Volume 7, Issue 3, 2017, 2072 - 2084 ISSN 2069-5837

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

Review Article Open Access Journal

Received: 18.04.2017 / Revised: 20.05.2017 / Accepted: 28.05.2017 / Published on-line: 15.06.2017

Corroborative assessment of mushroom as the graceful ageing and lifespan promoting agent

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ABSTRACT

The unprecedented increase in the elderly population poses the threat of "ageing tsunami". Thus, graceful ageing representing the healthy life span is of immense importance in the modern world. Mushrooms, harboring numerous bio-active components, appear to be a promising anti-ageing agent. Mushroom myco-components' protective role against cellular ageing mediators, as well as those components' supportive effects for cellular longevity; have been reviewed in this article. Among multiple strategies, the direct life span extension of model organisms (*Saccharomyces cerevisiae, Caenorhabditis elegans* and *Drosophila melanogaster*) and human cell lines, along with oxidative stress attenuating, immune-modulating, anti-ageing, and anti-andropausal effects of mushrooms have been explored in this review. Assessment of edible-medicinal mushrooms with respect to their anti-ageing and lifespan promoting capabilities, stand them in ideal stead as a therapeutic agent for the global ever-mushrooming aged population.

Keywords: Ageing hallmarks; free radicals; healthy life span; immunomodulation; mitochondrial decline; oxidative stress.

1. INTRODUCTION

"Ageing" is an age-old, complex, inter- and multi-disciplinary concept which, all the living organisms undergo as a normal life spanning process [1,2]. It entails a diversified array of biochemical, molecular biological, physiological and pathophysiological features. It remains unclear whether ageing is the cause of physiological alterations, or inevitable effect of the pathophysiological abnormalities [1,2]. August Weismann proposed that ageing occurs as a response to environmental, physiological, and other stressors to which the body is constantly exposed [3]. This led to the concept of "stochastic theory of ageing" indicating the imbalance between the damaged and repaired cellular micro- and macromolecules, in which damaged bio-products influence cellular senescence, organ dysfunction, and ageing. As he considered ageing to be the gradual increased rate of damage to cells and tissues mediated by the free radicals, Harman (1955) put forwarded the "free radical theory of ageing", "(FRTA)" [4]. FRTA represented ageing as the gradual increased rate of morbidity and mortality along with free radical-induced, oxidative stress-mediated damage to cells and tissues. Beckman and Ames (1998) proposed a "mitochondrial decline theory of ageing" (MDTA) that correlated increased reactive oxygen species (ROS) generation by the mitochondrial respiratory chain with reduced energy production during cellular ageing [5]. Besides, cellular macromolecules, especially proteins, undergo configurational and conformational alteration during the ageing process. Repair and removal of the altered proteins by ubiquitin is essential for cellular functioning. Structural modification of proteins leading to misfolding, unfolding, or error-prone conformation and configuration have been identified to be associated with age-onset degenerative diseases like Alzheimer's and Parkinson's [6]. However, ageing research involving genetic markers has indicated organismal ageing as a predetermined and inherent process, much like other genetic information transfer [7]. Thus, the "genetic theory of ageing" has emerged. It postulates that ageing-specific genes become turned on or off whose manifestations are the ageing processes themselves. In addition, epigenetic mechanisms involving methylation of DNA and histones have also been linked with ageing processes which entail the "epigenetic theory of ageing'' [8].

Among many other theories, the "free radical theory of ageing'' has prevailed over the last few decades despite some criticism from several schools of anti-oxidant research [9]. López-Otín, Blasco, Partridge, Serrano & Kroemer (2013) have recently posited nine "hallmarks of ageing" including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [10]. Contrary to the previous notion, Gladyshev (2013) identified "ageing" as the imperfectness in the biological system emanated from non-random biomolecular damage that might be inherent, genetic and an inevitable program of life [11].

Although numerous studies have been conducted and more are ongoing worldwide, the mechanism of ageing remains a mystery. Ageing might not be properly described within the boundary of any single theory. It is likely that all theories and hallmarks have combined and/or collateral (so-called bystander) effects upon ageing, as depicted in Fig. 1. Thus, it is rather apt to consider "ageing as a special form of disease whose pathologies soars in advanced life''[12] and anti-ageing agents are supposed to withstand, albeit slow down, the pathologies of ageing. Human life span has increased globally, and advanced age has become a platform for multiple life threatening diseases and multi-morbidity [13, 14]. Elderly people negatively impact the labor force and economy. Thus, finding an active or graceful ageing agent is an

urgent need of the current world, and the quest for graceful ageing agent is leading to high-level breakthroughs in modern biological research. The present review has been aimed at corroborating mushrooms as graceful ageing and healthy life span-promoting agents. The information given here would greatly benefit the ageing tsunami-affected humanity, their care-givers, personnel involved in ageing and age-onset disease studies, as well as members of the general public searching for graceful ageing agents.

