio-components that substantiate their usage in maintaining global public health (Cheung, 2010; Wasser, 2011). However, there is a scarcity of information regarding the common usage of mushrooms for ameliorating AD and CVD pathogenesis. In this review, mushrooms' cardio-protective and AD ameliorating effects have been reviewed with special emphasis upon the common etiological and preventive approaches of both the diseases. To our knowledge, this is the first review in this aspect of the subject.

Interpretation of mushroom as the common therapeutic agent

Mushrooms against CVD

Antihypertensive mushroom bioactives

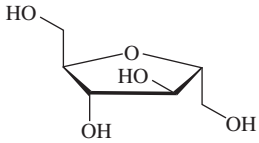
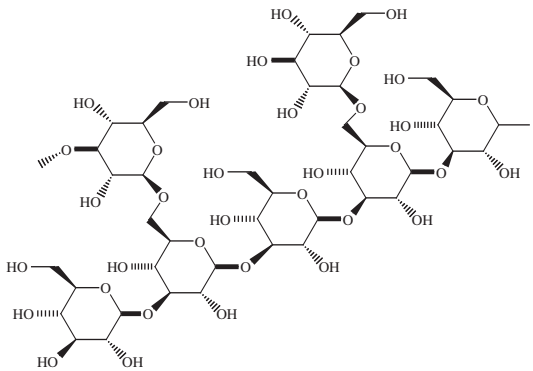
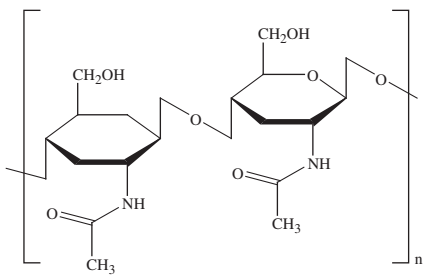
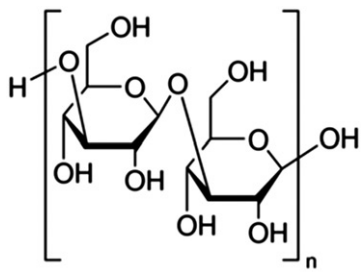
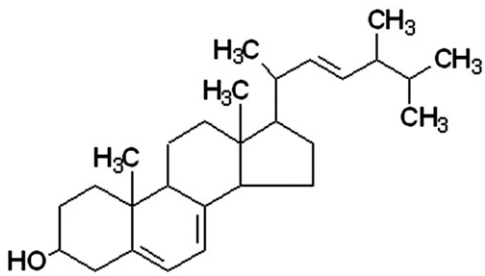
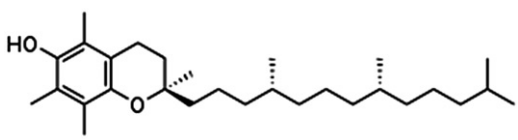
Anti-hypertensive treatments have been successful in reducing the risk of CVD from 55% to as low as 18% (Mancia, 2007). Both edible and medicinal mushrooms contain anti-hypertensive bio-components (Yahaya et al., 2014). Most of the mushroom bio-components exert their anti-hypertensive effects by inhibiting the angiotensin-converting enzyme (ACE) that modulates the activity of the renin-angiotensin-aldosterone system (RAAS) and lowers blood pressure (Yahaya et al., 2014). Among the *Ganoderma*, bioactives are the triterpenoids and polysaccharides including ganoderic acids, ganoderic aldehydes (ganoderals) and ganoderic alcohols (ganoderol). Recently, Ansor and colleagues indicated the effect of *Ganoderma lucidum* ACE inhibitory peptides in lowering hypertension (Ansor et al., 2013). An anti-hypertensive peptide from *Tricholoma giganteum* has been found to be more potent than the commercially available anti-hypertensive drug, captopril (Lee et al., 2004) (Table 1). ACE inhibitory anti-hypertensive peptides from other mushrooms have also been reported among which the most notable species are *Pleurotus* species, *Grifola frondosa*, *Pholiota adipose*, *Hericium erinaceus, Hypsizigus marmoreus*, *Agaricus bisporus*, *Flammulina velutipes* and *G. lucidum* (Yahaya et al., 2014). Other anti-hypertensive mushroom bioactives, worth mentioning, include lentinan, chitin and K^+ from *Lentinula edodes,* L-pipecolic acid from *Sarcodona spratus*, 3,3,5,5-tetramethyl 4-piperidone (TMP) from *Marasmius androsaceus* and D-mannitol from *Pleurotus cornucopiae* (Yahaya et al., 2014) (Table 1).

Hypocholesterolemic effect

Both edible and medicinal mushrooms lower blood total cholesterol (TC), very low density lipoproteins (VLDL) and low density lipoproteins (LDL) in rats (Hossain et al., 2003). Investigations involving the potentiality of mushrooms as the inhibitor of cholesterol biosynthetic key enzyme 3-hydroxy 3-methyl glutaryl co-enzyme A reductase (HMGCo-AR) has yielded a promising outcome. Among others, *Pleurotus* spp. has undergone extensive studies in this aspect and mevinolin (lovastatin), the HMGCo-AR inhibitor has been extracted from *Pleurotus ostreatus* agent (Gunde-Cimerman et al., 1993a, b; Gunde-Cimerman & Cimerman, 1995). The content of lovastatin varies between fruiting bodies and the mycelium. For fruiting bodies, the highest amount of lovastatin has been reported to be 606.5 mg/kg of *P. ostreatus* and 565.4 mg/kg dry weight of *Agaricus bisporus* (Park et al., 2002 2009). In case of mycelia, the highest lovastatin content has been found to be 995.7 mg/kg dry weight of *Cyathus striatus*, followed by 254.9 mg/kg, 220.5 mg/kg and 200.4 mg/kg for *Cordyceps cicadae, Clonorchis sinensis* and *Agaricus blazei*, respectively (Chen et al., 2012; Lo et al., 2012). The mushroom cultivating environment also influences the content of lovastatin. For fruiting bodies of wild *P. ostreatus,* a lovastatin content up to 2.80% dry weight and for those cultures cultivated on wheat straw, up to 2.07% dry weight and lovastatin concentration in liquid culture up to 30 mg/l had been found (Alarcon et al., 2003).

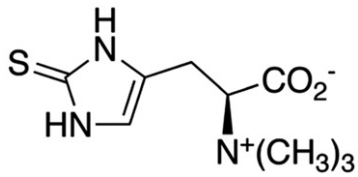
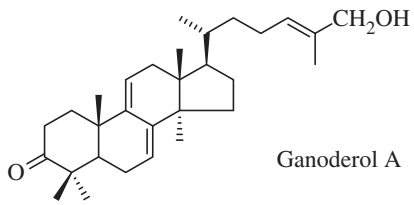
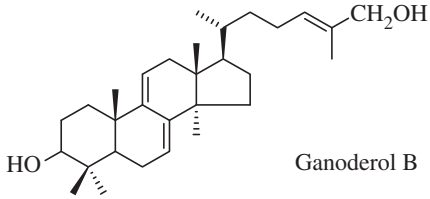
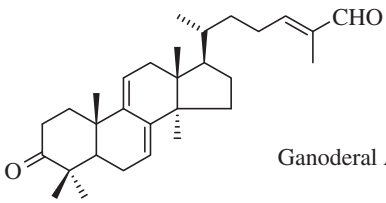
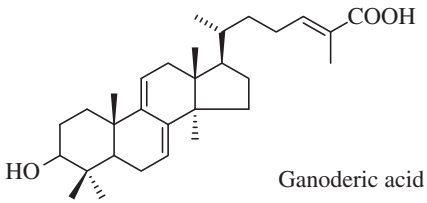
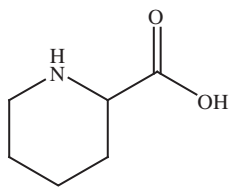
Gil-Ramirez et al. (2011, 2013a) screened 26 species of edible and medicinal mushrooms and reported that their aqueous and methanolic extracts have *in vitro* HMGCo-AR inhibitory effects. At 50 mg/ml concentration, the HMGCo-AR inhibitory effects were 54.4% for *P. ostreatus,* 60% for

Table 1. Mushroom bio-components conferring protection against Alzheimer's Disease (AD) and Cardiovascular Diseases (CVD).

