Food Research International 105 (2018) 517–536

Contents lists available at ScienceDirect

Food Research International

journal homepage: www.elsevier.com/locate/foodres

Review

The potential applications of mushrooms against some facets of atherosclerosis: A review

Nur Amalina Amirullah[a,*], Nurhayati Zainal Abidin[a], Noorlidah Abdullah[a,b]

[a] Institute of Biological Sciences, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia
[b] Mushroom Research Centre, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia

ARTICLE INFO

Keywords:
Cardiovascular diseases
Fungi
Hyperlipidemia
Inflammation
Oxidative stress
Thrombosis

ABSTRACT

Atherosclerosis is a complex pathology that involves several factors in its development, like oxidative stress, inflammation, hyperlipidemia, platelet aggregation and thrombus formation. Several drugs and therapeutic approaches have been developed to handle these aspects of atherosclerosis. However, some of these treatments can be costly and have undesirable side effects. Many constituents of mushrooms have been shown to have potential anti-atherosclerotic effects in several *in vitro* and *in vivo* studies. Recently, the possible mechanisms in which they exert these effects have also been elucidated. In this review, some of the research focusing on mushrooms and their potential anti-atherosclerotic effects are examined. Many mushroom species exhibited anti-oxidative, anti-inflammatory and hypolipidemic effects that can potentially attenuate the progression of atherosclerosis, either through their isolated compounds or use of crude extracts. More studies are focused on the effect that mushrooms have on gene expressions that are involved in oxidative stress, inflammation, and hyperlipidemia. These studies could provide us with a better understanding on the mechanisms in which the consumption of mushrooms could exert their possible anti-atherosclerotic effects. Further research needs to be done to uncover other possible mechanisms that are affected by mushroom use.

1. Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVDs) are the number one cause of death globally (World Health Organization, 2017). CVDs have multifactorial etiology, but atherosclerosis is the main underlining pathology (George & Johnson, 2010; Mensink et al., 2003). Some potential risk biomarkers of CVDs include lipid and lipoprotein metabolism, hemostatic function, oxidative damage, homocysteine metabolism, and blood pressure (Guillamón et al., 2010).

Research for the past three decades has shown that various compounds obtained from a range of mushroom species have potent and distinctive properties (Wasser, 2011). Mushrooms can be added to normal diet and be consumed orally without the need to undergo phases I/II/III trials. Thus, they are considered as a safe and convenient approach for disease therapy (Lull, Wichers, & Savelkoul, 2005). These research findings bring about an increased interest in mushrooms both as a nutritional source and a potential mine of biopharmacological products (Gao, Chan, & Zhou, 2004; Mattila, Suonpää, & Piironen, 2000). As such, this review aims to summarize some *in vitro* and *in vivo* beneficial effects that several mushroom species have demonstrated against the multiple factors of atherosclerosis.

1.1. Atherosclerosis

Atherosclerosis is a disease in which the inner lining of arterial walls gradually thicken due to the formation of atheromatous plaques (Libby, Ridker, & Hansson, 2011; Lusis, 2000; Tortora & Derrickson, 2011). It is a multi-faceted, chronic disease, with decades of development before symptoms would become noticeable. It is thought that atherosclerosis is initiated when the endothelium is damaged, and the injury subsequently alters the endothelial function. The damage triggers various inflammatory and fibro-proliferative responses. This response-to-injury hypothesis was initially proposed by Russel Ross and colleagues about 30 years ago (Ross, Glomset, & Harker, 1977), and it has been further developed since then. Several risk factors are associated with atherosclerosis, such as diabetes mellitus, hypercholesterolemia, hypertension, obesity, oxidative stress, smoking, and sedentary lifestyle, among many others (Doll, Peto, Boreham, & Sutherland, 2005; Garcia, McNamara, Gordon, & Kannel, 1974; World Health Organization, 2002; Yusuf et al., 2004). The risk factors may exert their negative effects through intermediaries such as oxidized lipoproteins, free radicals like reactive oxygen species (ROS), elevated plasma homocysteine concentration, low blood shear stress, and inflammatory signals like

* Corresponding author.
E-mail address: amalinaamirullah@siswa.um.edu.my (N.A. Amirullah).

https://doi.org/10.1016/j.foodres.2017.11.023
Received 21 July 2017; Received in revised form 8 November 2017; Accepted 19 November 2017
Available online 21 November 2017
0963-9969/

cytokines (Ross, 1999). To add to the complexity, some of the risk factors may also interact in ways that would further worsen the disease (Lusis, 2000). The following sections focus on the beginning and progression of the atherosclerotic plaque, and also how the different risk factors play their roles in atherogenesis.

1.1.1. Endothelial dysfunction and inflammation

Atherosclerosis is considered to be a lipid metabolism disorder, but an estimated 50% of all strokes and myocardial infarction (MI) cases happened in individuals without increased cholesterol levels. This observation suggests that some other underlying pathophysiologic processes also contribute to atherosclerosis (Ridker, 2003). As mentioned previously, the "response-to-injury" hypothesis proposes maladaptive and chronic inflammatory responses as one such process that might promote this disease (Ross, 1999). Inflammation is a complex process that requires the participation of different cells, receptors, transcription factors, cytokines and molecules. Some of the most recognized inflammatory mediators include interleukins (ILs) such as IL-1β, IL-6, and IL-8, tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1), inducible cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), nuclear factor κB (NF-κB), and activator protein-1 (AP-1), among many others. Overproduction of these mediators can bring about various cell damage (Levine & Levine, 2012).

Endothelial dysfunction can be defined as the impairment of the vasorelaxation of the endothelium caused by the loss of nitric oxide (NO) bioactivity in the vascular walls (Cai & Harrison, 2000). NO is a small gaseous signaling molecule that is recognized as an atheroprotective species in the body, and it regulates several cardiovascular processes such as blood pressure and flow, smooth muscle cell (SMC) contraction, inflammation, and platelet activation. When endothelial dysfunction occurs as a result of reduced NO bioavailability and activity, it can lead to various vascular pro-inflammatory conditions (Hamilton et al., 2004).

The intima is made up of a single layer of endothelium, which sits atop of a basal lamina, while the media is mostly made up of smooth muscle cells (SMCs) embedded in extracellular matrix (ECM). When the endothelium is injured by aggravating stimuli (such as dyslipidemia, hypertension, or pro-inflammatory molecules), the biological responses elicited include upregulated adhesion molecule expression by endothelial cells (ECs), and increased permeability of the endothelium (Libby et al., 2011; Tabas, Williams, & Borén, 2007).

Platelets are the first to arrive at the site of injury, and they start adhering to the endothelium and aggregate (Massberg et al., 2002). These platelets are activated by various factors such as integrins, P-selectins, fibrin, thromboxane A_2 (TXA_2), and tissue factors (Ross, 1999). Once activated, the platelets release a variety of inflammatory factors, proteases, and vasoactive substances, thus further encouraging the effects of inflammation and endothelial damage (Langer & Gawaz, 2008).

In a normal healthy artery, leukocytes do not usually adhere to the endothelium. But endothelial damage causes the increased expression of adhesion molecules by the ECs, which results in leukocyte adhesion (Libby et al., 2011). Damaged vascular cells also express chemokines to signal and recruit leukocytes, such as monocytes, to the site of injury (Libby, 2002). The leukocytes that are recruited originally adhere weakly to the endothelium *via* adhesion molecules such as selectins, then they roll on the endothelial surface before transmigrating into the intima. Leukocyte extravasation from the arterial lumen into the intima is aided by integrin and immunoglobulin superfamily (Ig superfamily) molecules, such as the vascular cell adhesion molecule-1 (VCAM-1) and ICAM-1 (Huo & Ley, 2001).

The increased permeability of the endothelium also helps in the process of transmigration of the leukocytes (Huo & Ley, 2001). Other molecules such as LDL particles may also invade into the intimal layer due to the increased endothelial permeability. The retention, accumulation, and modification of LDL particles within the intima lead to further atherosclerotic development, especially when they are consumed by macrophages within the atherosclerotic plaque (Tabas et al., 2007).

1.1.2. Oxidative stress, foam cells and fatty streaks formation

ROS are involved in various intracellular signaling pathways, and usually the body has its own antioxidant systems to balance these reactive species. Some examples of ROS include superoxide (O^{2-}) hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl). Various enzymes can produce ROS in the body, such as NADPH oxidase (NOX), xanthine oxidase, and nitric oxide synthase (NOS). Although they are needed in several biological processes and pathways, overproduction of these reactive species can upset and disrupt many physiological processes (Hamilton et al., 2004). These reactive species are implicated in various atherosclerotic processes such as inflammation, apoptosis, vascular smooth muscle cells (VSMCs) replication, angiogenesis, and matrix turnover (Muzaffar, Shukla, & Jeremy, 2005).

Lipoprotein oxidation, particularly the oxidation of LDL, is known as one of the major risk factors in atherogenesis (Steinberg, 2002). The oxidative modification hypothesis postulates that oxidized LDL (ox-LDL), or any other lipoprotein, is involved in the process of atherogenesis (Witztum & Steinberg, 2001). Ox-LDL has several properties that makes it particularly proatherogenic, such as its enhanced uptake by macrophages, its ability to induce monocyte chemoattractant protein-1 (MCP-1) and macrophage colony stimulating factor (M-CSF) from ECs, it can cause an increase in collagen production in SMCs, it enhances the expression of VCAM-1, it can induce a number of proinflammatory cytokines in macrophages, and it can raise the tissue factor activities in ECs which are implicated in the process of thrombogenesis (Steinberg, 2009). The modified-LDL uptake by macrophages are believed to be mediated by several classes of scavenger receptors on the cells, such as scavenger receptor (SR) classes A, B, and C (Li & Glass, 2002).