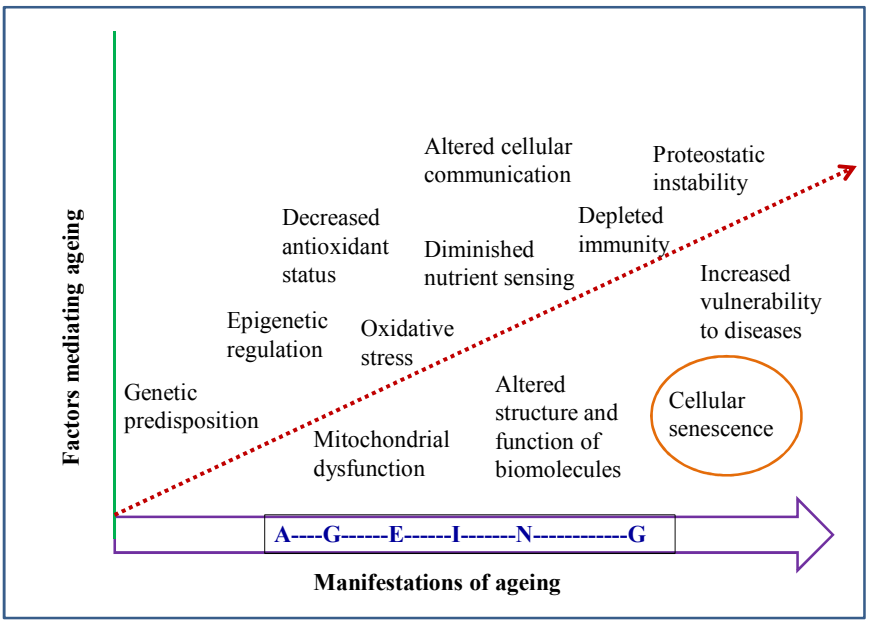


Figure 1. Multiple factors mediating ageing and ageing manifestations.

2. VALIDATION OF MUSHROOM AS A GRACEFUL AGEING AGENT

From ancient times, the usage of mushroom in culinary and medicinal practice has been practiced [15]. The following section interprets the mushroom, through justification of research findings, as a graceful ageing agent.

2.1. Regulation of ageing associated signaling pathways. Genomic studies have identified several conserved signaling pathways associated with ageing both in model organisms (C. elegans, D. melanogaster, mice, rat, chimpanzees) and in humans such as insulin/insulin like growth factor (IGF)-1, target of rapamycin (TOR) and Silent information regulators (sirtuins) signaling [16].

a. Insulin/IGF-1 signaling. Insulin/IGF-1 signaling is the first pathway identified to be associated with ageing [17]. It senses nutrients and its decreased signaling provides enhanced stress resistance as well as increased lifespan of the organisms [18, 19]. Its lifespan enhancement cascade involves the FOXO transcription factor, DAF 16; heat shock transcription factor, HSF-1 and Nrf-like xenobiotic-response factor SKN-1 [20]. Later on, these transcription factors regulate downstream genes involved in life span extension such as genes involved in stress resistance proteins (catalases, and metallothioneins, glutathione S-transferases) peptides, apolipoproteins, chaperones, ion-channels and lipases [21].

The regulatory mechanism for life span extension of C. elegans is associated with the insulin/IGF-1 signaling pathway that includes the trans-membrane receptor DAF-2, intracellular kinases and the DAF-16 protein [22]. DAF-16 is a forkhead/winged-helix transcript factor involved in the extension of normal life span of *C. elegans*. DAF-16 mutants have been found to have shorter lifespans than their non-mutant counterparts. DAF-2 is another homolog of the insulin/IGF-1 receptor, and its mutants have been claimed to achieve even up to doubled life span than those of their normal counterparts [22]. The entire process has been linked in such a way that DAF-2 signals to the DAF-16 through the phosphatidylinositol 3-kinase (PI 3-kinase)/Akt pathway. Phosphorylation of DAF-16 results in depleted nuclear accumulation and a shortened life span for *C. elegans* [22].

Chuang et al., (2009) studied the comparative cellular longevity effects of natural anti-oxidants, such as vitamins E and C, the vitamin B-complex group, acetic acid, *Ganoderma lucidum* (polysaccharide fraction, RF3), *Anthrodia camphorata* and *Hericium erinaceus* extracts on wild-type *C. elegans* [23]. *Ganoderma lucidum* (RF3 fraction) and the extracts of *A. camphorata* and *H. erinaceus* extend the lifespan of *C. elegans* by about 20–30%. All mushroom extracts increase the expression of the daf-16 gene [23]. In addition, *H. erinaceus* and acetic acid led to a decreased expression of daf-2 [23]. In another study, *G. lucidum* polysaccharide stimulated the transcription of tir-1 and rab-1/pmk-1 of the MAPK pathway, thus revealing the co-ordination between the life span and mitochondrial energy metabolism of *C. elegans* [24].

Ganodermasides A and B, isolated from *G. lucidum* spores, extended the replicative life span (RLS) of *S. cerevisiae*. They

stimulated the expression of the oxidative stress-responsive gene uth1 [25].

b. TOR signaling. TOR kinase is another nutritent sensor whose inhibition increases lifespan extension through heightened resistance to stressors [26]. Resveratrol had been identified as a cellular longevity increasing agent in *S. cerevisiae, C. elegans*, *D. melanogaster* and short-lived fishes [27, 28, 29]. Resveratrol content of 1.1mg/kg dry weight of *P. eryngii* has been reported [30]. Resveratrol inhibits TOR signaling through Sirt1-independent mechanism and promoting TOR/DEPTOR interaction [31].

c. Sirtuins. Sirtuins are the NAD+-dependent protein deacetylases involved in caloric restriction mediated cellular longevity [32]. In *S. cerevisiae*, over-expression of Sir2 increases the replicative lifespan (RLS) and its deletion decreases RLS [33, 34]. Sirtuin2 mediated lifespan extension involves reduced formation of toxic extrachromosomal rDNA and maintenance of telomeric gene silencing [33, 34]. Resveratrol can directly bind at the substrate binding site of sirtuins (Sirt1 and Sirt5) and stimulate cellular longevity up to 70% through sirt1-dependent deacetylation of p53 and sirt2-dependent enhanced DNA stability [27, 35].