Biocomponent	Structure	Source
Tripeptide	Gly-Glu-Pro	*Tricholoma giganteum*
Hexapeptide	Val-Ile-Glu-Lys-Tyr-Pro	*Grifola frondosa*
D-Mannitol		*Pleurotus cornucopiae*
Oligo peptides	Arg-Leu-Pro-Ser-Glu-Phe-Asp-Leu-Ser-Ala-Phe-Leu-Arg-Ala	*P. cornucopiae*
Potassium	K^+	*Lentinula edodes*
Lentinan		*L. edodes*
Chitin		*L. edodes*
Beta-D-glucan		*Pleurotus* spp., *Ganoderma* spp., *Agaricus* spp.
Ergosterol		*Hericium erinaceus, Flammulina velutipes, G. lucidum*
Tocopherol		*H. erinaceus, F. velutipes, G. lucidum.*

(*continued*)

Table 1. Continued

Biocomponent	Structure	Source
Ergothioneine		*H. erinaceus, F. velutipes, G. lucidum.*
Ganoderics	 Ganoderol A	*Ganoderma* spp.
	 Ganoderol B	
	 Ganoderal A	
	 Ganoderic acid Y	
L-Pipecolic acid		*Sarcodona spratus*

Agaricus bisporus and 76% for *L. edodes* (Gil-Ramirez et al., 2011, 2013a). The responsible bio-components were β-D glucans and ergosterol (Gil-Ramirez et al., 2011, 2013b). In case of the 70% methanolic extracts of *Pholiota* spp. fruiting bodies, the *in vitro* HMGCo-AR inhibitory effects were 55.8% for *Pholiota adiposa,* 28.1 % for *Pholiota squarrosa,* 51.3% for *Pholiota nameko,* 36.5% for *Pholiota malicola* and 11.3% for *Pholiota squarrosides,* respectively (Yu et al., 2007). The HMG Co-AR inhibitory component identified was stigmasterol (Yu et al., 2007).

Antioxidative effects

Mushroom-based antioxidative bio-components include polysaccharides, phenolics, triterpenes, nicotinic acid, sterol (ergosterol) and vitamin E (tocopherol) (Barros et al., 2007, 2008; Ferreira et al., 2009). *Ganoderma* polysaccharides are noteworthy in relation to this mushroom's anti-oxidative and other medicinal properties (Ferreira et al., 2014; Paterson, 2006; Zhou et al., 2007). In rats' thoracic aorta endothelial cells, *L. edodes* polysaccharide increased anti-oxidative enzymatic activity along with reduced expression of

VCAM-1 mRNA that corresponds towards its anti-oxidative and anti-atherosclerotic performance (Xu et al., 2008). Phenolic compounds abound in both edible and medicinal mushrooms (Cheung et al., 2003; Kim et al., 2008; Palacios et al., 2011). Ergosterol, present in mushroom, has also been reported to provide an anti-oxidative and anti-atherosclerotic defense (Kim et al., 1999) (Table 1).

Ergothioneine (ERT) is another anti-oxidative mushroom bioactive that has been demonstrated to reduce the expression of pro-inflammatory mediators VCAM-1, ICAM-1, E-selectin and binding of monocytes to the endothelial cells, thus contributing to anti-atherosclerotic and CVD preventing effects (Martin, 2010; Xu et al. 2008).

Rajasekaran and Kalaimagal (2012) reported a cardioprotective role of *G. lucidum* as they noted increased levels of antioxidative enzymes and reduced glutathione levels in rats fed with *G. lucidum* extract.

Anti-platelet aggregation and anti-thrombotic effect

In rabbit aorta and coronary arteries, *Pleurotus* spp. have showed inhibitory effects on atheromatous plaque and atherosclerotic lesion formation (Bobek & Galbavý, 1999; Percario et al., 2008). Dissolution of the thrombus or fibrinolysis in blood vessels is an important strategy for maintaining normal vasculature. Intravenous injection of commercial fibrinolytic enzymes very often develop uncontrolled fibrinolysis and hemorrhage. Fibrinolytic enzymes from several edible and medicinal mushrooms have been found to lower the plausibility of thrombus formation without increasing the risk of hemorrhage. Artificial fibrin plate assay showed a *Schizophyllum commune* fibrinolytic enzyme possessing more potent fibrinolytic activity than the commercial fibrinolytic agent, plasmin (Lu & Chen, 2012). Only 0.5 μg of *S. commune* fibrinolytic enzyme was capable of causing the same amount of clot degradation (degradation zone 9 mm) as plasmin did at 1 μg concentration (Lu & Chen, 2012). Other mushrooms, from which fibrinolytic enzymes have been isolated and purified, include *Armillaria mellea*, *P. ostreatus*, *Cordyceps militaris*, *C. sinensis*, *F. velutipes*, *Fusarium sp.* and *G. lucidum* (Lu & Chen, 2012). They are the reservoirs of the fibrinolytic enzymes, and mushrooms function as thrombolytic and cardio-protective agents.

Anti-inflammatory effects

Mushrooms have been reported to be a potential source of anti-inflammatory molecules. They lower the expression of adhesion molecules (VCAM-1, ICAM-1, E-selectin-1) and decrease the rate of monocyte binding to the endothelium *in vitro* (Martin, 2010). Anti-inflammatory substances present in common mushrooms showed inhibitory effects towards nitric oxide (NO) and TNF-α production and they were heat labile (Gunawardena et al., 2014; O'Callaghan, 2014). Their anti-inflammatory led immunomodulatory effects have also been documented (Lull et al., 2005). Jedinak et al. (2011), through murine macrophage RAW264.7 cell line and murine splenocytes-based studies, elucidated that the anti-inflammatory effects of oyster mushrooms is mediated by the inhibition of NF-κB and AP-1 signaling. An ethanolic extract of *Lentinus polychrous* has been implicated in the decreased production of pro-inflammatory markers NO, iNOs, IL-1β, IL-6, TNF-α, COX-2 in lipopolysaccharide-induced RAW264.7 cell line (Junlatat et al., 2013). Suppressive effects upon carageenan-induced rats' paw edema was also observed for this mushroom (Junlatat et al., 2013). Cell line-based studies have identified mushroom anti-inflammatory molecules to be belonging to polysaccharides, triterpenes, peptides and phenolics group of substances (Table 1).

Table 2. Vitamin D and ergosterol content of mushrooms.

Mushroom species	Ergosterol (mg/100 g)	Vitamin D2 (μg/100 g fresh weight)
Agaricus bisporus	56.3	0.11
Flammulina velutipes	35.5	0.14
Lentinula edodes	84.9	0.44
Grifola frondosa	79.2	0.28
Pleurotus ostreatus	68.0	0.72

Vitamin content of mushrooms

Animal studies have suggested vitamin D to act as a hypotensive agent by inhibiting the RAAS (Li et al., 2002). Both *in vitro* and *in vivo* studies have indicated the ameliorating effects of vitamin D on CVD through improvement of vascular injury (Rahman et al., 2007). Mushrooms produce ergosterol, the precursor of vitamin D (Mattila et al., 2001). Mushrooms are amongst the rare natural sources of vitamin D2 and by sunlight or UV exposure, the rate of conversion of ergosterol to vitamin D2 is high (Phillips et al., 2011). From 100 g of *A. bisporus*, UV exposure produces about 11.2 μg of vitamin D2 as compared to only 0.2 μg in non-UV condition (Koyyalamudi et al., 2009). Table 2 describes the content of ergosterol (mg/100 g) and vitamin D2 (μg/100 g fresh weight) in different mushroom species (Phillips et al., 2011). Ergosterol has been identified as a novel inhibitor of 3-hydroxy 3-methyl glutaryl co-enzyme A reductase (HMGCo-AR), and thus a unique inhibitory mode of cholesterol biosynthesis has been ascribed to mushrooms (Gil-Ramirez et al., 2011). In humans, high absorption of vitamin D from mushrooms and its bioavailability have been reported (Outila et al., 1999). Vitamin D, obtained from mushrooms exposed to ultra violet light, has also been found to be safe for consumption and of high bioavailability (Calvo et al., 2013; Jasinghe et al., 2005).