Foam cell formation is thought to occur when LDL particles, especially modified ones, are taken up by macrophages in the intima (Witztum & Steinberg, 2001). Foam cells are relatively less mobile, and they become trapped in the intima and medial layers. They release cytokines, such as IL-1β and TNF-α, chemokines such as MCP-1, and ROS, which cause further recruitment of leukocytes at the site of injury and cause lipid modification at the vessel wall (Moore & Rayner, 2010).

Macrophages also have the ability to remove excess lipids through the reverse cholesterol transport (RCT) mechanism. This efflux mechanism is mediated by the ATP-binding cassette transporters (ABC transporters), such as ABCA-1 and ABCG-1. Cholesterol efflux has atheroprotective effects, thus it has been proposed that initially, lipid intake by macrophages is likely to be beneficial at the onset of endothelial injury (Ouimet, Wang, Cadotte, Ho, & Marcel, 2008). However, as the lipid accumulation increases within the macrophages, it overwhelms the efflux mechanism and ultimately results in the formation of foam cells (Moore & Rayner, 2010).

Chemokines and growth factors released by intimal cells and the damaged endothelium further recruit more cells, such as the T cells, to the site of injury (Boring, Gosling, Cleary, & Charo, 1998; Gosling et al., 1999). Accumulated cells in the intima, like monocytes and T cells, continue to release chemokines to further amplify the signaling and increase the inflammatory condition. The monocytes differentiate into macrophages when stimulated by various growth factors, like the M-CSF, and cytokines such as interferon-γ (IFN-γ) and TNF-α (Lusis, 2000). Chemokines also promote macrophage retention, and encourage VSMC migration and proliferation in the intima (Barlic, Zhang, Foley, & Murphy, 2006). As the inflammation progresses, more pro-inflammatory cytokines are produced, such as IFN-γ, IL-1, IL-2, IL-18, and TNF-α. However, some atheroprotective cytokines may also be released, like the transforming growth factor-β (TGF-β) and IL-10

(Askenasy, Kaminitz, & Yarkoni, 2008; Tedgui & Mallat, 2006).

The combined actions of the platelet aggregation, foam cell formation, chemokine and cytokine release, and increase in inflammation result in the formation of the fatty streak. Fatty streaks are prevalent in young people, asymptomatic, and they are the first visible indication of atherogenesis (Hansson, 2005; Steinberg, 2002). At this point, the atherosclerotic plaque is starting to develop and it marks the onset of atherosclerosis, but this development can still regress (Hansson, 2005).

1.1.3. Advanced plaque

In the event that the fatty streaks continuously develop into becoming more complex, then an advanced plaque is formed, which is characterized by the formation of a fibrous cap. The plaque can become established due to VSMC migration and proliferation in the intima, deposition of ECM components into the lesion, and apoptosis of foam cells. The VSMCs migrate from the medial layer into the intimal layer, and they proliferate in the intima. Secretion of several types of proteases, such as matrix metalloproteinases (MMPs), helps ease the migration of VSMCs into the intima (Newby, 2006). The fibrous cap is formed by the VSMCs, where it acts as a protective layer between the plaque and the arterial lumen (Libby et al., 2011). Several cytokines and growth factors, like platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2) and TGF-β stimulate the fibrous cap formation. These cytokines and growth factors are produced by degranulated platelets, ECs, macrophages, foam cells, and VSMCs. The VSMCs also secrete various ECM components into the lesion, further augmenting the plaque (George & Beeching, 2006; George & Dwivedi, 2004).

In the lesion, T cells and macrophages further accumulate, and there is a high chance for the immobile foam cells to undergo apoptosis, which can be triggered by several inflammatory cytokines. The dead cells deposit extracellular lipids, growth factors, and several other contents, which further contribute to the inflamed state of the lesion. The inability of the body to clear up the dead cell debris could lead to the formation of a necrotic core in the plaque (Tabas, 2010). The composition of a plaque is thought to contribute to its stability. A stable plaque has a relatively smaller necrotic core, lower contents of inflammatory cells, and a thick fibrous cap. In contrast, an unstable plaque has a bigger necrotic core with a thin fibrous cap, making it more likely to become ruptured (Lusis, 2000; Tabas, García-Cardeña, & Owens, 2015).

1.1.4. Unstable plaque

The unstable plaque is more likely to become ruptured due to several factors such as thinning of the fibrous cap, degradation of the matrix, and formation and thrombosis of microvessels in the plaque (van der Wal & Becker, 1999). Thinning of the fibrous cap can happen when plaque cells undergo apoptosis and proteases degrade the ECM. When VSMCs undergo apoptosis, the production of matrix contents is reduced, thus decreasing the tensile strength of the fibrous cap (Clarke & Bennett, 2006; Libby, 2009).

The different types of proteases produced in the plaque by different cell types worsen the inflammatory condition when they degrade the ECM components and cause further thinning of the fibrous cap. Macrophages secrete serine proteases, cathepsins, and MMPs, while mast cells produce serine proteases like chymase, tryptase, and cathepsin G, all of which further activate MMPs. Chymase can cause further VSMCs apoptosis by degrading ECM fibronectin and focal adhesion kinase (George & Johnson, 2010; J. L. Johnson, Jackson, Angelini, & George, 1998; Saarinen, Kalkkinen, Welgus, & Kovanen, 1994; Shamamian et al., 2001).

1.1.5. Thrombogenesis

Thrombogenesis can occur when the atherosclerotic plaque is ruptured or eroded. The rupture or erosion of the vessel endothelium can reveal many ECM components, such as collagen fibers and Von Willebrand factor (vWF) to the blood. Platelets adhere to these components *via* their specific receptors. Activated platelets secrete various soluble messengers and proteins, synthesize TXA_2 to recruit more platelets and inflammatory cells, and form a platelet plug that becomes the center for other coagulation factors in order to form a stable clot (Rauch et al., 2001).

The tethering of platelets to the endothelium is mediated by glycoprotein Ib (GPIb) on the platelets. GPIb interacts with vWF of the endothelium to first bind the platelets on the endothelium (Jackson, Nesbitt, & Kulkarni, 2003; Varga-Szabo, Pleines, & Nieswandt, 2008). Collagen receptors such as glycoprotein VI (GPVI), integrin $\alpha_2\beta_1$, fibronectin receptors $\alpha_5\beta_1$, and integrin $\alpha_{IIb}\beta_3$ are needed for more stable adhesion. The low-affinity collagen receptor GPVI can activate several signaling pathways once it binds to collagen, including activation of integrins $\alpha_2\beta_1$ and $\alpha_{IIb}\beta_3$ (Sachs & Nieswandt, 2007; Watson, Auger, McCarty, & Pearce, 2005). Once integrin $\alpha_2\beta_1$,which is a high-affinity collagen receptor, is activated, it strengthens the signaling induced by GPVI (Inoue, Suzuki-Inoue, Dean, Frampton, & Watson, 2003; Kuijpers et al., 2004).

Platelets also have mitogen-activated protein kinases (MAPK), that includes the extracellular signal regulated kinase 2 (ERK2), p38 MAPK, and c-Jun NH_2-terminal kinase 1 (JNK-1), all of which are activated by different agonists (Adam, Kauskot, Rosa, & Bryckaert, 2008). There have been reports indicating that ERK2 is involved in ADP-induced TXA_2 synthesis (Delgado-Lista, Garcia-Rios, Perez-Martinez, Lopez-Miranda, & Perez-Jimenez, 2011), while JNK-1 and p38 MAPK are implicated in platelet aggregation due to collagen binding (Kauskot et al., 2007). Thrombus that forms due to platelet aggregation can lead to many clinical symptoms, and it accounts for 30%–40% acute thrombotic events (Kolodgie, Burke, Wight, & Virmani, 2004).

Under normal circumstances, blot clot formation is needed to maintain the integrity of the blood vessel. The fibrin clot formed should then be disassembled rapidly and removed efficiently by the fibrinolytic system. Central to this system is the Serine protease enzyme plasmin, which is derived from the proenzyme plasminogen. Plasmin activators (PAs) such as tissue-type plasmin activator (tPA) and urokinase-type plasmin activator (uPA) are responsible for triggering the conversion of plasminogen into plasmin. Plasmin can then cleave fibrin to produce soluble fibrin degradation products and subsequently lead to clot disintegration (Collen, 1999). Various components such as fibrin, specific inhibitors, plasminogen and its activators, along with many others are needed to regulate the fibrinolytic system (Medved & Nieuwenhuizen, 2003). The overview of the platelet aggregation and fibrinolytic system is shown in Fig. 1.

Abnormal fibrin accumulation is one of the common causes of cardiovascular diseases. A thrombus could occlude blood vessels, and may cause conditions such as acute MI, high blood pressure, and stroke (Hansson, 2005; Mine, Kwan Wong, & Jiang, 2005).