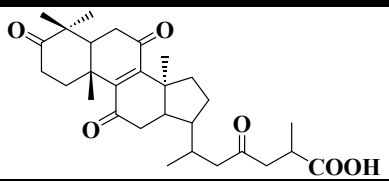
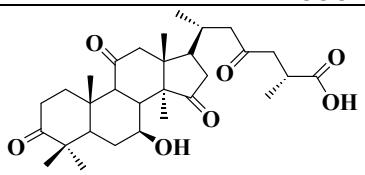
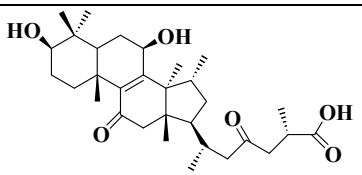
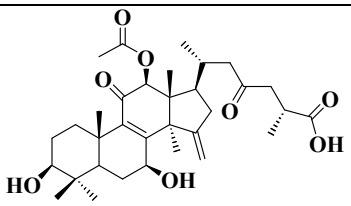
2.2. Mushroom bio-component mediated life span extension.

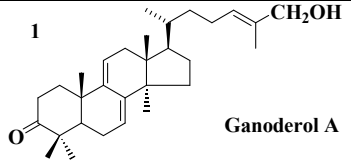
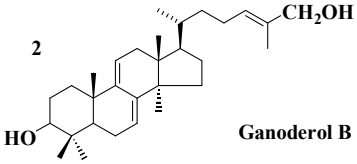
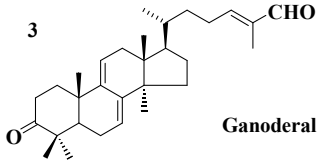
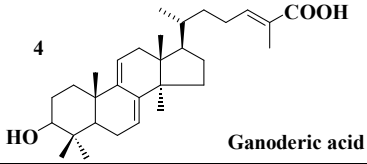
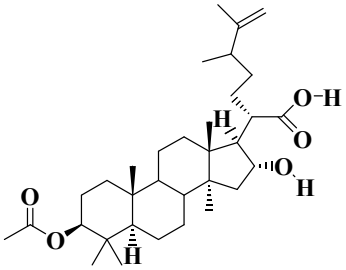
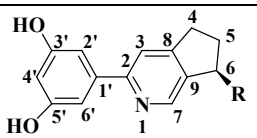
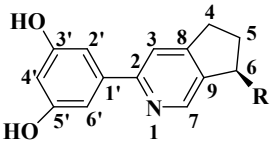
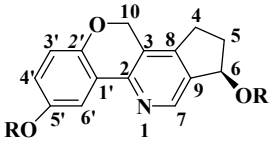
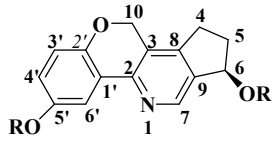
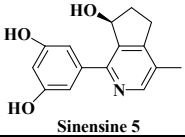
a. Protocatechuic acid. Rahman et al., (2014) showed the presence of polyphenol protocatechuic acid in *Flammulina velutipes* (Table 1) [36]. Inclusion of protocatechuic acid (PCA) in the medium at 200 µM concentration significantly increased the average lifespan of *C. elegans* from11.76 days up to 16.34 days with increased tolerance towards osmotic, thermal (transfer of worms containing NGM agar medium from 20°C to 36°C temperature for a 10 h) and oxidative stress (addition of 60 mM paraquant to the medium for 24 h) [37]. Protocatechuic acid had been found potent in withstanding ageing related oxidative stress and increasing aged rat's splenic weight, spleen and liver anti-oxidative enzymatic (catalase, glutathione peroxidase) levels and decrease lipid peroxidation [38].