For some wild species, the total tocopherol level has been detected up to 250.35 ng/g fresh weight, α tocopherol up to 27.13 ng/g fresh weight and β tocopherol up to 40.46 ng/g and γ tocopherol up to 25.69 ng/g fresh weight. In another study, Heleno et al. (2010) detected the level of total tocopherol to be 8.04 μg/g fresh weight in the wild mushroom, *Laccaria laccata.*

Fatty acid content of mushrooms

The content of saturated, unsaturated and essential fatty acids in mushrooms has been reported (Günç Ergönül, 2013; Kavishree et al., 2008; Reis et al., 2012). Their content of *cis* fatty acids might mediate an increased ratio of HDL to TC

Table 3. Fatty acid content (μg/g dried fruiting body) of some edible and medicinal mushrooms (Hossain et al., 2007).

Mushroom species	Palmitic acid ($C_{16:0}$)	Stearic acid ($C_{18:0}$)	Oleic acid ($C_{18:1}$)	Linoleic acid ($C_{18:2}$)	Linolenic acid ($C_{18:3}$)	Arachidoinc acid ($C_{20:4}$)
Agaricus bisporus	783	100	141	370	5.20	64.0
Pleurotus ostreatus	510	184	364	533	11.6	10.8
Ganoderma lucidum	153	89.0	173	161	1.6	13.0

Table 4. Dietary fiber content in mushrooms (Cheung, 2010, 2013).

Mushroom species	Total dietary fiber (% dry weight)	Water – insoluble dietary fiber (% dry weight)	Water – soluble dietary fiber (% dry weight)
Agrocybe aegerita	26.7	26.2	0.51
Agaricus blazei	29.6	27.6	1.93
Agrocybe chaxinggu	36.4	34.9	1.52
Coprinus comatus	34.6	32.8	1.79
Flammulina velutipes	38.2	33.8	4.42
Grifola frondosa	44.0	43.1	0.91
Hericium erinaceus	34.0	31.8	2.12
Hericium ramosum	26.9	23.6	3.25
Hypsizigus marmoreus	32.0	30.1	1.89
Lentinus giganteus	34.8	34.3	0.50
Pholiota adipose	30.8	27.7	3.08
Pholiota nameko	37.9	34.8	3.15
Stropharia ruguso-annulata	28.4	26.2	2.26

level that is beneficiary for cardiovascular health. Table 3 represents fatty acid content of some edible and medicinal mushrooms (Hossain et al., 2007).

Dietary fiber in mushroom

Mushrooms are a rich source of dietary fibers of which water-insoluble part (IDF) is about 90% and water-soluble one is 10% of mushroom dry weight (Table 4) (Cheung, 2010, 2013). Mushrooms alone are capable of fulfilling the 25% of the recommended dietary intake of dietary fiber (Cheung, 2010, 2013).

IDF, present in mushrooms, aids in reduced absorption of TC and triacylglycerol through the intestine and lowers CVD risks (Bajaj et al., 1997). Besides, the increased excretion of short chain fatty acids, like propionate, withstands incorporation of acetate for further fatty acid and sterol biosynthesis (Cheung, 2010, 2013).

Mushrooms as an anti-diabetic agent

According to International Diabetes Federation's 2014 statistics, 387 million (1 in every 12) people are living with diabetes, one in every 7 s, one person died of diabetes that caused a death toll of 4.9 million (http://www.idf.org/worlddiabetesday/toolkit/gp/facts-figures). Mushrooms' hypoglycemic and diabetes controlling effects have been reviewed by several reports (Lo & Wasser, 2011; Perera & Li, 2011). Ingestion of *G. lucidum* polysaccharide (ganopoly) lowered blood glucose levels in human subjects (Chang et al., 2007; Gao et al., 2004). *Agaricus bisporus* and *Pleurotus eryngii* have been documented as having hypoglycemic and hypolipidemic effects that might be implicated in its anti-diabetic and anti-CVD roles (Jeong et al., 2010; Kim et al., 2010). Enhanced adiponectin levels mediated amelioration of insulin resistance in type 2 diabetic patients have also been reported for *A. blazei* (Hsu et al., 2007). Insulin releasing and content of insulin-like components have been reported in the case of *Agaricus campestris* (Gray & Flatt, 1998). Incorporation of *A. campestris* at 62.5 g/kg of the diet and its aqueous extract at 1 mg/ml drinking water of mice, ameliorated streptozotocin-induced hyperglycemia, increased glucose transport two times, conversion rate of glucose to glycogen by 1.8 times and enhanced insulin secretion by 4.6 times (Hsu et al., 2007). In addition to hypoglycemic effects, it lowered cellular DNA damage in diabetic rats that had also been observed for *Inonotus obliquus* (Chaga mushroom) (Park et al., 2009). *Grifola frondosa* (maitake mushroom) has been implicated in increasing peripheral insulin sensitivity along with a blood glucose lowering effect in mice (Manohar et al., 2002). In rat models, a blood glucose lowering effect up to more than 52% has been reported for *Phellinus baumi* exopolysaccharide (Hwang et al., 2005). Recently, Abd Wahab et al. (2014) characterized four anti-diabetic-like proteins from the ammonium sulphate precipitation of *Pleurotus pulmonarius*. They were profilin-like, glyceraldehyde-3-phosphate dehydrogenase-like, trehalose phosphorylase-like and catalase-like anti-diabetic proteins in nature (Abd Wahab et al., 2014).

Mushrooms against AD

Reduced rate of synaptic degeneration

Synaptic degeneration (loss of synaptic connection)-driven neurodegeneration is an important step in AD pathogenesis. Loss of synaptic density proteins such as synaptophysin, synaptotagmin and PSD-95 parallel Aβ-induced synaptotoxicity during AD progression (Reddy et al., 2005), consequently, neurotransmission became severely weakened.

An aqueous extract of *G. lucidum* at 500 μg/ml concentration *in vitro,* contributed significantly to the restoration of synaptic density proteins, synaptophysin and thus attenuated Aβ-induced synaptotoxicity in rat cortical neurons (Lai et al., 2008). Mechanisms involved attenuation of phosphorylation of c-Jun N-terminal kinase (JNK), c-Jun, and p38 MAP kinase (Lai et al., 2008).

Aβ causes decreased synaptophysin immunoreactivity along with its increased accumulation and aggregation in AD neuritis (Stagi et al., 2005). Thus, axonal transport of synaptic vesicles becomes blocked. The stress signaling pathway JNK participates in this mechanism where NO exacerbates the situation. Inhibition of the phosphorylation of the JNK can overcome the blockage of synaptophysin transport (Stagi et al., 2005). Aqueous extracts of *G. lucidum* (500 μg/ml, 14 days treatment *in vitro*) significantly inhibited the phosphorylation of JNK in Aβ-stressed rat cortical neurons that potentiated it to overcome the Aβ-induced blockage of synaptophysin transport (Lai et al., 2008).

Reversion of neuronal apoptosis

Neuronal apoptosis is another phenomenon in AD pathogenesis where Aβ stimulates the activity of caspase-3 (Harada & Sugimoto, 1999). The apoptotic signaling pathway involves the protein kinase pathways including the JNK c-Jun and p38 MAP kinase (Harada & Sugimoto, 1999). An aqueous extract of *G. lucidum* reverted back Aβ-induced neuronal apoptosis by inhibiting these pathways (Lai et al., 2008). Specifically, *G. lucidum* inhibited phosphorylation at serine 67 and serine 73 of c-Jun, the substrate for JNK (Lai et al., 2008). Orally administered, *G. lucidum* polysaccharide (GLPS) at 100, 200 and 400 mg/kg body weight significantly lowered neuronal apoptosis in rats (Zhou et al., 2010). In cultured rat cortical neurons, (GLPS) at 0.1, 1.0 and 10 μg/ml, reduced neuronal apoptosis in a dose dependent manner. GLPS induced a neuro-protective mechanism that involves downregulation of the expression of caspases-3, -8 and -9 and Bax, and inhibition of the reduction of Bcl-2 expression resulting in altered Bcl-2/Bax ratio (Zhou et al., 2010). Lysophosphatidylethanolamine (LPE), derived from *G. frondosa* stimulated the activation of MAP kinase of rat pheochromocytoma PC12 cells and showed anti-apoptotic effects such as suppressed cell condensation and DNA ladder generation (Nishina et al., 2006). LPE also upregulated the expression of neurofilament M and thus promoted neuronal differentiation of PC 12 cells (Nishina et al., 2006).