1.2. Mushrooms

Mushrooms have been consumed and used in several regions and cultures of the world since ancient times (Wasser, 2011). In China, Japan, Korea, and eastern Russia, mushrooms like *Ganoderma lucidum* (Ling Zhi/Reishi), *Lentinula edodes* (Shiitake), and *Inonotus obliquus* (Chaga) have been gathered and used for therapeutic purposes for hundreds of years (Wasser, 2002). In rural areas of parts of eastern European countries, mushrooms such as *I. obliquus*, *Fomitopsis officinalis*, *Formes fomentarius*, and *Piptoporus betulinus* have been used to treat various types of ailments (Poder, 2005). In Mesoamerican cultures, the genus Psilocybe was especially used in traditional remedies, while in the African continent, reports of mushroom use can be traced in countries like Algeria, Benin, Egypt, and Nigeria. The Fly Agaric mushroom (*Amanita muscaria*) is especially prominent in various cultures or practices, such as in Buddhism, Celtic myths, and Siberia and Tibetan shamanism (Van Griensven, 2009; Wasser, 2010, 2011; Wasser

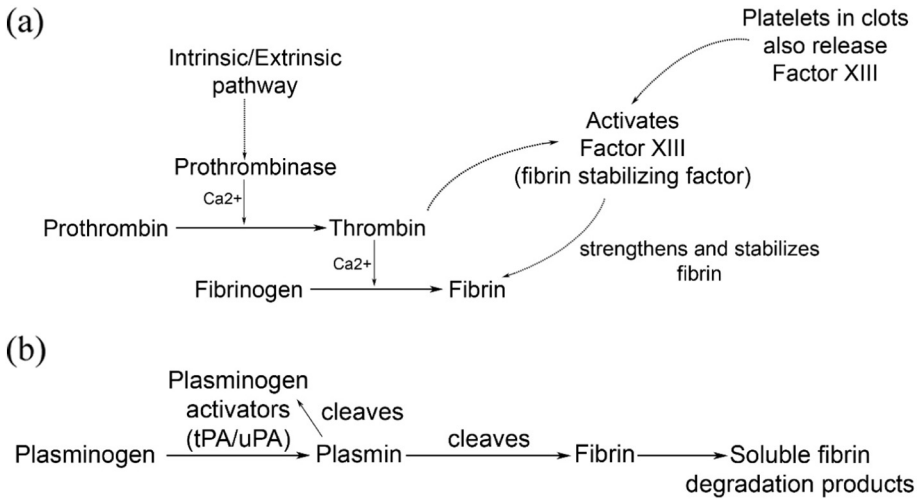

Fig. 1. (a): The pathways that lead to the formation of fibrin, which contributes to blood clot development.
(b): Overview of the fibrinolytic system, in which the insoluble fibrin is degraded by plasmin into soluble degradation product.

& Weis, 1999; Wasson, 1968).

According to Cheung (2010), mushrooms can generally be categorized into three groups, which are edible, medicinal, and poisonous. Edible mushrooms are usually fruiting bodies that can be consumed, either fresh (such as *Agaricus bisporus* and *Pleurotus ostreatus*), or in dried form (such as *L. edodes*) (Cheung, 2010; Paterson & Lima, 2014). Medicinal mushrooms are those not necessarily used for gastronomic reasons due to their tough texture and bitter taste, and they have bioactive constituents that have medicinal uses (such as *G. lucidum*) (Paterson & Lima, 2014; Wasser, 2010). Medicinal mushrooms are usually ingested in the form of powdered concentrates or extracts in hot water (Paterson & Lima, 2014). Poisonous mushrooms are the ones that have been confirmed to be or suspected of being poisonous (such as *Amanita phalloides*, the death cap) (Cheung, 2010). This review will focus on mushrooms that have the potential to alleviate some aspects of atherosclerosis, without necessarily distinguishing them as edible or medicinal ones.

Contemporary research corroborates the use of mushrooms for medicinal and therapeutic purposes. Some examples of medicinal functions by mushrooms are antitumor, immunomodulating, antioxidant, radical scavenging, cardiovascular, antihypercholesterolemia, antiviral, antibacterial, detoxification, hepatoprotective, and antidiabetic effects (Dai, Yang, Cui, Yu, & Zhou, 2009; Didukh, Wasser, & Nevo, 2003; Gao, Chan, et al., 2004; Gao, Lan, Dai, Ye, & Zhou, 2004; Gao, Zhou, Huang, & Xu, 2003; Ichinohe et al., 2010; Masuko et al., 2005; Rowan, Smith, & Sullivan, 2003; Sullivan, Smith, & Rowan, 2006; Wasser, 2010; M. Zhang, Cui, Cheung, & Wang, 2007).

The basic approach for mushroom extract preparation is to isolate, characterize, and administer pure active compounds to examine their biological effects. However, different components in a mushroom extract may act in a synergistic fashion in exerting their therapeutic effects (Borchers, Keen, & Gershwin, 2004; Vickers, 2002). For instance, there have been multiple reports of one mushroom species with many types of polysaccharides that have antitumor activities. This observation may be due to the different polysaccharides interacting with different cell receptors, thus resulting in different downstream responses. Consequently, the use of different combination of polysaccharides, with their concerted effort, may produce better antitumor effect than an application of only one single isolated polysaccharide (Borchers et al., 2004). Therefore, sometimes a pure mushroom compound may be utilized, but at other times the crude mushroom extracts might also be used.

1.2.1. Bioactive compounds of mushrooms

Mushroom bioactive metabolites can be obtained from their fruiting bodies, pure culture mycelia, and culture broth (Jong & Birmingham, 1992). However, the content, concentration, and type of these bioactive components may substantially vary depending on the strain substrate, cultivation techniques, developmental stage, age, storage condition, processing, and cooking methods of the mushrooms (Barros et al., 2007; Barros, Correia, Ferreira, Baptista, & Santos-Buelga, 2008; Mattila et al., 2001).

The bioactive compounds of mushrooms include polysaccharides, glycoproteins, proteins, lipids, and secondary metabolites (Lull et al., 2005). The polysaccharides are usually cell wall components, such as β-glucans (Sánchez, 2017). Some proteins from mushrooms have been discovered to have biological activities, such as lectins, proteases and protease inhibitors, ribosome-inactivating proteins, and fungal immunomodulatory proteins (Erjavec, Kos, Ravnikar, Dreo, & Sabotič, 2012). Some examples of secondary metabolites found in mushrooms are phenolic compounds, organic acids, terpenes, steroids, terpenoids, alkaloids, lactones, metal chelating agents, and vitamins (Sánchez, 2017; Valverde, Hernández-Pérez, & Paredes-López, 2015).

1.2.1.1. Polysaccharides. Polysaccharides are the renowned and most potent mushroom-based substance, with beneficial properties such as anti-tumor, antioxidative, antidiabetic, antimicrobial, anti-inflammatory, and immunomodulation (Bartczak et al., 2012; Valverde et al., 2015). The total carbohydrate content of mushrooms, comprising of both digestible and non-digestible ones, varies according to the species, ranging from 35% to 70% dry weight (Diez & Alvarez, 2001; Longvah & Deosthale, 1998; Mau, Lin, Ma, & Song, 2001). The digestible carbohydrates of mushrooms are usually present in small quantities at < 1% DW, while glycogen tend to be around 5–10% DW. Non-digestible carbohydrates include oligosaccharides like trehalose, and non-starch polysaccharides, such as chitin, β-glucans, and mannans (Cheung, 2010).

The major polysaccharide found in various mushrooms is the β-glucan, and around half the mass of mushroom cell walls are made up of β-glucans (Valverde et al., 2015). The β-glucans from several mushroom species have been shown to have several health properties, including anticancer, immunomodulating, anticholesterolemic, antioxidant, and neuroprotection. One possible explanation for these properties is their ability to bind to membrane receptors to induce biological responses (Falch, Espevik, Ryan, & Stokke, 2000; Ishibashi, Miura, Adachi, Ohno, & Yadomae, 2001; Kataoka, Muta, Yamazaki, & Takeshige, 2002; Khan, Tania, Liu, & Rahman, 2013). These β-glucans are not recognized as self-molecules and they are not synthesized by humans, thus β-glucans can induce both the innate and adaptive immune systems (Vetvicka & Yvin, 2004).

A number of biologically-active glucans have been isolated from several mushroom species. For instance, pleuran from *P. ostreatus*

(Karácsonyi & Kuniak, 1994), lentinan from *L. edodes* (T. Sasaki & Takasuka, 1976), schizophyllan from *Schizophyllum commune* (Bae et al., 2004), Maitake D-fraction from *Grifola frondosa* (Nanba, Hamaguchi, & Kuroda, 1987), and polysaccharide K (PSK) and polysaccharide-peptide (PSP) from *Trametes versicolor*. Some of these glucans have passed Phases I, II, and III in clinical trials in Japan and China (Smith, Rowan, & Sullivan, 2002). Nevertheless, the standards of these trials may not meet the current Western regulatory requirements. However, considerable improvements in the quality of life and survival of patients have been reported. A number of these compounds are currently in use in Japan, Korea, and China as adjuncts to the standard radio- and chemotherapy (Paterson & Lima, 2014).

Most of the studies involving polysaccharides use models to examine their effects on immunomodulation, and fewer studies have been carried out to discover their anti-inflammatory effects (Ramberg, Nelson, & Sinnott, 2010). The various bioactive properties of mushroom polysaccharides have been demonstrated in a number of *in vivo* and *in vitro* studies, however, the mechanisms of actions are still not fully understood (Cheung, 2009; Reshetnikov, Wasser, & Tan, 2001; Wasser, 2002; M. Zhang et al., 2007).