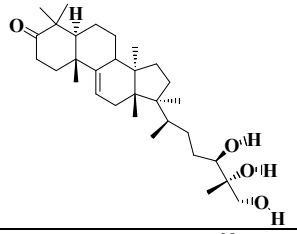
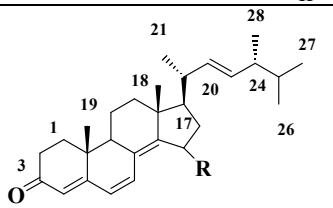
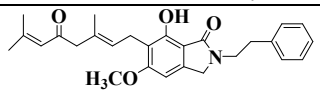
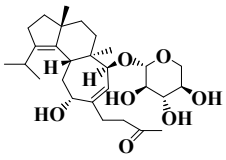
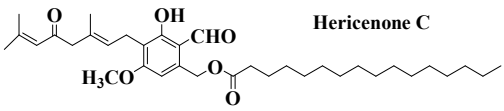
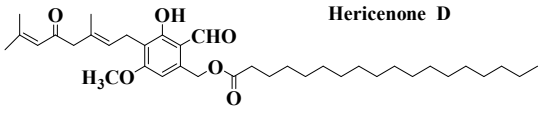
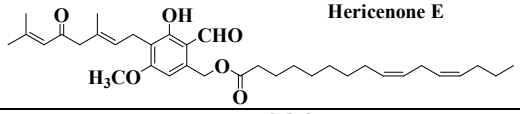
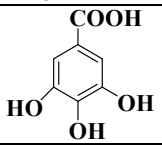
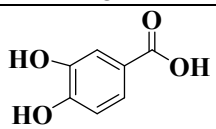
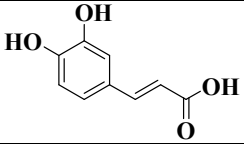
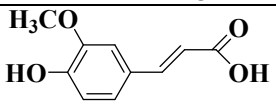
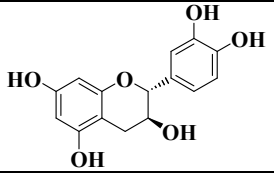
b. Caffeic acid. Caffeic acid concentration of 0.34µg/g dry weight of *S. commune* had been reported [39]. Caffeic acid phenyl ester (CAPE) also promotes lifespan extension of the *C. elegans* [40]. Medium supplanted with 100µM of CAPE increased median lifespan by 9% and maximum lifespan by 17%, respectively [40]. This lifespan promotion was performed through activation of the redox-sensitive insulin-like signaling pathway DAF-16 [40]. CAPE at 100µM concentration, increased nuclear localization of the transcription factor DAF-16, lowered cellular ROS level of C. elegans by about 50% and increased their thermo tolerance at 37°C (Table 1) [40].

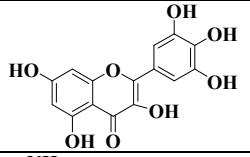
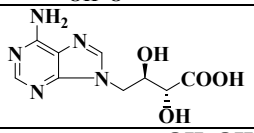
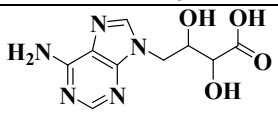
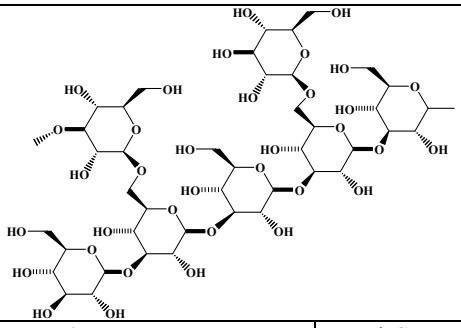
c. Lignan. Lignans are the polyphenolic substances having both *in vitro* and *in vivo* anti-oxidative effects (Table 1) [41]. Medicinal mushroom *Anthrodia camphorate* has been reported to contain lignan [42, 43]. Lignan matairesinol at 100µM has been found to increase the life span of *C. elegans* up to 25% [44]. They stimulate translocation and expression of the transcription factor DAF-16 and jnk-1[44]. Thus, lignans might be involved in lifespan prolonging effect of *C. elegans* through the JNK-1-DAF-16 mediated signaling cascade [44].

Table 1. Structures of the mushroom bio-components providing graceful ageing.

Compound	Structure	Source	Reference
Ganoderic acid T		*Ganoderma atrum*	[58]
Ganoderic acid C		*G. atrum*	[58]
Ganoderic acid C_2		*G. atrum*	[58]
Ganoderic acid K		*G. atrum*	[58]

Compound	Structure	Source	Reference
	 Ganoderol A  Ganoderol B  Ganoderal A  Ganoderic acid Y	*G. lucidum*	[57]
Tsugaric acid		*G. tsugae*	[57]
Sinensin(s)	 Sinensine B; [R=H]  Sinensine C; [R=OH]  Sinensine D  Sinensine E; [R=H]  Diacetyl Sinensine E; [R=Ac]  Sinensine 5	*G. sinense*	[58]

Compound	Structure	Source	Reference
Ganoder manotriol		*G. lucidum*	[58]
Ganoder masides A (1) and B(2)		*G. lucidum*	[25]
Hericinones and Ericanines	 Hericenone B  Erinacine K  Hericenone C  Hericenone D  Hericenone E	*Hericium erinaceus*	[52, 53]
Gallic acid		*Agaricus bisporus*	[39,58,72]
Protocatechuic acid		*A. bisporus*	[39,58,72]
Caffeic acid		*A. bisporus*	[39,58,72]
Ferulic acid		*A. bisporus*	[39,58,72]
Catechin		*A. bisporus*	[39,58,72]

Compound	Structure	Source	Reference
Myricetin		*A. bisporus*	[39,58,72]
Lentinacin		*Lentinula edodes*	[97]
Eritadenine		*L. edodes*	[74, 97]
Lentinan		*L. edodes*	

2.3. Experiments in *Drosophila melanogaster*. In *D. melanogaster*, both edible and medicinal mushroom extracts have been found to prolong the life span in a dose- and sex-dependent manner, as shown in the following chart [45]:

Mushroom species	Increased life span (%) in male *D. melanogaster*	Increased life span (%) in female *D. melanogaster*
A. auricular	31.41 (at 5 mg/ml)	16.85 (at 20 mg/ml)
A. blazei	32.13 (at 5 mg/ml)	2.69 (at 5 mg/ml)
L. edodes	40.53 (at 5 mg/ml)	6.03 (at 5 mg/ml)
G. lucidum	42.32 (at 80 mg/ml)	29.24% (at 5 mg/ml)

Recently, Zou *et al.,* (2015) reported the oxidative stress attenuation-coupled lifespan prolonging effect of *C. sinensis* upon *D. melanogaster* [46]. Lifelong feeding of *C. sinensis* oral liquid (CSOL) at 0.02, 0.06 and 0.20 mg/ml to the *D. melanogaster*, prolonged the average lifespan of the fruit flies by 25, 31 and 32%, respectively [46]. CSOL at the same dosage significantly increased the activities of anti-oxidant enzymes superoxide dismutase 1 (SOD1) and catalase (CAT) and inhibited the accumulation of lipofuscin in the fruit fly homogenate [46]. Thus, *C. sinensis* had been found promoting anti-aging effect through anti-oxidative mode of action in both physiological and pathophysiological states.

2.4. Experiments upon rodents. Feeding of *C. sinensis* hot water extract ameliorated aging related physiological complications such as memory enhancement, anti-oxidative defense and sexual functions in D-galactose-induced aged mice [47]. Mice fed hot water extract (10 ml/kbw) of *C. sinensis* had improved memory and learning abilities in water maze test [47]. Their blood level of anti-oxidative enzymes such as catalase, glutathione peroxidase and superoxide dismutase increased along with decreased rate of lipid peroxidation and monoamine oxidase activity [47]. Aging is associated with decreased desire of sexual functionality. *Cordyceps sinensis* improved sexual desire and function in the aged Sprague Dawley rats as evidenced by the decreased penile erection latency and mount latency [47].

2.5. Cell line studies. Ranging from model organisms, cellular longevity extending effects of mushrooms upon human cell lines has also been shown to be prospective. Extracts of both *G. pfeifferi* and *G. maresome* prolong the life span of human amniotic epithelial cell line (FL cells, ATCC, CCL 62) [48]. The perfusion cell culture study showed an increased longevity of the extracts treated cells up to 270 h, compared to 210 h for the controls [48]. Neuroactive compounds contained in *G. lucidum* and *G. neo-japonicum* has been reported to potentiate neuritogenic activities rat PC12 neuronal cells [49, 50]. The proposed mechanism of action entails the Ras/Erk and cAMP-response element-binding protein (CREB) signaling pathways, as *G. lucidum* extracts has been found to induce phosphorylation of Erk 1, Erk 2, and CREB [49, 50].

H. erinaceus is one of the most studied culinary mushroom for its neuro-health giving properties [51]. Polysaccharide from its aqueous extract has been reported to induce neuronal differentiation and promotion of neuronal survival [52]. Responsible bio-active components isolated included hericinones from the fruiting bodies and erinacines from the mycelium of *H. erinaceus* (Table 1) [52, 53]. Mild cognitive improvement in the *H. erinacus*-fed Japanese people has also been reported [54].

2.6. Anti-oxidative effects. Oxidative stress induced modification of biomolecules (lipids, protein and DNA) afflict physiological normalcy that is manifested through ageing associated diseases like cancer, atherosclerosis and Alzheimer's [55]. Thus, mitigation of oxidative stress seems promising in hindering the progression of cellular ageing. Both edible and medicinal mushrooms have been found to be oxidative stress retardant and thus pro-longevity agents. A double-blinded, cross-over intervention study reported the anti-oxidant status improving effects of *G. lucidum,* along with no deleterious action towards liver and kidney of the human subjects [56]. Ganoderic acids such as 3-oxo-5a-lanosta-8,24-dien-21-oic acid and tsugaric acid A, isolated from *G. lucidum* and *G. tsugae,* respectively, inhibited superoxide anion formation in

fMLP/CB-stimulated rat neutrophils and NO production in lipopolysaccharide (LPS)/interferon-c (IFN-c)-stimulated N9 microglial cells (Table 1) [57]. Ganoderic acids have been found to help prevent the proliferation of HeLa human cervical carcinoma cells. Underpinning mechanisms might involve alteration of the expression of the proteins involved in oxidative stress and other cellular mechanisms involved in carcinogenesis [25]. Sinensine, an alkaloid isolated from the fruiting bodies of *G. sinense*, has been found having ameliorating effect upon hydrogen peroxide-induced oxidative stress up on human vascular endothelial cell lines (HUVEC, EC50 value 6.2 mmol/L) (Table 1) [58].