Decreased Aβ deposition

A mouse diet supplemented with 0.3%, 0.6% and 1.8% of *G. lucidum* powder, had been found to significantly lower Aβ deposition in their brain along with increased anti-oxidative enzymatic levels and improved memory-related learning abilities (Wang et al., 2004). Studies involving SH-SY5Y neuroblastoma cell lines identified enhanced non-amyloidogenic protein secretion (sAPPα) activity of *G. lucidum*. In this case, *G. lucidum* mycelial extract mimicked the nerve growth factor (NGF) activity and it stimulated the phosphorylation of ERK 1/2 and PKC and involved the signaling cascades of PI3K and ERK (Pinweha et al., 2008).

Stimulatory effects towards neurite outgrowth and neurogeneration

Normal maintenance and differentiation of the neurons require supportive assistance from the neurotrophic factors (neurotrophins) such as brain-derived neurotrophic factor (BDNF), glia-derived neurotrophic factor (GDNF), nerve growth factor (NGF) and neurotrophin 3 (NT-3). The NGFs are polypeptides and too large to cross the BBB. Cyrneines A and B isolated from *Sarcodon cyrneus* have shown a stimulatory effect towards neurite outgrowth in both PC12 and NG108-15 cells and NGF generation in 1321N1 cells (Marcotullio et al., 2007). Glaucopine C from *Sarcodon glaucopus* also stimulated NGF production and the structural features of these components have been implicated to be responsible for different extents of neurite outgrowth and NGF generation in different cell lines (Marcotullio et al., 2007). Similarly, the position of the aldehyde group has been identified as the crucial factor in promoting neurite outgrowth and NGF generation for the cyathane diterpenoids scarbonines of *Sarcodon scabrosus* (Shi et al., 2011) (Table 1). Positive role of *H. erinaceus* upon neurite outgrowth and NGF generation have been reported by several studies (Moldavan et al., 2007; Mori et al., 2008; Wong et al., 2007, 2009, 2011). In an attempt to identify the neuro-supportive component of *H. erinaceus,* Park et al. (2002) demonstrated that an exopolysaccharide from its culture broth had neurite outgrowth promotive effect in PC12 cells. As *in vitro* mechanistic approaches very often differ from *in vivo*, these polysaccharides' mode of action could not be explained. However, for three decades studies for identifying the memory and brain function improving effects of *H. erinaceus* have identified different members of benzyl alcohol group such as hericenones (A-I), diterpenoids, eriancins (A-R) and cyathadien 14β ol, erinacol as reviewed by Phan et al. (2014).

In rat pheochromocytoma (PC) 12 neuronal cell lines, stimulatory effect of *G. lucidum* towards *in vitro* neurite outgrowth and neuronal differentiation has been demonstrated (Cheung et al., 2000). The mushrooms were also effective in guarding against NGF-mediated apoptosis (Cheung et al., 2000). The probable mode of action is ras/extracellular signal-regulated kinase (Erk) and signaling cascade involving cAMP-response element binding protein (CREB) (Cheung et al., 2000). The lipophilic fraction of *G. lucidum* at 125 and 500 mg/L was found to promote neurtie outgrowth, stimulate NGF activity and potentiate PC 12 neuronal differentiation (Zhang et al., 2005). Seow et al. (2013) reported the comparatively enhanced neuritogenic effect of the aqueous extract of *G. neo-japonicum* than those of the *G. lucidum* and *G. frondosa* in PC 12 cells (Seow et al., 2013). At 50 μg/ml concentration, the *G. neo-japonicum* stimulated 14.22% neuritogenesis, whereas at 75 μg/ml concentration, the effect was 12.61% for the *G. lucidum* and 12.07% for the *G. frondosa* extract (Seow et al., 2013). Bio-components present in these mushroom extracts activated the MEK/ERK1/2 and PI3K/Akt signaling pathways to promote neuritogenesis (Seow et al., 2013). At 20 μg/ml concentration, the aqueous sclerotium of *Lignosus rhinocerotis* induced PC 12 cells' neurite outgrowth of 24.4% (Eik et al., 2012). Both aqueous and ethanolic extracts of *Pleurotus giganteus* had been found

to induce neurite outgrowth of PC12 cells in dose- and time-dependant fashion (Phan et al., 2012). Similar patterns of neurite-outgrowth stimulatory effect, along with restoration of impaired memory in rats, have been observed for *Tremella fuciformis* (Park et al., 2012; Kim et al., 2007). In scopolamine-induced learning and memory deficient rats, *C. militaris* reverted back memory loss of the rats and promoted dose-dependent (5–20 μg/ml) neuritogenesis in Neuro2A mouse neuroblastoma cells (Lee et al., 2011).

Acetylcholine esterase inhibitory effects

Decreased availability of the cholinergic neurotransmitter acetylcholine leads towards AD consequences (Inestrosa et al., 1996; Recanatini & Valenti, 2004). The reason for this is the activity of the enzyme acetyl choline esterase (AchE) (Inestrosa et al., 1996; Recanatini & Valenti, 2004). Thus, developed treatment strategies targeted at anti-acetyl choline esterase (AchEI) activities would have an ameliorating effect on AD (Inestrosa et al., 1996; Recanatini & Valenti, 2004). Since 1970s, different AchEIs have been developed, namely donepezil, galantamine, rivastigmine and tacrine (Benzi & Moretti, 1998; Francis et al., 1999). They have been reported to improve cognitive and behavioral performance of the AD subjects (Terry & Buccafusco, 2003). Mushrooms, in parallel with the synthetic AchEIs, have been regarded for maintaining the neurotransmitter acetylcholine level up to appreciable amounts by inhibiting its degrading enzyme acetylcholine esterase. *Ganoderma lucidum* at 2 mg/ml concentration showed 57% inhibition of the acetylcholine esterase activity *in vitro* (Hasnat et al., 2013). Patocka et al. (2003) isolated AchEIs from the fruiting bodies of the agaricoid fungus *Cortinarius brunneus.* The AchEIs included beta-carboline alkaloids brunneins A-C and 3 -(7-hydroxy-9H-beta-carboline-1-yl) propanoic acid (Patocka, 2012). AchEIs have more selectivity than the synthetic agent galantamine, and have also been isolated from the mushroom *Cortinarius infractus*, where the responsible compounds were infractopicrin and 10-hydroxy-infractopicrin (Geissler et al., 2010). Tel et al. (2012) reported the *in vitro* AchE inhibitory effect of the hexane extract of *Tricholoma imbricatum* (71.8% inhibition at 0.2 mg/ml concentration). The coral mushroom, *Clavicorona pyxidata* showed significant potent AchEI effects. At 100 μg/ml concentration, its water, ethanol and butanolic extracts showed 91.7%, 93.7% and 99.3% AchEI effects, respectively (Lee et al., 2006). Restoration of impaired memory in rats by *T. fuciformis* has been reported to be through activation of the cholinergic system (Park et al., 2012). Thus, mushrooms possess cholinergic functions and the cholinergic deficiency that occurred in AD could be ameliorated with the mushroom.

Dopaminergic activity

Shielding effects against dopaminergic neuronal loss through reduced production of microglial proinflammatory factors have been associated with *G. lucidum* (Zhang et al., 2011). A methanolic extract of *G. lucidum* at 400 μg/ml, significantly inhibited the dopaminergic neurodegeneration of MES 23.5 cell membranes (Zhang et al., 2011). In the cerebral cortex of rats fed with diet containing *Mycoleptodonoides aitchisonii,* a 1.5-fold increased level of dopamine was detected (Okuyama et al., 2004). Aqueous extracts of *M. aitchisonii* also increased dopamine release from rat striatum (Okuyama et al., 2004). Its mode of action involved antioxidative enzymatic defense through activation of the signaling factor Nrf2 (Kokubo et al., 2011).

BACE1 inhibitory effect

Aβ is generated from the amyloid precursor protein (APP) by the sequential proteolytic cleavage of aspartyl protease beta-site APP-cleaving enzyme 1 (BACE1) and gamma secretase. BACE1 is an aspartyl protease of the pepsin family and a type-1 transmembrane protein (Yang et al., 2003). BACE1 catalyzes the regulatory step for the production of toxic Aβ, whose level increases in AD subjects and in aged individuals (Fukumoto et al., 2002).