1.2.1.2. Peptides and proteins. Mushrooms produce many bioactive proteins, which are an essential portion of the functional component in mushrooms, and they have the potential for pharmaceutical applications. Mushrooms produce proteins and peptides with biological activities, which include lectins, fungal immunomodulatory protein (FIPs), ribosome inactivating proteins (RIPs), ribonucleases, and laccases (Xu, Yan, Chen, & Zhang, 2011).

Lectins are nonimmune proteins or glycoproteins that bind specifically to cell surface carbohydrates. It is probably the most researched mushroom protein, and over the past few years, several mushroom-derived lectins have been discovered. Some of these lectins possess antiproliferative, antitumor, and immunomodulatory activities. Some lectins have been isolated from *Pholiota adiposa*, *Hericium erinaceus*, and *Russula lepida* (Li, Zhang, Ng, & Wang, 2010b; Zhang, Sun, Wang, & Ng, 2009; Zhang, Sun, Wang, & Ng, 2010).

The ribosome inactivating proteins (RIPs) are enzymes that inactivate ribosomes by eliminating one or more adenosine residues from rRNA. Many RIPs have been purified from a number of mushroom species, including *Calvatia caelata*, *Flammulina velutipes*, *Hypsizygus marmoreus*, *Lyophyllum shimeji*, and *Pleurotus tuber-regium* (Lam & Ng, 2001a, 2001b; Ng, Lam, & Wang, 2003; H. X. Wang & Ng, 2001).

Laccases are phenol oxidases that can be found in basidiomycetes and ascomycetes. Some laccases isolated from mushrooms showed antiviral activities, such as those isolated from *Pleurotus eryngii* and *P. ostreatus* (El-Fakharany, Haroun, Ng, & Redwan, 2010; H. X. Wang & Ng, 2006), and those that showed antiproliferative activities, like those purified from *Tricholoma mongolicum* and *Clitocybe maxima* (Li, Zhang, Wang, & Ng, 2010a; Zhang, Wang, Zhang, Ng, & Wang, 2010).

The fungal immunomodulatory proteins (FIPs) are a new family of bioactive proteins that have been isolated from mushrooms. These proteins have biological activities including anti-tumor and immunomodulation. Researchers are studying the mechanisms of actions of these proteins. Some FIPs have been isolated from *F. velutipes*, *Ganoderma microsporum*, *Agaricus blazei*, *Coprinus comatus*, *G. frondosa*, *Volvariella volvacea*, *L. edodes*, *P. ostreatus*, and *Pleurotus citrinopileatus* (Chen, de Mejia, & Wu, 2011; Jeurink, Noguera, Savelkoul, & Wichers, 2008; Ko, Hsu, Lin, Kao, & Lin, 1995; Lin et al., 2010).

1.2.1.3. Lipids. Mushrooms in general have low fat content. Often, the unsaturated fatty acids are predominant over saturated fatty acids (Guillamón et al., 2010). Some of the common fatty acids found in mushrooms include palmitic acid, oleic acid, and linoleic acid (Carneiro et al., 2013; Reis, Martins, Barros, & Ferreira, 2012). The transisomers of unsaturated fatty acids have not been detected in mushrooms (Barros et al., 2007; Guillamón et al., 2010).

Terpenes are one of the most diverse group of bioactive compounds that can be found in mushrooms. Around 120 different types of triterpenes have been isolated from *G. lucidum* (H. W. Kim & Kim, 1999). Some of the triterpenes from *G. lucidum* have been shown to inhibit cholesterol synthesis (Komoda, Shimizu, Sonoda, & Sato, 1989) and to inhibit angiotensin converting enzymes (Morigiwa, Kitabake, Fujimoto, & Ikekawa, 1986), as well as having anti-viral (El-Mekkawy et al., 1998) and anti-platelet aggregation activities (Su, Shiao, & Wang, 1999).

The main sterol found in edible mushrooms is ergosterols, which has been proven to have antioxidant activities (Ferreira, Barros, & Abreu, 2009). Diets rich in sterols have been shown to be important in the prevention of CVDs (Kalač, 2013). Tocopherols, which are found in the lipid portion, are natural antioxidants and they act as free radicals scavengers (Heleno et al., 2012). Antioxidants are thought to confer protection to various diseases such as degenerative diseases, cancer, and CVDs (Hensley et al., 2004).

1.2.1.4. Phenolic compounds. Phenolic compounds are secondary metabolites, with aromatic ring structures that contain one or more hydroxyl groups. Their structures can range from simple phenolic molecule to complex polymer. Some examples of mushroom phenolics include phenolic acids, hydroxybenzoic acids, hydroxycinnamic acids, lignans, tannins, and oxidized polyphenols (Sánchez, 2017; Valverde et al., 2015).

These compounds display a wide array of physiological activities, including antiatherogenic, anti-inflammatory, antimicrobial, antithrombotic, cardioprotective, and vasodilator effect. These effects are often attributed to their antioxidant capabilities, which include their ability as reducing agents, free radical scavengers, and metal ion chelators (Balasundram, Sundram, & Samman, 2006; Ferreira et al., 2009; Heleno et al., 2012).

One study examined the content of phenolic compounds and antioxidant activities of *A. bisporus*, *Boletus edulis*, *Calocybe gambosa*, *Cantharellus cibarius*, *Craterellus cornucopioides*, *Hygrophorus marzuolus*, *Lactarius deliciosus* and *P. ostreatus*. The mushrooms *C. cibarius* and *C. cornucopioides* showed the greatest antioxidant activities. In the study, *C. cornucopioides* had the highest amount of myricetin while *C. cibarius* had the highest amounts of caffeic acid and catechin compared to the other mushrooms studied (Palacios et al., 2011). Another study was conducted to examine the phenolics content and antioxidant activities of edible (*P. ostreatus*, *A. bisporus*, *F. velutipes*, and *P. eryngii*) and medicinal (*A. blazei*, *Sparassis crispa*, *G. lucidum*, *I. obliquus*, and *Phellinus linteus*) mushrooms from Korea. The phenolics compounds found in the medicinal mushrooms studied, which include gallic acid, homogentisic acid, 5-sulfosalicylic acid, catechin, caffeic acid, syringic acid, *p*-coumaric acid, benzoic acid, myricetin, resveratrol, and kaempferol, all showed positive correlation with their antioxidant abilities (Kim et al., 2008).

1.2.2. Safety of mushroom use

The safety of several mushrooms has been studied, with some accounts of toxicity. Despite this, mushroom polysaccharides have shown few adverse effects in Phase I clinical trials (Smith et al., 2002). A number of purified mushroom polysaccharides have been in clinical use in Japan, Korea, China, and recently in USA for several years, with no reports of short-term or long-term toxicity. The safety of mushroom polysaccharides is mainly based on the No-Observed-Adverse-Effect-Level (NOAEL) acute and/or chronic toxicity testing in rodents (Paterson & Lima, 2014).

A study was conducted to evaluate the safety of orally-administered *L. edodes* on male Wistar rats for 30 days. From this study, the authors suggested that the daily intake of 100 mg/kg of *L. edodes* was safe (Grotto et al., 2016). A pilot study was done to investigate the effect of *L. edodes* mycelia extract (L.E.M) on 7 patients undergoing chemotherapy in Japan. The patients underwent the first course of

Table 1
Some mushroom species and their effects on cardiovascular diseases.

Mushroom species	Animal model	Effects on cardiovascular diseases	Reference
Ganoderma lucidum	SHR rats	Lowered blood pressure, plasma and liver total cholesterol	Kabir et al. (1988)
Grifola frondosa	SHR rats	Decreased total cholesterol level and VLDL-cholesterol	Kabir et al. (1987)
Hypsizygus marmoreus	ApoE$^{-/-}$ mice	Lowered serum total cholesterol, decreased atherosclerotic lesion	Mori et al. (2008)
Lentinula edodes	SHR rats	Decreased plasma free cholesterol level	Kabir et al. (1987)
Pleurotus nebrodensis	SHR rats	Inhibited elevation of blood pressure	Miyazawa et al. (2008)
Pleurotus ostreatus	Wistar rats	Decreased VLDL, LDL, and HMG-CoA reductase activity	Bobek et al. (1995)

HMG-CoA reductase, 3-hydroxy-3-methylglutaryl CoA reductase; LDL, low-density lipoprotein; SHR, spontaneously hypertensive rats; VLDL, very low-density lipoprotein.

chemotherapy treatment on the first 4 weeks, then a second course of chemotherapy along with L.E.M. oral consumption at 1800 mg/day for the following 4 weeks. The authors concluded that the ingestion of L.E.M. was safe and effective for cancer patients undergoing chemotherapy, but acknowledged the need for a larger scale study to be conducted to verify the results obtained (Yamaguchi, Miyahara, & Hihara, 2011).

One report documented the possible hepatotoxicity of *Agaricus subrufescens* extract in advanced cancer patients. In this report, one patient's liver function returned to normal after she stopped taking the *A. subrufescens* extract, while the other two patients died due to fulminant hepatitis. The specific doses or duration of consumption of the *A. subrufescens* extract by each patient was not reported. While there were strong correlations between the *A. subrufescens* extract consumption and liver dysfunction in these patients, there are other possible factors that might have also played a role in the observed hepatotoxicity and/or death (Mukai, Watanabe, Ando, & Katsumata, 2006; Paterson & Lima, 2014; Ramberg et al., 2010). However a different study conducted on 46 healthy adults showed that ingestion of freeze-dried *A. subrufescens* was safe. The participants consumed the mushroom treatment (3 g) twice a day for 12 weeks, and there was no evidence of toxicity found at the end of the study (Kajimoto, Ikeda, Yabune, Sakamoto, & Kajimoto, 2006). Another study conducted on F344/DuCrj rats also showed that diet supplemented with *A. subrufescens* for 90 days did not cause any severe toxicity, even at the highest dose of 5% supplementation (Kuroiwa et al., 2005).