Four polysaccharides (GLP-I, GLP-II, GLP-III and GLP-IV) extracted from *G. lucidum* grown on fermented soybean curd residue have shown anti-oxidant activities in a concentration-dependent manner along with stimulatory effects towards macrophage proliferation and NO production [59]. *Ganoderma lucidum* polysaccharide at 0.1, 1.0 and 10 µg/ml has been found to help prevent rat cerebral ischemic injury. The mechanism involves inhibition of apoptosis through down regulation of the caspase-3 activity and modulation of the Bcl-2/Bax ratio [60]. *Ganoderma lucidum* polysaccharide at 60, 120 and 180 mg/kg body weight has been reported to increase both nonenzymic and enzymic anti-oxidative defense along with increased serum insulin level and decreased lipid peroxidation and blood glucose levels in STZ-diabetic rats in a dose-dependent fashion [61]. *Ganoderma atrum* polysaccharide, PSG-1, has been reported to have a potent anti-oxidative, antihyperglycemic, antihyperlipidemic, antitumor activity and cardiomyocyte protective effects [62, 63]. PSG-1 increases SOD, CAT, GPx and glutathione reductase (GSH-Rd) activities, and reduced glutathione (GSH) contents in mice brain along with causing decreased MDA production and oxidized glutathione (GSSG) content [62]. Extract of *G. lucidum* grown on germinated rice, increases the activities of anti-oxidant enzymes (SOD, CAT and GPx) in different organs (livers and brains) and sera of mice [64]. This might be attributed towards its high phenolic and flavonoid contents [64].

Recently, we reported the *in vitro* anti-oxidative effect of *H. erinaceus* based on its solvent-solvent partitioned fractions' inhibitory effect upon human low density lipoprotein (LDL) oxidation and thereby the anti-atherosclerotic action of it (Figure 2) [65]. Ergosterol peroxide, a detoxificant of reactive oxygen species, present at appreciable amount in *H. erinaceus* might be attributed for this effect [65].

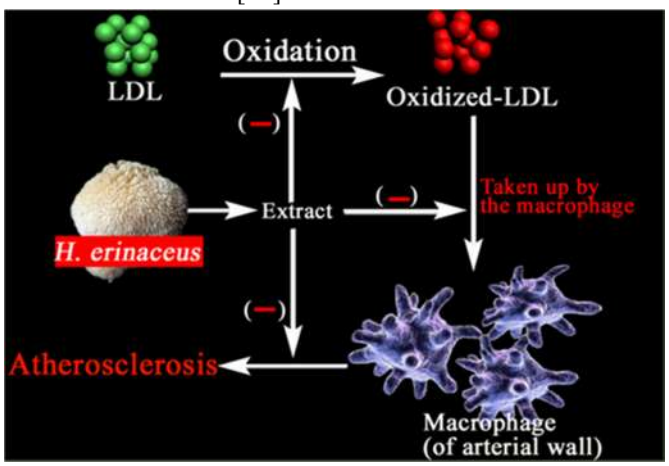


Figure 2. Anti-oxidative and anti-atherosclerotic effects of *Hericium erinaceus* extract.

The cyto-protective role of oyster mushrooms *(Pleurotus* spp.*)* against oxidative stress has been deduced by several studies. Oke and Aslim (2011) studied the *in vitro* anti-oxidant effects of the aqueous and methanolic extracts of *Pleurotus eryngii* and also evaluated their effect on the H_2O_2-induced cellular cytotoxicity. The aqueous extract showed better cyto-protective effect as evidenced by the 83.1% cell viability at 0.1 mg/ml in the MTT assay [66]. However, the ferrous ion chelating ability of the methanolic extract surpasses that of aqueous at 1 mg/ml concentration [66]. Polyphenolics present in the aqueous as well as carotenoid and ascorbic acid content of the methanolic extracts have been considered responsible for these effects [66]. Abdullah *et al.,* (2012) evaluated the comparative anti-oxidant potency of the edible-medicinal mushrooms and based on their relative antioxidative performance in percentage scale (100% for quercetin, the synthetic anti-oxidant control) graded them with individual anti-oxidant index [67]. Among the *Pleurotus* species, they graded the decreasing anti-oxidant index of the species at 10 mg/ml extract concentration as *Pleurotus flabellatus, P. florida, P. eryngii, P. sajor-caju, P. cystidiosus* [67].

Jayakumar *et al.,* (2007) reported that experimentally-induced, oxidative stress-mediated, multi-disrupted biochemical parameters' profile was ameliorated with the administration *P. ostreatus* extract [68]. Multi-organ specific (heart, kidney and liver) tests involving both antioxidative enzymes (CAT, SOD and Gpx) and vitamins (C and E) as well as lipid peroxidation and GSH, revealed the rejuvenating effect of *P. ostreatus* in such an extent that aged rats' diminished anti-oxidant status reverted back as if they were the young [69, 70]. Thus, the anti-oxidant arsenal of *P. ostreatus* was potent enough to retard oxidation-prone ageing processes and relevant physiological disorders. *Pleurotus sajor-caju* and *P. florida* has been reported to ameliorate the oxidative modification of the hypercholesterolemic rats [71]. Free radical scavenging intracellular polysaccharide (IPS) present in *P. nebrodensis, P. eryngii* and *P. cornucopiae* enabled these mushroom species to be superb anti-oxidant and anti-ageing agents [72]. Polysaccharide derived from *P. florida-Calocybe indica* somatic hybrid had also been reported performing oxidation-attenuating role (Maity *et al.,* 2011) [73].

Button mushrooms (*Agaricus bisporus)* are among the most popular culinary macrofungi. Reis *et al.,* (2012) compared the *in vitro* antioxidative and reducing capacities of some common mushrooms and found *A. bisporus* to be the best [74]. Comparatively high content of phenolic acids, protocatechuic acid, p-coumaric acid and cinnamic acid was supposed to confer this effect [74]. In another study, the antioxidative potential of *A. bitorquis* and *A. essettei* surpassed those of *A. bisporus* [75].