Modification of the BACE1-mediated APP-cleavage results in altered AD pathology (Jonsson et al., 2012). Thus, it is the enzyme of choice for AD drug development. Unfortunately, the active site of BACE1 is comparatively large and compounds withstanding its effects are also larger in size that impedes their crossing of the BBB. This poses a threat to development of BACE1 inhibitors. Interestingly, some mushrooms have been found to inhibit BACE1 activity. For instance, different extracts of the coral mushroom *C. pyxidata* inhibited BACE1 activity to different extents (ethanolic 28.7%, hexane 20.8%, butanol 20.2% inhibition at 100 μg/ml) (Lee et al., 2006). A methanolic extract of *L. edodes* was found to inhibit BACE1 activity (by 40.1%) followed by *P. eryngii* (33.7%), *F. velutipes* (22.3%) and *A. bisporus* (18.3%) (Seo et al., 2008). Through characterization of the cell-free extracts of different bacteria, fungi and yeast, Lee et al. (2007) identified the BACE1 inhibitory effects (percentage scale) of mushrooms second only to *Saccharomyces cerevisiae* (Lee et al., 2007). Mushroom species having anti-BACE1 effects were *F. velutipes*, *P. ostreatus*, *G. frondosa*, *Dictyophora echinovolvata*, *P. adipose*, *Fomitella fraxinea* and *I. obliquus* (Lee et al., 2007).

BACE1 inhibitory components have been identified as heat stable through further studies with *Auricularia polytricha* (Bennett et al., 2013). Hispidin, isolated from *Phellinus linteus*, had been found to non-competitively inhibit the BACE1 (Park et al., 2004). It also inhibited the activity of α-secretase, the non-pathological enzyme in Aβ generation.

The therapeutic potentiality of the AD drug warrants a molecular weight lower than 700 Da, specifically in order to cross the blood brain barrier (BBB). Peptide-based agents having a large size and relatively high molecular weight fail to fulfill this criterion very often and thus non-peptidyl agents like hispidine seems promising in this aspect. Hispidine is a polyphenolic compound found in abundance in the mushroom *P. linteus*. It non-competitively inhibits BACE1 and scavenges free radicals (Park et al., 2004). BACE1 inhibitory effect of *A. polytricha* has also been indicated to be hispidine mediated (Bennett et al., 2013).

Antioxidative and memory enhancing effect of mushrooms

An aqueous extract of *G. lucidum,* grown on germinated brown rice was shown to possess both *in vitro* and *in vivo* anti-oxidant activities (Hasnat et al., 2013). In mice sera, liver

and brain homogenates, this mushroom increased the level of anti-oxidative enzymes catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Hasnat et al., 2013). In senescent accelerated SAMP8 mice, *G. lucidum* powder at 0.3%, 0.6% and 1.8% of diet, significantly increased the activities of SOD, GPx, glutathione reductase (GSH-Rd) of RBC, brain and liver (Wang et al., 2004). The same dose lowered the level of mice brain Aβ level and the *G. lucidum* fed to mice performed better in the active shuttle avoidance test. Thus, free-radical scavenging and anti-oxidative mode of action of *G. lucidum* might impart their protective role against Aβ deposition that represents this mushroom's memory enhancing effect (Wang et al., 2004).

Conclusion

AD and CVD have common etiology and preventive strategy. Mushrooms stand at the linking point of both of the diseases especially due to their bio-active components capable of withstanding the pathogenesis of both. Thus, mushrooms function as excellent food-based alternative therapeutic agents for both of these diseases. However, up to the present time, most of these findings are based on *in vitro, ex vivo,* cell line and animal models based rather than on human subjects. Large scale clinical studies involving humans and efficacy and safety of individual mushrooms is now essential to further their usage in AD and CVD therapeutics.

Declaration of interest

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References

Abd Wahab NA, Abdullah N, Aminudin N. (2014). Characterisation of potential antidiabetic-related proteins from *Pleurotus pulmonarius* (Fr.) Quel. (grey oyster mushroom) by MALDI-TOF/TOF mass spectrometry. BioMed Res Intl. doi: 10.1155/2014/13160.

Alarcon J, Aguila S, Arancibia-Avila P, et al. (2003). Production and purification of statins from *Pleurotus ostreatus* (Basidiomycetes) strains. Zeitschrift Fur Naturforschung C, 58, 62–4.

Ansor NM, Abdullah N, Aminudin N. (2013). Anti-angiotensin converting enzyme (ACE) proteins from mycelia of *Ganoderma lucidum* (Curtis) P. Karst. BMC Complement Alt Med, 13, 256.

Annweiler C, Rolland Y, Schott, AM, et al. (2012). Higher vitamin D dietary intake is associated with lower risk of Alzheimer's disease: a 7-year follow-up. J Gerontol Series A: Biol Sci Med Sci, 67, 1205–11.

Backer GD, Ambrosioni E, Borch-Johnsen E, et al. (2003). European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). Eur J Cardiovas Prevent Rehab, 10, S1–78.

Bajaj M, Vadhera S, Brar A, Soni G. (1997). Role of oyster mushroom *(Pleurotus florida)* as hypocholesterolemic/antiatherogenic agent. Ind J Exp Biol, 35, 1070–5.

Barros L, Ferreira MJ, Queiros B, et al. (2007). Total phenols, ascorbic acid, β-carotene and lycopene in Portuguese wild edible mushrooms and their antioxidant activities. Food Chem, 103, 413–19.

Barros L, Cruz T, Baptista P, et al. (2008). Wild and commercial mushrooms as source of nutrients and nutraceuticals. Food Chem Toxicol, 46, 2742–7.

Bennett L, Sheean P, Zabaras D, Head R. (2013). Heatstable components of wood ear mushroom, *Auricularia polytricha* (higher Basidiomycetes), inhibit in vitro activity of beta secretase (BACE1). Intl J Med Mushrooms, 15, 233–249.

Benzi G, Moretti A. (1998). Is there a rationale for the use of acetylcholinesterase inhibitors in the therapy of Alzheimer's disease? Eur J Pharmacol, 346, 1–13.

Bobek P, Galbavý Š. (1999). Hypocholesterolemic and antiatherogenic effect of oyster mushroom *(Pleurotus ostreatus)* in rabbits. Food/Nahrung, 43, 339–42.

Bullain SS, Corrada MM. (2013). Dementia in the oldest old. CONTINUUM: Lifelong Learn Neurol, 19, 457–69.

Buxbaum JD, Geoghagen NS, Friedhoff T. (2001). Cholesterol depletion with physiological concentrations of a statin decreases the formation of the Alzheimer amyloid Aβ peptide. J Alzh Dis, 3, 221–9.

Calvo M, Babu U, Garthoff L, et al. (2013). Vitamin D2 from light-exposed edible mushrooms is safe, bioavailable and effectively supports bone growth in rats. Osteopor Intl, 24, 197–207.

Casserly I, Topol EJ. (2004). Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet, 363, 1139–46.

Chang JH, Kim MS, Kim JY, et al. (2007). Effects of mushroom supplementation on blood glucose concentration, lipid profile, and antioxidant enzyme activities in patients with type 2 diabetes mellitus. Kor J Nutr, 40, 327–33.

Chen SY, Ho KJ, Hsieh YJ, et al. (2012). Contents of lovastatin, γ-aminobutyric acid and ergothioneine in mushroom fruiting bodies and mycelia. LWT-Food Sci Technol, 47, 274–8.

Cheung WM, Hui WS, Chu PW, et al. (2000). *Ganoderma* extract activates MAP kinases and induces the neuronal differentiation of rat pheochromocytoma PC12 cells. FEBS Lett, 486, 291–6.

Cheung L, Cheung PC, Ooi VE. (2003). Antioxidant activity and total phenolics of edible mushroom extracts. Food Chem, 81, 249–55.

Cheung P. (2010). The nutritional and health benefits of mushrooms. Nutr Bull, 35, 292–9.

Cheung PC. (2013). Mini-review on edible mushrooms as source of dietary fiber: preparation and health benefits. Food Sci Hum Well, 2, 162–6.

De Kosky ST. (2005). Statin therapy in the treatment of Alzheimer's disease: what is the rationale? Am J Med, 118, 48–53.

Dokken BB. (2008). The pathophysiology of cardiovascular disease and diabetes: beyond blood pressure and lipids. Diabet Spectr, 21, 160–5.