There was one report of hepatotoxicity in a 78-year-old woman after the ingestion of a powdered form of *G. lucidum* for 4 weeks. All her liver biochemical parameters improved 5 months later, after she stopped taking the *G. lucidum* powder formulation. It is worth noting that the patient had been consuming *G. lucidum* preparation by boiling the fungus in water for a duration of one year prior, and had no complications. However, she changed to the powdered formulation and began consuming it for 4 weeks, after which her liver symptoms began appearing. It is possible that the powdered form had some additional additives that might have contributed to the hepatotoxicity observed (Yuen, Ip, Ng, & Lai, 2004).

One study on Charles River rats showed that consumption of *Coriolus versicolor* (CV) biomass administered as food supplement for 90 days was safe, with the NOAEL of the CV biomass being 7.5 g/kg. In a different study, erinacine A from the mycelium of *H. erinaceus* was orally-administered to Sprague-Dawley female rats. The results showed no systemic toxicity could be attributed to the mushroom treatment, and the NOAEL of the erinacine A is > 3 g/kg body weight/day (Li et al., 2014).

Mushroom extracts are often considered to have low toxicity, even when they are consumed on a regular basis and in high dosages (Chang & Miles, 2004). Despite this, there are many more mushroom species that still need to be verified in terms of their toxicological effects and safety. Adding to the complexity is the various methods of preparations of mushrooms (e.g. crude extract, concentrated powder, purified extracts) and the lack of standardization for the determination of safety of these mushrooms or mushroom preparations. This is a subject matter that needs attention and more vigorous research. Double blind, placebo-controlled with a large sample size studies should be conducted to help shed some light into this issue (Wasser, 2011).

1.2.3. Mushrooms and cardiovascular diseases

Where CVDs are concerned, various mushroom species have been shown to exert positive effects in managing these diseases. *L. edodes*, *H. marmoreus*, *F. velutipes*, and *A. bisporus* have been shown to have hypocholesterolemic effects on murine models (Kaneda & Tokuda, 1966; Mori, Kobayashi, Tomita, Inatomi, & Ikeda, 2008). *P. ostreatus* has been shown to inhibit lipid peroxidation and suppress 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) in normal and hypercholesterolemic animal models (Bobek & Galbavý, 1999; Bobek, Hromadová, & Ozdín, 1995; Bobek, Ondreicka, Klvanova, & Ozdin, 1994; Bobek, Ozdín, & Galbavý, 1998). HMG-CoA reductase is an enzyme that is involved in a committed and rate-limiting step in the cholesterol biosynthesis pathway. Inhibiting the activity of this enzyme has been shown to aid in lowering plasma cholesterol level (Nelson, Lehninger, & Cox, 2008). HMG-CoA reductase competitive inhibitors have been isolated from mushrooms, such as mevinolin from the *Pleurotus* sp. Mevinolin, also known as lovastatin, is the first statin to be approved for clinical use (Alberts, 1990). Mushroom species such as *L. edodes*, *G. lucidum*, *G. frondosa*, and *Pleurotus nebrodensis* also show hypotensive effects in rats when blood pressure is already high (Kabir, Kimura, & Tamura, 1988; Kabir, Yamaguchi, & Kimura, 1987; Miyazawa, Okazaki, & Ohga, 2008). Furthermore, various antioxidant and anti-inflammatory compounds of mushrooms may contribute in the prevention or treatment of CVDs (Guillamón et al., 2010). Table 1 shows some mushroom species and their effects on CVDs.

Up until now, the mechanism of action of most mushroom species in the prevention or treatment of CVDs (and other diseases) remains unclear (Guillamón et al., 2010; Wasser, 2011). Despite that, some studies have shown that mushrooms have the possibility to ameliorate certain disease conditions (Ahn et al., 2004; Førland et al., 2011; Gunde-Cimerman, 1999; Hsu, Hwang, Chiang, & Chou, 2008; Johnson et al., 2009; RP et al., 2010). It is considered beneficial to utilize mushrooms in complementing standard medicinal practices (Chang & Miles, 2004).

2. Antioxidative effects of mushrooms

Antioxidant defense in an organism depends on the endogenous antioxidant systems, and also its dietary intake. The major ROS defense mechanisms include the enzymatic and non-enzymatic systems. The enzymatic system involves many different antioxidant enzymes, and some of the major ones include catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase. The non-enzymatic antioxidants include low-molecular weight molecules such as vitamins A, C, and E, carotenoids, and polyphenols, large molecules such as albumin, cerruloplasmin, transferrin, and ferritin, trace elements such as zinc, copper, manganese, iron, and selenium, hormones with antioxidative properties such as estrogen and angiotensin, and some major antioxidative substances such as glutathione (GSH) and melatonin (Chakrabarti, Lekontseva, & Davidge, 2008; Díaz-Reinoso, Moure, Domínguez, & Parajo, 2007; Finkel & Holbrook, 2000; Kozarski et al., 2015; Newman & Maisels, 1992; Strehlow et al., 2003).

Various substances detected in the mushroom fruit body, mycelia, and broth have been shown to contain antioxidative-related compounds such as phenolics, flavonoids, glycosides, polysaccharides, tocopherols, ergothionine, and ascorbic acid (Kozarski et al., 2015). There are two main types of mushroom antioxidants. The primary mushroom antioxidants have properties such chain-breaking and free radical-scavenging. The secondary or preventive mushroom antioxidants are able to deactivate metals, inhibit or break down lipid hydroperoxides, and induce regeneration of primary antioxidants. Some mushroom extracts are also able to affect cellular signaling, which enable them to cause changes in gene expression and subsequently activate antioxidative enzymes (Finley et al., 2011; Guo, Ji, & Ping, 2009; Jia et al., 2009; Ping et al., 2009).

Over the past decade, vigorous *in vitro* and *in vivo* research has been done to elucidate the antioxidative properties of different mushroom species. Fu, Wang, Wang, Yang, and Hao (2013) investigated the effects of *Morchella esculenta* extracellular polysaccharide (MEEP) in aging mice models for 60 days (Fu et al., 2013). They found that subcutaneous insertion of MEEP at doses of 200 and 400 mg/kg of body weight were able to significantly increase the total antioxidant content (T-AOC), SOD, and CAT enzymes in the blood, and increased in T-AOC, SOD, CAT, and GPx enzymes in the liver of the animal models. Added to that, at 400 mg/kg of MEEP, the extract was able to significantly reduce the malondialdehyde (MDA) levels in mice. MDA is a byproduct of lipid peroxidation that is often used as an indicator of the extent of damage done by oxidation, and a lower MDA level signifies lesser oxidative-induced damage (Fu et al., 2013). The authors suggested that the MEEP might have exerted its antioxidative effects by inducing the expressions of endogenous antioxidative enzymes like SOD, GPx, and CAT. However their exact mechanisms were not known (Fu et al., 2013).

The *in vitro* and *in vivo* effects of the ethanolic extract of *A. bisporus* were studied (Liu, Jia, Kan, & Jin, 2012). However, they discovered that the extract showed better antioxidant effects in the *in vivo* experiments using mice than it did in the *in vitro* ones. In all of the *in vitro* tests, which includes superoxide, hydroxyl, 2,2-diphenyl-1-picrylhydrazyl (DPPH), and hydrogen peroxide scavenging assays, the control using vitamin C had lower IC_{50} values in all of them than did the extract. However, the *in vivo* experiments showed otherwise, with mice fed 1200 mg/kg of body weight of the ethanolic extract for 30 days having higher levels of SOD, GPx, and CAT in their blood, liver, and heart compared to saline- and vitamin C-treated mice. They suggested that the *in vivo* results may be more important to be taken into consideration than did the *in vitro* ones when it comes to evaluating mushrooms' antioxidant properties, since *in vivo* trials took into account the various physiological and metabolic conditions in the body. The main phenolic compounds identified from the ethanolic extract include gallic acid, protocatechuic acid, catechin, caffeic acid, ferulic acid, and myricetin. The antioxidative effects of the studied *A. bisporus* ethanol extract might be attributed to these phenolics. Further fractionation and identification of ethanolic compounds have to be carried out to better understand their antioxidative mechanism of actions (Liu et al., 2012).