Among others, the lipid peroxidation inhibitory effect of *Volvariella volvacea* has been imparted to the phenolic compounds present [76]. Ear mushroom *(Auricularia auricula-judae)* has been reported having protective effect upon H_2O_2-induced oxidative cellular damage. *Auricularia auricula-judae* extracts (at 0.100 mg/ml) showed 89.5% viability of the baby hamster kidney fibroblast cell line (BHK 21) (Oke & Aslim, 2011) [66].

Thus, both the *in vitro* and *in vivo* studies involving multiple parameters of antioxidative studies support the oxidation-

withstanding effects of mushrooms that would promote the cellular longevity extending effect of this macrofungi.

2.7. Immuno-stimulating effects. The immune system of any organism becomes weak and prone to numerous diseases as ageing continues. The total decline in immunity of the aged individual is known as "immune-senescence", and the process is further exacerbated by the impaired communication among immunity-rendering cells, as well as their reduced responses [77, 78]. Sustained immune-senescence leads to the production and accumulation of excessive pro-inflammatory cytokines leading towards "inflamm-ageing". Inflamm-ageing is further compounded by genetic back-up which paves the way for pathogenesis of age-onset inflammatory diseases such as Alzheimer's. Thus, agents capable of retarding immune-senescence would also aid in healthy ageing.

The immune-stimulating effect of medicinal mushrooms has been performed by stimulating both the innate and adaptive immunity [79, 80]. Typically, innate immunity is the first line of defense where the phagocytic cells (dendritic cells, monocytes, macrophages, mast cells, natural killer cells, NK and polymorphonuclear neutrophils, PMN) engulf and/or attenuate the invading pathogens or the pathogenic components.

Mushrooms mediate innate immuno-stimulatory effects through their active bio-components such as polysaccharide glucan (both α and β) and glycoproteins. Their mode of action involves (i) enhanced production of cytokines (IL-10, IL-12p70 and IL-12p40) by dendritic cells (DC), (ii) stimulation of natural killer (NK) cells, and (iii) higher production of TNF-α, IL-1, IL-6, IL-8, IL-12p40, and NO, and expression of iNOS by macrophages [80, 81].

Agaricus bisporus has been reported to enhance the production of IFN- γ and thus upgrade the NK cell activity in mice along with the increased production of TNF-α and IL-12 [82]. Increased secretion of IFN-γ and IL-4 from T-cells through the induction of glycosphingolipid derived from *P. eryngii* have been reported [79]. β- D-glucan, extracted from *P. pulmonarius* and *P. ostreatus* have shown anti-inflammatory and inhibitory effect on leukocyte migration, respectively [83]. *Agaricus blazei* Murill (AbM) abounds with proteoglucans and β glucans [84]. These glucans are potent stimulators of macrophages, PMN and NK cells [84]. Binding of β glucan with the complement receptor 3 (CR3) (CD11b / 18), toll-like receptor 2 (TLR2) and dectin-1 causes the receptor stimulation followed by the release of the pro-inflammatory cytokines, nitric oxide and hydrogen peroxide lysosomal enzyme and activation of arachidonic acid metabolism [84]. Similar activities have been reported for other mushrooms, especially *G. lucidum* and *H. erinaceus* [85].

Adaptive immunity stands as the second line of defense and its actions are mediated by humoral and cell mediated sub-immunological processes. In humoral immunity, B cells produce antibody and fight against respective antigens. In cell mediated immunity, T cells of multivariate types guard against pathogens. For example, helper T cells (Th1 and Th2) produce cytokines, Th1 activates the macrophages, Th2 stimulates the B cells, and the cytotoxic T cells (Tc) lyse the infected cells.

Myco-components present in mushrooms aid in the modulation of both humoral and cell mediated adaptive immunity. For instance, lentinan from the *L. edodes* has been reported by Chihara *et al.,* (1986) to act as a T cell adjuvant [86]. Glucan derived from *Sclerotinia sclerotiorum* has been implicated in the development of Th1 cells [87]. Fungal immuno-modulatory proteins (FIPs) such as Fve, from *F. velutipes* and Vvo, from *V. volvaceae* stimulate Th1 cells activity and relevant cytokine production [88]. *Ganoderma lucidum* polysaccharide (GLP)-based enhanced production and proliferation of B lymphocytes along with increased antibody synthesis has also been evidenced [89]. *Ganoderma lucidum*-derived proteoglycan, GLIS, stimulates the expression of protein kinase genes, *PKC α* and *PKC γ* in B cells [90]. Schizophyllan, derived from the mushroom *Schizophyllum commune* has been reported to be equally potent immunostimulator as β-D-glucans for both adaptive and innate immunity (Table 1). Recently, development of schizophyllan-based drug delivery system for inflammatory bowel diseases (IBD) justifies its suitability and promises new vistas for the development of mushroom-based immuno-stimulating and anti-ageing approaches [91].

2.8. Skin anti-ageing property of mushrooms.

Extracts and nutricosmetics (bio-components ingested orally for skin revitalization) and cosmeceuticals (bio-component-based cosmetics used topically) derived from mushrooms have received considerable attraction world-wide [92]. Some of those mushroom species and the relevant myco-components' effect on skin revitalization have been depicted in table 2.

Table 2. Skin anti-ageing effects of mushroom and mushroom bio-components [92].