Eik LF, Naidu M, David P, et al. (2012). *Lignosus rhinocerus* (Cooke) Ryvarden: a medicinal mushroom that stimulates neurite outgrowth in PC-12 cells. eCAM. 2012. Article ID 320308, http://dx.doi.org/10.1155/2012/320308.

Fassbender K, Simons M, Bergmann C, et al. (2001). Simvastatin strongly reduces levels of Alzheimer's disease β-amyloid peptides Aβ42 and Aβ40 *in vitro* and *in vivo*. Proc Nat Acad Sci, 98, 5856–61.

Federico L, Steve P, Ludovica C, et al. (2000). Increased plasma levels of interleukin-1, interleukin-6 and α-1-antichymotrypsin in patients with Alzheimer's disease: peripheral inflammation or signals from the brain? J Neuroimmunol, 103, 97–102.

Ferreira IC, Barros L, Abreu R. (2009). Antioxidants in wild mushrooms. Curr Med Chem, 16, 1543–60.

Ferreira IC, Heleno SA, Reis FS, et al. (2014). Chemical features of *Ganoderma* polysaccharides with antioxidant, antitumor and antimicrobial activities. Phytochem, pii: S0031-9422(14)00415-4. doi: 10.1016/j.phytochem.2014.10.011. [Epub ahead of print].

Francis PT, Palmer AM, Snape M, Wilcock GK. (1999). The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psych, 66, 137–47.

Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. (2006). ω-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer's disease: Omeg AD study: a randomized double-blind trial. Arch Neurol, 63, 1402–8.

Fukumoto H, Cheung BS, Hyman BT, Irizarry MC. (2002). β-Secretase protein and activity are increased in the neocortex in Alzheimer's disease. Arch Neurol, 59, 1381–9.

Gao Y, Lan J, Dai X, et al. (2004). A phase I/II study of ling zhi mushroom *Ganoderma lucidum* (W. Curt.: Fr.) Lloyd (Aphyllophoromycetideae) extract in patients with type II diabetes mellitus. Intl J Med Mush, 6. doi: 10.1615/IntJMedMushr.v6.i1.30.

Geissler T, Brandt W, Porzel A, et al. (2010). Acetylcholinesterase inhibitors from the toadstool *Cortinarius infractus*. Bioorg Med Chem, 18, 2173–7.

Gil-Ramirez A, Clavijo C, Palanisamy M, et al. (2011). Edible mushrooms as potential sources of new hypocholesterolemic compounds. Proceedings of the 7th International Conference on Mushroom Biology and Mushroom Products (ICMBMP7) 2011, Section Poster:110-119; 2011 4–7 October; Arcachon, France.

Gil-Ramírez A, Clavijo C, Palanisamy M, et al. (2013a). Screening of edible mushrooms and extraction by pressurized water (PWE) of 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitors. J Func Foods, 5, 244–50.

Gil-Ramirez A, Clavijo C, Palanisamy M, et al. (2013b). Study on the 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitory properties of *Agaricus bisporus* and extraction of bioactive fractions using pressurised solvent technologies. J Sci Food Agric, 93, 2789–96.

Girouard H, Iadecola C. (2006). Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer's disease. J Appl Physiol, 100, 328–35.

Gray A, Flatt P. (1998). Insulin-releasing and insulin-like activity of *Agaricus campestris* (mushroom). J Endocrinol, 157, 259–66.

Gunawardena D, Bennett L, Shanmugam K, et al. (2014). Anti-inflammatory effects of five commercially available mushroom species determined in lipopolysaccharide and interferon-γ activated murine macrophages. Food Chem, 148, 92–6.

Günç Ergönül P, Akata I, Kalyoncu F, Ergönül B. (2013). Fatty acid compositions of six wild edible mushroom species. Sci World J. http://dx.doi.org/10.1155/2013/163964.

Gunde-Cimerman N, Friedrich J, Cimerman A, Benički N. (1993a). Screening fungi for the production of an inhibitor of HMG CoA reductase: Production of mevinolin by the fungi of the genus *Pleurotus*. FEMS Microbiol Lett, 111, 203–6.

Gunde-Cimerman N, Plemenitaš A, Cimerman A. (1993b). *Pleurotus* fungi produce mevinolin, an inhibitor of HMG CoA reductase. FEMS Microbiol Lett, 113, 333–7.

Gunde-Cimerman N, Cimerman A. (1995). *Pleurotus* fruiting bodies contain the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase–lovastatin. Exp Mycol, 19, 1–6.

Harada J, Sugimoto M. (1999). Activation of caspase-3 in β-amyloid-induced apoptosis of cultured rat cortical neurons. Brain Res, 842, 311–23.

Harrison DG, Gongora MC. (2009). Oxidative stress and hypertension. Med Clin North Am, 93, 621–35.

Hasnat MA, Pervin M, Lim BO. (2013). Acetylcholinesterase inhibition and *in vitro* and *in vivo* antioxidant activities of *Ganoderma lucidum* grown on germinated brown rice. Molecules, 18, 6663–78.

Heleno SA, Barros L, Sousa MJ, et al. (2010). Tocopherols composition of Portuguese wild mushrooms with antioxidant capacity. Food Chem, 119, 1443–50.

Hirvonen J, Virtanen KA, Nummenmaa L, et al. (2011). Effects of insulin on brain glucose metabolism in impaired glucose tolerance. Diabetes, 60, 443–7.

Hossain S, Hashimoto M, Choudhury EK, et al. (2003). Dietary mushroom *(Pleurotus ostreatus)* ameliorates atherogenic lipid in hypercholesterolaemic rats. Clin Exp Pharmacol Physiol, 30, 470–5.

Hossain MS, Alam N, Amin SR, et al. (2007). Essential fatty acid contents of *Pleurotus ostreatus, Ganoderma lucidum* and *Agaricus bisporus*. Bangladesh J Mush, 1, 1–7.

Hsu CH, Liao YL, Lin SC, et al. (2007). The mushroom *Agaricus Blazei* Murill in combination with metformin and gliclazide improves insulin resistance in type 2 diabetes: a randomized, double-blinded, and placebo-controlled clinical trial. J Alt Complement Med, 13, 97–102.

Hwang HJ, Kim SW, Lim JM, et al. (2005). Hypoglycemic effect of crude exopolysaccharides produced by a medicinal mushroom *Phellinus baumii* in streptozotocin-induced diabetic rats. Life Sci, 76, 3069–80.

Hyman BT, Strickland D, Rebeck GW. (2000). Role of the low-density lipoprotein receptor-related protein in β-amyloid metabolism and Alzheimer's disease. Arch Neurol, 57, 646–50.

Jasinghe VJ, Perera, CO, Barlow PJ. (2005). Bioavailability of vitamin D2 from irradiated mushrooms: an *in vivo* study. Brit J Nutr, 93, 951–5.

Jedinak A, Dudhgaonkar S, Wu Q, et al. (2011). Anti-inflammatory activity of edible oyster mushroom is mediated through the inhibition of NF-kB and AP-1 signaling. Nutr J, 10, 52.

Jeong SC, Jeong YT, Yang BK, et al. (2010). White button mushroom *(Agaricus bisporus)* lowers blood glucose and cholesterol levels in diabetic and hypercholesterolemic rats. Nutr Res, 30, 49–56.

Jonsson T, Atwal JK, Steinberg S, et al. (2012). A mutation in APP protects against Alzheimer/'s disease and age-related cognitive decline. Nature, 488, 96–9.

Junlatat J, Sripanidkulchai B, Fangkrathok N. (2013). *In vivo* and *in vitro* anti-inflammatory activity of *Lentinus polychrous* extract. J Ethnopharmacol, 147, 631–7.

Inestrosa NC, Alvarez A, Perez CA, et al. (1996). Acetylcholinesterase accelerates assembly of amyloid-β-peptides into Alzheimer's fibrils: possible role of the peripheral site of the enzyme. Neuron, 16, 881–91.

Kavishree S, Hemavathy J, Lokesh B, et al. (2008). Fat and fatty acids of Indian edible mushrooms. Food Chem, 106, 597–602.

Kendrick J, Targher G, Smits G, Chonchol M. (2009). 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atheroscler, 205, 255–60.