Another experiment was conducted to study *Mycoleptodonoides aitchisonii* ethyl acetate extract (EAMA) on murine macrophage RAW 264.7 cells and on mice (Kokubo et al., 2011). RAW 264.7 cells that were treated with 100 μg/mL and 200 μg/mL of EAMA showed increased expression of the Antioxidant Response Elements (ARE) than untreated cells. Macrophage cells treated with 400 μg/mL of the extract also showed increased levels of detoxifying enzymes such as NAD(P)H dehydrogenase [quinone] 1 (NQO1), and glutathione S-tranferase (GST), as well as endogenous antioxidant enzymes like heme oxygenase 1 (HO-1), and glutamate cysteine ligase catalytic subunit (GCLC). The expressions of *NQO1*, *GSTM1*, *HO-1*, and *GCLC* were dose-dependently induced by EAMA in peritoneal macrophages from wildtype mice, but the induction of *NQO1*, *GSTM1*, and *GCLC* was not detected in the macrophages of Nrf2-deficient mice. For the *in vivo* approach, oral feeding of EAMA to mice at 15 mg/day and 30 mg/day could increase NQO1 and GST transcription in the liver and small intestine, and increased NQO1 enzyme activity. Eleven bioactive compounds were isolated from EAMA, of which dihydro-4-phenyl-2(3H)-furanone showed the highest ability to induce NQO1. The major transcription factor for activating ARE-dependent genes is the Nrf2. It is thought that under low oxidative stress, Nrf2 is activated to stimulate the expression of antioxidant enzymes (Gloire, Legrand-Poels, & Piette, 2006). The results showed that EAMA might have exerted its antioxidative effects by modulating the activity of Nrf2 at the transcription level (Kokubo et al., 2011).

Many research has been done to test the *in vivo* antioxidative effects of different mushroom extracts. Some examples of mushrooms include *Morchella esculenta*, *P. eryngii*, *P. ostreatus*, *L. edodes*, and *A. bisporus*, all of which have been shown to be able to increase antioxidant enzymes such as CAT, SOD, GPx and/or GST in many murine models. A majority of the mushroom species studied also had the ability to reduce MDA or carbonyl levels in animal organs (Jayakumar, 2010; Meng et al., 2010; Reis et al., 2012; Sun et al., 2014). More research are being carried out to identify bioactive compounds that contribute to the antioxidative properties of mushrooms. Some studies show that these bioactive components might modulate the activity of transcription factors involved in activating antioxidant enzymes. Some of the results of the *in vitro* and *in vivo* antioxidant effects of several mushrooms have been summarized in Table 2.

3. Anti-inflammatory effects of mushrooms

In recent times, more attention has been given into utilizing mushrooms and their metabolites for their anti-inflammatory activities. For example, many water, methanolic, ethanolic, and ethyl acetate extracts of mushrooms have been shown to lower the production of inflammatory mediators by down-regulating the gene expression of these molecules (Elsayed, El Enshasy, Wadaan, & Aziz, 2014).

3.1. Cytokines and transcription factors

A study on apolipoprotein-E deficient male mice ($ApoE^{-/-}$) showed that the low-molecular weight extract of *Grifola gargal* (GGE) was able to ameliorate atherosclerosis (Harada et al., 2015). Atherosclerosis was induced in the animals *via* intraperitoneal injection (i.p.) of angiotensin II (Ang II), then saline or GGE was administered to the mice by the same route for 28 days. Atheroma lesions on the thoracic and abdominal aorta were significantly lowered in mice treated with GGE. Mice treated with GGE had lower plasma level of MCP-1, but elevated levels of $CD4^+CD25^+$ T regulatory cells (T_{reg}), CXCL12, and vascular endothelial growth factor (VEGF). T_{reg} cells are a population of T cells that suppress other immune cells once the immune response is completed. Increase in this cell population is thought to alleviate atherosclerotic effects (Mor et al., 2007; Sasaki, Yamashita, Takeda, & Hirata, 2012; Shimada, 2009). The authors proposed that *G. gargal* exerted its anti-atherosclerotic effects by stimulating T_{reg} cell populations and increasing levels of CXCL12, VEGF and TGF-β1, all of which might contribute to better vascular repair while also reducing inflammation in the lesions. Since only fractions with molecular weight of < 6000 Da were used in this study, the oral consumption of GGE was expected to be readily absorbed from the digestive tract (Harada et al., 2015).

The methanolic extract of *Antrodia cinnamomea* mycelia (MEMAC) was able to reduce the levels of TNF-α, IL-6, NO, PGE2, iNOS, and COX-2 in stimulated macrophage cells. Two compounds, camphorataanhydride A and camphorataimide B, which are maleic and succinic acid derivatives, were isolated from the extract. These derivatives might have contributed to the anti-inflammatory activities of *A. cinnamomea* (Wen et al., 2011). Moro et al. (2012) studied the methanolic extracts of *A. bisporus*, *B. edulis*, *C. cibarius*, *C. cornucopioides*, *L. deliciosus*, and *P. ostreatus*. Of these, only *A. bisporus*, *C. cibarius*, *C. cornucopioides*, and *L. deliciosus* extracts reduced iNOS mRNA expression and lowered NO

Table 2
The *in vitro* and *in vivo* antioxidative effects of various mushroom species.

Species	Mushroom constituent(s)	*In vitro/in vivo*	Extract dose(s)	*In vitro* and/or *in vivo* effects	Reference
Morchella esculenta	Extracellular polysaccharide (MEEP)	*In vitro*	0.081, 9.163, 0.325, 0.650, 1.300 mg/mL	Dose-dependent effect on hydroxyl and DPPH-scavenging activity and reducing power.	(Fu et al., 2013)
		In vivo	100, 200, 400 mg/kg b. w.	Male ICR strain mice; extract administered via gastric intubation for 60 days: ↑ T-AOC, SOD, and CAT enzymes in mice blood. ↑ T-AOC, SOD, CAT, and GPx enzymes in mice liver. ↓ MDA levels in mice blood and liver.	
	Exo-polysaccharide (EPS)	*In vivo*	25, 50, 100, 200, 400 mg/kg b. w.	Male Kunming mice; extract administered via oral gavage for 28 days: ↑ SOD, GPx enzymes, ↓ MDA levels in heart, liver, spleen, kidney and blood of mice treated 400 mg/kg b. w. EPS.	(Meng et al., 2010)
Agaricus bisporus	Ethanolic extract	*In vitro*	0–5.0 mg/mL 0–0.5 mg/mL 0–2.0 mg/mL 0–2.0 mg/mL	O_2^- scavenging: IC_{50} value for extract: 8.08 mg/mL, Vc: 0.30 mg/mL. Hydroxyl scavenging: IC_{50} value for extract: 5.23 mg/mL, Vc: 0.15 mg/mL. DPPH scavenging: IC_{50} value: 0.38 mg/mL, Vc: 0.014 mg/mL. H_2O_2 scavenging: IC_{50} value: 0.65 mg/mL, Vc: 0.16 mg/mL.	(Jun Liu et al., 2012)
		In vivo	300, 600, 1200 mg/kg b. w.	Female Kunming mice; extract administered by oral gavage for 30 days: 1200 mg/kg b. w. extract ↑ SOD, GPx, and CAT enzymes in serum. 600 and 1200 mg/kg body weight extract ↑ SOD, GPx, and CAT enzymes in liver and heart.	
Pleurotus eryngii	*P. eryngii* superfine powder (PESP)	*In vivo*	1.0 g/kg b. w.	Female specific pathogen-free (SPF) mice; fed diet supplemented with PESP for 4–5 weeks: ↑ GPx and SOD enzymes in mice serum. ↑ GPx enzyme and ↓ MDA in mice liver.	(Sun et al., 2014)
Pleurotus ostreatus	Ethanolic extract	*In vivo*	200 mg/kg b. w.	Male albino Wistar rats; extract administered via i.p. route for 30 days: ↑ CAT gene transcripts in liver and kidney of extract-treated rats ↓ carbonyl levels in liver and kidney of extract-treated rats	(Jayakumar, 2010)
A. bisporus, P. ostreatus, P. eryngii, Lentinula edodes	Methanolic extracts (gallic acid, protocatechuic acid, *p*-hydroxybenzoic acid, *p*-coumaric acid, cinnamic acid)	*In vitro*	0–20 mg/mL	*A. bisporus* fruit bodies: Ferricyanide/Prussian blue assay EC_{50}: White (1.80 mg/mL); brown (1.47 mg/mL); DPPH scavenging EC_{50}: White (3.13 mg/mL); brown (2.29 mg/mL). Beta-carotene/linoleate assay EC_{50}: brown *A. bisporus* mycelia (0.15 mg/mL), *P. eryngii* (1.43 mg/mL). TBARs assay EC_{50}: *P. ostreatus* mycelia (1.00 mg/mL)	(Reis et al., 2012)
Mycoleptodo-noides aitchisonii	Ethyl acetate extract (EAMA) (11 compounds purified and identified)	*In vitro*	100, 200 μg/mL 25, 50, 100 μg/mL 200, 400 μg/mL	↑ ARE expression in 100 and 200 μg/mL EAMA-treated RAW 264.7 cells. Protection from H_2O_2-induced damage in 100 μg/mL EAMA-treated RAW 264.7 cells. ↑ NQO1, GST, HO-1, and GCLC in 400 μg/mL EAMA treated $Nrf2^{+/+}$ macrophages.	(Kokubo et al., 2011)
		In vivo	15, 30 mg/day	Male C57BL/6N mice; EAMA administered via oral gavage every 24 h for 3 days: ↑ NQO1 and GST transcription in mice liver and small intestine in EAMA-treated mice. ↑ NQO1 enzyme activity in EAMA-treated mice.	