Cosmeceutical/ Nutricosmetic	Effects on skin	Source mushroom
Schizophyllan	decreases skin damages originated from UV and toxic component exposure	*S. commune*
Polysaccharide	Enhancing effect upon the skin anti-oxidant enzymes matrix metalloproteinase (MMT-1), tissue inhibitor of matrix metalloproteinase (TIMP-1) and collagen levels	*H. erinaceus*
Ganoderic acids	Antioxidative and antiageing effect	*G. lucidum*
Ergothioneine	Antioxidative and antiageing effect	*A. bisporus*
Ceramides	Epidermal moisturising effect	*Panellus serotinus, Lyophyllum connatum, Amanita pantherina, Sarcodon aspratus* and *Lepista nuda*
Chitin	Epidermal moisturising effect	*G. lucidum, L. edodes*
β-D-Glucan	Antioxidative and antiageing effect	*A. blazei, G. lucidum L. edodes Pleurotus* sp.
Superoxide dismutase	Anti-fibrosis effect through reverting myofibroblasts back to fibroblasts	*L. edodes*
Omega-3, omega-	Antioxidative and antiageing effect, inhibition of collagen	*A. blazei, C. sinensis, P. sajor-caju*

Cosmeceutical/ Nutricosmetic	Effects on skin	Source mushroom
6and omega-9 fatty acids	breakdown and improvement of cellular functions	
Trehalose	Anti-ageing supportive effects	*L. edodes, G. frondosa, Pholiota nameko, Auricularia auricular-judae*
Skin lightening and anti-ageing component	Anti-tyrosinase activity	*G. lucidum, Anthrodia camphorate, A. brasiliensis, Cordyceps militariss*
Skin lightening and anti-ageing component	Anti-oxidative, and anti-tyrosinase activity	*Pleurotus abalonus, Pholiota squarrosa, Pleurotus nebrodensis*

2.9. Age-onset menopausal problem amelioration. "Male menopause", also called "andropause" and/or "irritable male syndrome (IMS)" refers to hormonal, physiological and psychological abnormalities due especially to the decreased testosterone level or a reduction in the bioavailability of testosterone in aged males. About 40% of men in their 40s, 50s, and 60s experience some degree of andropause [93]. It has been associated with decreased libido, increased irritability, erectile dysfunction, depression, lethargy and cognitive dysfunction. Chung and Tong (2005) demonstrated the male menopause relieving effect of *G. lucidum* spores [94]. A 3 - week study involving 138 male subjects of average 66 years, showed significant improvements in all of the menopausal symptoms. These findings have reinforced the usage of mushrooms as a remedy for male geriatric diseases, including impotency.

2.10. Other cellular longevity and anti-ageing agents present in mushrooms. L-arginine has been suggested to have anti-ageing effects [95]. Mushrooms contain moderately high amount of this semi-essential or conditionally essential amino acid [96]. Arginine content has been reported to be as high as 179 mg, 127 mg and 116 mg per 100 g of fresh weight for *P. ostreatus, L. edodes,* and *A. bisporus,* respectively [96]. Thus, arginine-boosted mushrooms might come forward in guarding against ageing onslaught.

Lentinan, isolated from *L. edodes,* possess antihypertensive and antitumor effects while lentinacin and eritadenine have potent antihypercholesterolemic effects [97].

Selenium, a trace element in human nutrition, has been implicated having anti-ageing, anti-oxidant and numerous other functions [98]. However, its excessive amount and/or direct consumption would be cytotoxic and thus it necessitates biotransformation for its optimal and safe action [98]. Mushrooms have been proven to be the excellent biotransforming agent of selenium [99]. *Agaricus bisporus*, *Boletus edulis* and *G. lucidum* have been reported to be top-notch edible-medicinal mushrooms in providing anti-ageing trace element, selenium to human nutritional supplement [99].

3. CONCLUSIONS

Longevity is a multifactorial process that is influenced by genetic, biochemical, environmental and other known and unknown parameters. Demographical studies indicate that by 2017, the number of people over 65 years of age will surpass those under 5 years. By 2050, about one-fifth of all human beings will be over 60 years old [100 – 104]. Anxieties arising from the socio-economic burden of these "old folks" are experienced worldwide [105]. Understanding this crucial issue, the WHO coined the term 'active ageing' in the late 1990s and formulated its role under the program 'Active Ageing: a policy framework' [106, 107]. Mushrooms rank high as a tool for achieving WHO's goal of a healthy life span [108]. Myriad of bio-active components present in them confer their health-promoting as well as polypharmaceutic properties [108]. Mushrooms deserve "lifespan promoting" status due especially to their cellular longevity, immune-stimulating and antioxidative effects. They have also been highly reputed as "functional foods". Thus, as a food-based, safe and efficacious anti-ageing agent, the humble mushroom will be a strong help for ageing tsunami-affected humanity. Mushrooms fulfill the Greek maxim "to die as young as possible as old as possible".

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5. ACKNOWLEDGEMENTS

The authors gratefully thank University of Malaya for the grant UMRG RP014D-13AFR and the High Impact Research (HIR) grant UM.C/625/1/HIR/MoE/SC/02 from the Ministry of Education, Malaysia and Mohammad Azizur Rahman is grateful for the fellowship supported by the Bright Sparks Unit, University of Malaya.