Kim SW, Park SS, Min TJ, Yu KH. (1999). Antioxidant activity of ergosterol peroxide (5, 8-epidioxy-5α, 8α-ergosta-6, 22E-dien-3β-ol) in *Armillariella mellea*. Bull Kor Chem Soc, 20, 819–23.

Kim JH, Ha HC, Lee MS, et al. (2007). *Tremella fuciformis* on the neurite outgrowth of PC12h cells and the improvement of memory in rats. Biol Pharmacol Bull, 30, 708–14.

Kim JI, Kang MJ, Im J, Seo YJ, Lee YM, Song JH, Lee JH, Kim ME. (2010). Effect of king oyster mushroom (*Pleurotus eryngii*) on insulin resistance and dyslipidemia in db/db mice. Food Sci Biotechnol, 19, 239–242.

Kim MY, Seguin P, Ahn JK, et al. (2008). Phenolic compound concentration and antioxidant activities of edible and medicinal mushrooms from Korea. J Agril Food Chem, 56, 7265–70.

Kokubo T, Taniguchi Y, Kanayama M, et al. (2011). Extract of the mushroom *Mycoleptodonoides aitchisonii* induces a series of anti-oxidative and phase II detoxifying enzymes through activation of the transcription factor Nrf2. Food Chem, 129, 92–9.

Koyyalamudi SR, Jeong SC, Song CH, et al. (2009). Vitamin D2 formation and bioavailability from *Agaricus bisporus* button mushrooms treated with ultraviolet irradiation. J Agril Food Chem, 57, 3351–5.

Lai CSW, Yu MS, Yuen WH, et al. (2008). Antagonizing β-amyloid peptide neurotoxicity of the anti-aging fungus *Ganoderma lucidum*. Brain Res, 1190, 215–24.

Lee DH, Lee DH, Lee JS. (2007). Characterization of a new antidementia β-secretase inhibitory peptide from *Saccharomyces cerevisiae*. Enz Microb Tech, 42, 83–88.

Lee HD, Kim HJ, Park SJ, et al. (2004). Isolation and characterization of a novel angiotensin I-converting enzyme inhibitory peptide derived from the edible mushroom *Tricholoma giganteum*. Peptides, 25, 621–7.

Lee T, Park Y, Han Y. (2006). Effect of mycelial extract of *Clavicorona pyxidata* on the production of amyloid beta-peptide and the inhibition of endogenous beta-secretase activity in vitro. J Microbiol Seoul, 44, 665–70.

Lee B, Park J, Park J, et al. (2011). *Cordyceps militaris* improves neurite outgrowth in Neuro2a cells and reverses memory impairment in rats. Food Sci Biotech, 20, 1599–608.

Li YC, Kong J, Wei M, et al. (2002). 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest, 110, 229–38.

Lo HC, Wasser SP. (2011). Medicinal mushrooms for glycemic control in diabetes mellitus: history, current status, future perspectives, and unsolved problems (review). Int J Med Mushrooms, 13, 401–26.

Lo YC, Lin SY, Ulziijargal E, et al. (2012). Comparative study of contents of several bioactive components in fruiting bodies and mycelia of culinary-medicinal mushrooms. Int J Med Mushrooms, 14, 357–64.

Lu CL, Chen SN. (2012). Fibrinolytic enzymes from medicinal mushrooms. Protein Structure, InTech, Eshel Faraggi (Ed.), Rijeka, Croatia. ISBN 978-953-51-0555-8,978-953. http://www.intechopen.-com/books/proteinstructure/fibrinolytic-enzymes-from-medicinalmushrooms.

Lull C, Wichers HJ, Savelkoul HF. (2005). Antiinflammatory and immunomodulating properties of fungal metabolites. Mediat Inflamm, 2, 63–80.

Mancia G. (2007). Blood pressure reduction and cardiovascular outcomes: past, present, and future. Am J Cardiol, 100, S3–9.

Manohar V, Talpur N, Echard B, et al. (2002). Effects of a water soluble extract of maitake mushroom on circulating glucose/insulin concentrations in KK mice. Diabet Obes Metabol, 4, 43–8.

Marcotullio MC, Pagiotti R, Maltese F, et al. (2007). Cyathane diterpenes from *Sarcodon cyrneus* and evaluation of their activities of neuritegenesis and nerve growth factor production. Bioorg Med Chem, 15, 2878–82.

Martin KR. (2010). Both common and specialty mushrooms inhibit adhesion molecule expression and *in vitro* binding of monocytes to human aortic endothelial cells in a pro-inflammatory environment. Nutr J, 9, 29.

Mattila P, Könkö K, Eurola M, et al. (2001). Contents of vitamins, mineral elements, and some phenolic compounds in cultivated mushrooms. J Agril Food Chem, 49, 2343–8.

Moldavan M, Grygansky AP, Kolotushkina OV, et al. (2007). Neurotropic and trophic action of lion's mane mushroom *Hericium erinaceus* (Bull.: Fr.) Pers.(Aphyllophoromycetideae) extracts on nerve cells *in vitro*. Intl J Med Mushrooms, 9, 15–28.

Moreira PI, Santos MS, Seiça R, Oliveira CR. (2007). Brain mitochondrial dysfunction as a link between Alzheimer's disease and diabetes. J Neurol Sci, 257, 206–14.

Mori K, Obara Y, Hirota M, et al. (2008). Nerve growth factor-inducing activity of *Hericium erinaceus* in 1321N1 human astrocytoma cells. Biol Pharmaceut Bull, 31, 1727–32.

Mozaffarian D, Katan MB, Ascherio A, et al. (2006). Trans fatty acids and cardiovascular disease. N Engl J Med, 354, 1601–13.

Nishina A, Kimura H, Sekiguchi A, et al. (2006). Lysophosphatidylethanolamine in *Grifola frondosa* as a neurotrophic activator via activation of MAPK. J Lipid Res, 47, 1434–43.

O'Callaghan YC, O'Brien NM, Kenny O, et al. (2014). Anti-inflammatory effects of wild Irish mushroom extracts in RAW264.7 mouse macrophage cells. J Med Food, 18, 202–7.

Okuyama S, Lam NV, Hatakeyama T, et al. (2004). *Mycoleptodonoides aitchisonii* affects brain nerve growth factor concentration in newborn rats. Nutr Neurosci, 7, 341–9.

Outila TA, Mattila PH, Piironen VI, et al. (1999). Bioavailability of vitamin D from wild edible mushrooms *(Cantharellus tubaeformis)* as measured with a human bioassay. Am J Clin Nutr, 69, 95–8.

Ohara T, Doi Y, Ninomiya, T, et al. (2011). Glucose tolerance status and risk of dementia in the community the Hisayama Study. Neurol, 77, 1126–34.

Palacios I, Lozano M, Moro C, et al. (2011). Antioxidant properties of phenolic compounds occurring in edible mushrooms. Food Chem, 128, 674–8.

Pappolla MA, Bryant-Thomas TK, Herbert D, et al. (2003). Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. Neurol, 61, 199–205.

Park IH, Jeon SY, Lee HJ, Kim SI, Song KS. (2004). A beta-secretase (BACE1) inhibitor hispidin from the mycelial cultures of *Phellinus linteus*. Planta medica, 70, 143–146.

Park YS, Lee HS, Won MH, et al. (2002). Effect of an exo-polysaccharide from the culture broth of *Hericium erinaceus* on enhancement of growth and differentiation of rat adrenal nerve cells. Cytotechnol, 39, 155–62.

Park YK, Kim JS, Jeon EJ, Kang MH. (2009). The improvement of chaga mushroom *(Inonotus obliquus)* extract supplementation on the blood glucose and cellular DNA damage in streptozotocin-induced diabetic rats. Kor J Nutr, 42, 5–13.

Park HJ, Shim HS, Ahn YH, et al. (2012). *Tremella fuciformis* enhances the neurite outgrowth of PC12 cells and restores trimethyltin-induced impairment of memory in rats via activation of CREB transcription and cholinergic systems. Behav Brain Res, 229, 82–90.

Paterson, RRM. (2006). *Ganoderma* – A therapeutic fungal biofactory. Phytochem, 67, 1985–2001.

Patocka J, Kuca K, Jun D. (2003). Acetylcholinesterase and butyrylcholinesterase – important enzymes of human body. Acta Med, 47, 215–28.