Symbols: ↑, increase; ↓ decrease. Abbreviations: DPPH, 2, 2-diphenyl-1-picrylhydrazyl; ARE, antioxidant response elements; b. w., body weight; CAT, catalase; EC_{50}, effective concentration; GCLC, glutamate cysteine ligase catalytic subunit; GPx, glutathione peroxidase; GST, glutathione S-tranferase; HO-1, heme oxygenase 1; H_2O_2, hydrogen peroxide; i.p., intraperitoneal; MDA, malondialdehyde; NQO1, NAD(P)H dehydrogenase [quinone] 1; O_2^-, superoxide; SOD, superoxide dismutase; TBARs, thiobarbituric acid reactive substances; T-AOC, total antioxidant content; TPC, total phenolic content.

levels in stimulated macrophages. The *A. bisporus*, *C. cibarius*, and *L. deliciosus* extracts were also able to diminish the expression of IL-1β and IL-6 mRNAs, but the *C. cornucopioides* extract could not. The compounds of all the six mushrooms studied showed that they had different varieties and compositions of cinnamic acid derivatives, hydroxybenzoic acid derivatives, flavonoids, and pyrogallol. However, the phenolic compounds identified in these mushrooms did not correlate with their anti-inflammatory abilities. Interestingly, pyrogallol was only found in *A. bisporus*, *C. cibarius*, *C. cornucopioides*, and *L. deliciosus*, which might partly explain their ability to inhibit iNOS expression and subsequent ability to reduce NO levels. It was suggested that the pyrogallol might have interacted with other flavonoid or cinnamic acid derivatives to produce the different activities of the mushrooms (Moro et al., 2012).

NF-κB is a family of transcription factors that is central to innate and adaptive immunity. The more commonly found form of NF-κB dimer is the p65 with either p52 or p50. The p65 and p50 proteins are expressed in many types of cells (Ghosh, May, & Kopp, 1998; Silverman & Maniatis, 2001; Verma, Stevenson, Schwarz, Van Antwerp, & Miyamoto, 1995). Abnormal NF-κB activity contributes to a number of inflammatory disorders, including atherosclerosis (Baeuerle & Henkel, 1994; Karin, Cao, Greten, & Li, 2002; Tak & Firestein, 2001). AP-1 is another transcription factor that is also implicated in several diseases, including inflammatory disorders (Ye, Ding, Wild, Shen, & Zhou, 2014). A number of mushroom species have been shown to reduce the levels of inflammatory mediators such as NO, PGE2, COX-2, and iNOS in stimulated macrophages. These observations might be attributed to the mushrooms' abilities to modulate the activities of these transcription factors. In one study, the glycoprotein PCP-3A isolated from *P. citrinopileatus* was able to reduce the expression of p50 and p65 subunits in both the nuclear and cytoplasmic fractions of activated macrophages. It was proposed that PCP-3A exhibited its anti-inflammatory activities by inhibiting nuclear translocation of cytoplasmic NF-κB dimers. The glycoprotein might also reduce the DNA-binding of activated NF-κB to their pro-inflammatory target genes (Chen et al., 2011). Oyster mushroom concentrate (OMC) from *P. ostreatus* was shown to dose-dependently reduce the activity of AP-1, and at 100 μg/mL it was able to slightly suppress NF-κB. The OMC contained soluble α- and β-glucans, isoleucine, leucine, tyrosine, phenylalanine, cytidine phosphate, adenosine monophosphate, guanosine phosphate, and vitamin B2. The glucans present in OMC might have contributed to its anti-inflammatory activities, as previously shown that mushroom glucans have anti-inflammatory properties (Pacheco-Sánchez, Boutin, Angers, Gosselin, & Tweddell, 2007). Previously, isoleucine and leucine were shown to interfere with prostaglandin's actions and/or mechanism (Saxena, Pendse, & Khanna, 1984), and vitamin B2 was shown to suppress TNF-α, IL-1, IL-6, and iNOS (Kodama, Suzuki, Toyosawa, & Araki, 2005; Toyosawa, Suzuki, Kodama, & Araki, 2004). These components might have contributed to the anti-inflammatory properties observed in OMC (Jedinak, Dudhgaonkar, Wu, Simon, & Sliva, 2011). A different study showed that the chloroform fraction of *H. erinaceus* was able to reduce the activity of AP-1 and NF-κB, as well as inhibiting the phosphorylation of IκB. IκB is the inhibitor protein of NF-κB, and the prevention of its phosphorylation ensures that the NF-κB dimers are not activated. However, the composition of the *H. erinaceus* chloroform fraction was not elucidated, thus the bioactives that might have contributed to its anti-inflammatory properties could not be identified (Kim, Lee, Oh, & Rhee, 2012).

3.2. Adhesion molecules

In one study, it was discovered that the extracts of *A. bisporus*, *G. frondosa*, *L. edodes*, and *P. ostreatus* could inhibit the expression of certain adhesion molecules on human aortic endothelial cells (HAECs) and reduce the attachment of monocytes to HAECs (Martin, 2010a). Extracts of *A. bisporus* could significantly reduce the expression of VCAM-1 and ICAM-1 in IL-1β-stimulated HAECs, but the other three extracts did not show any significant reduction in these adhesion molecules. However, unlike the expressions of VCAM-1 and ICAM-1, all four mushroom species were able to significantly inhibit the expression of *E*-selectin on stimulated HAECs. Added to that, all of the studied mushroom species were also able to significantly decrease the attachment of U937 human monocytes to the HAECs. These anti-inflammatory activities were attributed to the various bioactive compounds found in these mushrooms, including the polyphenols and the antioxidant ergothioneine (Martin, 2010a). Ergothioneine is a naturally-occurring antioxidant, and it is exclusively synthesized in fungi, cyanobacteria and mycobacteria (Cheah & Halliwell, 2012). In a different study, the bioactive agent ergothioneine was studied for its inhibitory effects on adhesion molecules (Martin, 2010b). Ergothioneine was shown to reduce VCAM-1, ICAM-1, and E-selectin expressions on IL-1β-stimulated HAECs. Preincubation of HAECs with this compound at 1 mM and 3 mM was also able to reduce the adhesion of U937 human monocytes (Martin, 2010b).

Wu, Duan, Liu, and Cen (2010) studied the anti-inflammatory effects of *F. velutipes* polysaccharide on rats. They found that rats fed with the polysaccharide, at both low (100 mg/kg body weight) and high (300 mg/kg body weight) doses had significantly lowered levels of ICAM-1 in their plasma and colon (Wu et al., 2010). Another study was conducted by Xu, HaiYan, JianHong, and Jing (2008), investigating the effects of *L. edodes* polysaccharide on high-fat-diet rats. They found that rats fed with 300 mg/kg of body weight of the polysaccharide of *L. edodes* had significantly reduced mRNA levels of VCAM-1 in their thoracic aorta (C. Xu et al., 2008).

These observations suggest that several mushroom bioactive compounds have the potential to be used for their anti-inflammatory properties. There is a diverse set of compounds with anti-inflammatory activities that can be found in mushrooms, ranging from glucans, glycoproteins, phenolics, organic acids, and other small molecular weight compounds. It is also possible for these bioactive components to act in a synergy to produce the bioactivity of mushrooms. Further research needs to be done in order to identify the specific compounds responsible for these anti-inflammatory activities, and their mechanism of action. Some studies involving anti-inflammatory effects of mushrooms in *in vitro* and *in vivo* studies are compiled in Table 3.

4. Hypolipidemic effects of mushrooms

Hypercholesterolemia is one of the major risk factors associated with atherosclerosis, and many mushroom species have been proven to lower the level of lipids in animals and humans (Bobek & Galbavý, 1999; Bobek et al., 1994; Kaneda & Tokuda, 1966; Rony, Ajith, Nima, & Janardhanan, 2014; Schneider et al., 2010). One possible mechanism for this hypocholesterolemic property of mushrooms might be due to the presence of HMG-CoA reductase inhibitors in these fungi species, like mevinolin from *P. ostreatus* (Guillamón et al., 2010). *Pleurotus salmoneostramineus* and *P. eryngii* were shown to have hypolipidemic effects on hypercholesterolemic mice. Hypercholesterolemic mice that were fed with these mushrooms had significantly lower plasma triglyceride, LDL-cholesterol, and total lipid than mice that were not. The hepatocytes of mushroom-fed mice also bear similar appearance to those of normal mice, whereas hypercholesterolemic mice had more lipid-laden hepatocytes. These results show that both *P. salmoneostramineus* and *P. eryngii* had lipid-lowering effects on the plasma and liver of mice (Alam et al., 2011; Yoon, Alam, Shim, & Lee, 2012).

Despite several findings showing the hypolipidemic effects of mushrooms (Bobek, Kuniak, & Ozdín, 1993; Bobek et al., 1994, 1998; Lee et al., 2007; Mori et al., 2008), the mechanisms of how mushrooms can affect lipid levels or atherosclerotic lesion formation are still obscure, and not many research has been done to discover these mechanisms. In one study, de Miranda et al. (2016) studied the effects of diet supplemented with *Agaricus brasiliensis* on the expression of some

Table 3
The *in vitro* and *in vivo* anti-inflammatory effects of various mushroom species.