Patocka, J. (2012). Natural cholinesterase inhibitors from mushrooms. Mil Med Sci Lett, 81, 40–4.

Percario S, Odorizzi V, Souza D, et al. (2008). Edible mushroom *Agaricus sylvaticus* can prevent the onset of atheroma plaques in hypercholesterolemic rabbits. Cell Mol Biol, 54, OL1055–61.

Perera PK, Li Y. (2011). Mushrooms as a functional food mediator in preventing and ameliorating diabetes. Func Food Health Dis, 1, 161–71.

Phan CW, Wong WL, David P, et al. (2012). *Pleurotus giganteus* (Berk.) Karunarathna & KD Hyde: Nutritional value and *in vitro* neurite outgrowth activity in rat pheochromocytoma cells. BMC Complement Altern Med, 12, 102.

Phan CW, David P, Naidu M, et al. (2014). Therapeutic potential of culinary-medicinal mushrooms for the management of neurodegenerative diseases: diversity, metabolite, and mechanism. Crit Rev Biotechnol, 1–14.

Phillips KM, Ruggio DM, Horst RL, et al. (2011). Vitamin D and sterol composition of 10 types of mushrooms from retail suppliers in the United States. J Agril Food Chem, 59, 7841–53.

Pinweha S, Wanikiat P, Sanvarinda Y, Supavilai P. (2008). The signaling cascades of *Ganoderma lucidum* extracts in stimulating non-amyloidogenic protein secretion in human neuroblastoma SH-SY5Y cell lines. Neurosci Lett, 448, 62–6.

Praticò D. (2008). Evidence of oxidative stress in Alzheimer's disease brain and antioxidant therapy. Annal New York Acad Sci, 1147, 70–8.

Rahman A, Hershey S, Ahmed S, et al. (2007). Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. J Steroid Biochem Mol Biol, 103, 416–19.

Rajasekaran M, Kalaimagal C. (2012). Cardioprotective effect of a medicinal mushroom, *Ganoderma lucidum* against adriamycin induced toxicity. Intl J Pharmacol, 8, 252–8.

Recanatini M, Valenti P. (2004). Acetylcholinesterase inhibitors as a starting point towards improved Alzheimer's disease therapeutics. Curr Pharm Des, 10, 3157–66.

Reddy PH, Mani G, Park BS, et al. (2005). Differential loss of synaptic proteins in Alzheimer's disease: implications for synaptic dysfunction. J Alzh Dis, 7, 103–17.

Reis FS, Barros L, Martins A, Ferreira IC. (2012). Chemical composition and nutritional value of the most widely appreciated cultivated mushrooms: an inter-species comparative study. Food Chem Toxicol, 50, 191–7.

Reitz C, Brayne C, Mayeux R. (2011). Epidemiology of Alzheimer's disease. Nat Rev Neurol, 7, 137–52.

Schnell O. (2005). The links between diabetes and cardiovascular disease. J Interven Cardiol, 18, 413–16.

Seo DS, Lee EN, Seo GS, Lee JS. (2008). Screening and optimal extraction of a new antidementia β-secretase inhibitor-containing mushroom. Mycobiol, 36, 195–7.

Seow SLS, Naidu M, David P, et al. (2013). Potentiation of neuritogenic activity of medicinal mushrooms in rat pheochromocytoma cells. BMC Comp Alt Med, 13, 157.

Shi XW, Liu L, Gao JM, Zhang AL. (2011). Cyathane diterpenes from Chinese mushroom *Sarcodon scabrosus* and their neurite outgrowth-promoting activity. Eur J Med Chem, 46, 3112–17.

Shie FS, Jin LW, Cook DG, et al. (2002). Diet-induced hypercholesterolemia enhances brain Aβ accumulation in transgenic mice. Neuroreport, 13, 455–9.

Stagi M, Dittrich PS, Frank N, et al. (2005). Breakdown of axonal synaptic vesicle precursor transport by microglial nitric oxide. J Neurosci, 25, 352–62.

Suzanne M. (2014). Type 3 diabetes is sporadic Alzheimer's disease: Mini-review. Eur Neuropsychopharmacol, 24, 1954–60.

Tel G, Apaydın M, Duru ME, Öztürk M. (2012). Antioxidant and cholinesterase inhibition activities of three *Tricholoma* species with total phenolic and flavonoid contents: the edible mushrooms from Anatolia. Food Anal Method, 5, 495–504.

Terry AV, Buccafusco JJ. (2003). The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Ther, 306, 8211–827.

Virtanen JK, Mursu J, Tuomainen T, Voutilainen S. (2014). Dietary fatty acids and risk of coronary heart disease in men the Kuopio ischemic heart disease risk factor study. Arterioscler Thromb Vasc Biol, 34, 2679–87.

Wang MF, Chan YC, Wu CL, Wong YC, Hosoda K, Yamamoto S. (2004). Effects of Ganoderma on aging and learning and memory ability in senescence accelerated mice. Proceedings of the 2nd

International Conference on Senescence: The SAM Model, Sapporo, Japan.. In International congress series. Elsevier, 1260, 399–404.

Wasser SP. (2011). Current findings, future trends, and unsolved problems in studies of medicinal mushrooms. Appl Microbiol Biotechnol, 89, 1323–33.

Wolozin B, Kellman W, Ruosseau P, et al. (2000). Decreased prevalence of Alzheimer's disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol, 57, 1439–43.

Wolozin B. (2001). A fluid connection: cholesterol and Aβ. Proc Nat Acad Sci, 98, 5371–3.

Wong KH, Vikineswary S, Noorlidah A, et al. (2007). Activity of aqueous extracts of lion's mane mushroom *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae) on the neural cell line NG108-15. Intl J Med Mush, 9, 57–65.

Wong KH, Naidu M, David RP, et al. (2009). Functional recovery enhancement following injury to rodent peroneal nerve by lion's mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae). Intl J Med Mush, 11, 225–36.

Wong KH, Naidu M, David P, et al. (2011). Peripheral nerve regeneration following crush injury to rat peroneal nerve by aqueous extract of medicinal mushroom *Hericium erinaceus* (Bull.: Fr) Pers. (Aphyllophoromycetideae). eCAM, 2011, 580752.

Xu C, Yan HZ, Hong JZ, Jing G. (2008). The pharmacological effect of polysaccharides from *Lentinus edodes* on the oxidative status and expression of VCAM-1mRNA of thoracic aorta endothelial cell in high-fat-diet rats. Carbohydr Polym, 74, 445–50.

Yahaya NFM, Rahman MA, Abdullah N. (2014). Therapeutic potential of mushrooms in preventing and ameliorating hypertension. Trends Food Sci Technol, 39, 104–15.

Yang B, Kim G, Jeong Y, et al. (2003). Elevated β-secretase expression and enzymatic activity detected in sporadic Alzheimer's disease. Nature Med, 9, 3–4.

Yasojima K, Schwab C, McGeer E, et al. (2000). Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer's disease. Brain Res, 887, 80–9.

Yu HE, Lee DH, Seo GS, et al. (2007). Characterization of a novel β-hydroxy-β-methyl glutaryl coenzyme A reductase-inhibitor from the mushroom, *Pholiota adiposa*. Biotechnol Bioproc Eng, 12, 618–24.

Zandi PP, Anthony JC, Khachaturian AS, et al. (2004). Reduced risk of Alzheimer's disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol, 61, 82–8.

Zhang L, Peng SP, Han R, et al. (2005). A lipophilic fraction of *Ganoderma lucidum* promotes PC12 differentiation. Chin Pharmacol Bull, 21, 662.

Zhang R, Xu S, Cai Y, et al. (2011). *Ganoderma lucidum* protects dopaminergic neuron degeneration through inhibition of microglial activation. eCAM, 2011, 156810.

Zhao WQ, Alkon DL. (2001). Role of insulin and insulin receptor in learning and memory. Mol Cell Endocrinol, 177, 125–34.

Zhou X, Lin J, Yin, Y, et al. (2007). Ganodermataceae: natural products and their related pharmacological functions. Am J Chin Med, 35, 559–74.

Zhou ZY, Tang YP, Xiang J, et al. (2010). Neuroprotective effects of water-soluble *Ganoderma lucidum* polysaccharides on cerebral ischemic injury in rats. J Ethnopharmacol, 13, 154–64.