Species	Mushroom constituent(s)	*In vitro/in vivo*	Extract dose(s)	*In vitro* and/or *in vivo* effects	Reference
–	Ergothioneine	*In vitro*		↓ VCAM-1, ICAM-1, and E-selectin levels in IL-1β-stimulated HAECs. ↓ Attachment of U937 human monocytes to HAECs.	(Martin, 2010b)
Grifola gargal	Low molecular weight, water soluble extract (GGE)	*In vivo*	10 mg/kg b. w.	C57BL/6 mice; treated with angiotensin II and treatment of GGE via i.p. for 28 days: ↑ T_{reg} cell population, ↓ total atheroma lesion, granulocytes, and MCP-1 in GGE-treated mice.	(Harada et al., 2015)
		In vitro	100 μg/mL	↑ CXCL12, TGF-1β, and VEGF in mice lung fibroblast cells.	
Antrodia cinnamomea	Methanolic extract (MEMAC)	*In vitro*	25, 50, 75 μg/mL	↓ TNF-α, IL-6, NO, PGE2, iNOS, and COX-2 in a dose-dependent manner in stimulated RAW 264.7 cells.	(Wen et al., 2011)
Pleurotus citrinopileatus	Glycoprotein (PCP-3A)	*In vitro*	0.08, 1.56, 3.13, 6.25 μg/mL	In LPS-stimulated RAW 264.7 murine macrophage cells: ↓ iNOS, NO, and PGE2 levels ↓ p65/p50 expressions in both nuclear and cytoplasmic fractions	(J.-N. Chen et al., 2011)
Hericium erinaceus	Chloroform fraction	*In vitro*	10, 25, 50 μg/mL	In LPS-stimulated RAW 264.7 murine macrophage cells: ↓ iNOS, COX-2, and PGE2 levels ↓ phosphorylation of ERK and JNK in a dose-dependent manner ↓ AP-1 and NF-κB activities Inhibited IκB phosphorylation	(Y.-O. Kim et al., 2012)
Agaricus bisporus, Boletus edulis, Cantharellus cibarus, Craterellus cornucopioides, Lactarius deliciosus, Pleurotus ostreatus	Methanolic extracts (cinnamic acid derivatives, hydroxybenzoic acid derivatives, flavonoids, pyrogallol)	*In vitro*	0.5 mg/mL	In LPS-stimulated RAW 264.7 murine macrophage cells: ↓ iNOS mRNA and NO levels by *C. cibarius, C. cornucopioides, L. deliciosus, A. bisporus.* ↓ TNF-α and IL-6 mRNA by *A. bisporus, C. cibarius,* and *L. deliciosus.*	(Moro et al., 2012)
A. bisporus, Lentinula edodes, P. ostreatus, Grifola frondosa	DMSO extracts	*In vitro*	100 μg/mL	↓ VCAM-1 and ICAM-1 in IL-1β-stimulated HAECs treated with *A. bisporus.* ↓ E-selectin in IL-1β-stimulated HAECs treated with all mushrooms studied. ↓ Attachment of U937 human monocytes to HAECs treated with all mushrooms studied.	(Martin, 2010a)
P. ostreatus	Oyster mushroom concentrate (OMC) (α- and β-glucans, isoleucine, leucine, tyrosine, phenylalanine, cytidine monophosphate, adenosine monophosphate, guanosine monophosphate and vitamin B2)	*In vitro*	0, 12.5, 25, 50, 100 μg/mL	In RAW 264.7 murine macrophage cells: ↓ iNOS and COX-2 mRNA expression. ↓ TNF-α, IL-6, IL-12, NO, and PGE2 levels. ↓ AP-1 activity in dose-dependent manner ↓ NF-κB activity at 100 μg/mL	(Jedinak et al., 2011)

(*continued on next page*)

Table 3 (*continued*)

Species	Mushroom constituent(s)	*In vitro*/*in vivo*	Extract dose(s)	*In vitro* and/or *in vivo* effects	Reference
L. edodes	Polysaccharide	*In vivo*	100, 200, 300 mg/kg b. w.	Male rats (strain not specified); rats fed high-fat diet, and administered polysaccharide treatment via oral gavage for 40 days: ↓ VCAM-1 mRNA levels in thoracic aorta endothelial cells of rats treated with 300 mg/kg b. w. mushroom treatment ↓ NO levels in rat serum. ↓ Total cholesterol, total triacylglycerol in rat serum. ↑ SOD and GPx in rat serum.	(C. Xu et al., 2008)
Flammulina velutipes	Polysaccharide (GNP)	*In vivo*	100, 300 mg/kg	Male Wistar rats; fed diet containing GNP for 30 days: ↓ ICAM-1 and ↑ IL-10 in serum and colon of rats.	(Wu et al., 2010)

Symbols: ↑, increase; ↓ decrease. Abbreviations: AP-1, activator protein-1; COX-2, cyclooxygenase-2; DMSO, dimethyl sulfoxide; ERK, extracellular signal–regulated kinase; GPx, glutathione peroxidase; HAECs, human aortic endothelial cells; iNOS, inducible nitric oxide synthase; ICAM-1, intercellular Adhesion Molecule 1; IFN-γ, interferon-γ; IL-12, interleukin-12; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-6, interleukin-6; i.p.: intraperitoneal; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; NF-κB, nuclear factor-κB; PGE2, prostaglandin E2; T_{reg}, regulatory T cells; SOD, superoxide dismutase; TGF-1β, transforming growth factor-1β; TNF-α, tumor necrosis factor-α;VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

genes involved in cholesterol homeostasis (de Miranda et al., 2016). They discovered that hypercholesterolemic rats that were fed with the mushroom had higher mRNA levels of *LDLr*, *PPAR-α*, *LXR*, *ABCG5* and *ABCG8*. Liver X receptor (LXR) is a transcription factor that modulates the sterol regulatory element-binding proteins (SREBPs), and these SREBPs directly activate the expression of around 30 genes involved in the synthesis and uptake of fatty acids, cholesterol, triacylglycerol, and phospholipids. The peroxisome proliferator-activated receptor alpha (PPAR-α) is a transcription factor that is vital in lipid metabolism in the liver, and it is an attractive target for dyslipidemia. ABCG5/ABCG8 form a heterodimer that are responsible for cholesterol excretion from the liver to the bile. Increasing the expressions of these genes is expected to be beneficial in terms of cholesterol efflux in the liver. The results obtained suggested that the consumption of *A. brasiliensis* could modulate cholesterol excretion by affecting some genes that encode for proteins that are involved in cholesterol metabolism (de Miranda et al., 2016).

Chen et al. (2014) studied the effects of *P. eryngii* mycelia exopolysaccharide (EP) on the scavenger receptor CD36 expression on RAW 264.7 cells. The EP was able to lower the amount of lipid uptake by foam cells, as well as down-regulate the expression of CD36 at the mRNA and protein levels. This biological effects observed were most likely due to the structural feature of the EP, as the digested exopolysaccharide was not able to reduce lipid uptake as well as the undigested EP (Chen et al., 2014).

In another study, Sato et al. (2013) studied the expression of several genes involved in lipid metabolism in the liver of mice that were fed with powdered *G. frondosa*. They found that hypercholesterolemic mice fed with the mushroom had increased expressions of the *Abcg5* and *Abcg8* genes. ABCG5/ABCG8 form a heterodimer that are responsible for cholesterol excretion from the liver to the bile. Increasing the expressions of these genes is expected to be beneficial in terms of cholesterol efflux in the liver. On the other hand, the gene *Saa*, which encodes for serum amyloid A 1 (SAA), is downregulated in mice fed with the mushroom. SAA acts as an inhibitor for SR-B1, which is a vital scavenger receptor for RCT from the periphery to the liver. By downregulating the expression of SAA, it is speculated that SR-B1, and subsequently RCT, would be unhindered, leading to better cholesterol transport. Several other genes were also affected by the consumption of *G. frondosa* by the mice. However, it is sufficient to say that this study showed that mushrooms could possibly exert their hypocholesterolemic effects by altering the expression of several genes. Even if the change in the expression of one particular gene is small, the cumulative effect of changing the expression of several genes could result in an obvious change in the lipid profile of an animal (Sato et al., 2013).

With all these discoveries, it is clear that there is an abundance of evidence showing the benefits that mushrooms have on hyperlipidemic conditions. Table 4 shows the summary of some of these findings. More research are now focused on the potential effect of mushroom use on the genetic profile of animal models. Hopefully this will pave the way to help researchers understand the mechanisms of mushrooms hypolipidemic bioactivities.

5. Anti-platelet aggregation effects of mushrooms

Several research has been done to show that a variety of mushroom species do possess antiplatelet activities. Lu et al. (2014) studied the crude extract of *Antrodia camphorata* and its ability to inhibit aggregation. The mushroom extract was able to reduce collagen-induced platelet aggregation in a dose-dependent manner, but it did not decrease aggregation of platelets that were induced by U46619 (a TXA_2 mimetic), thrombin, and arachidonic acid. The extract was also shown to lower collagen-induced Ca^{2+} mobilization in washed platelets. However, the *A. camphorata* did not have any effect on the phosphorylation of various proteins often implicated in platelet aggregation, such as p38, ERK, and JNK. Further investigation showed that the

Table 4
The *in vitro* and *in vivo* hypolipidemic effects of various mushroom species.

Species	Mushroom constituent(s)	*In vitro/in vivo*	Extract dose(s)	*In vitro* and/or *in vivo* effects	Reference
Agaricus brasiliensis	Powdered fruit bodies	*In vivo*	Hypercholesterolemic diet supplemented with 1% mushroom	Female albino Fisher rats; fed with hypercholesterolemic diet (1% cholesterol, 25% soybean oil) supplemented with 1% mushroom powder: Total cholesterol, non-HDL, and HDL-cholesterol of mushroom-treated rats comparable to simvastatin-treated group. ↓Total cholesterol in rat fecal matter. ↑ *LDLr*, *PPAR-α*, *LXR*, *ABCG5* and *ABCG8* mRNA levels	de Miranda et al. (2016)
Pleurotus eryngii	Excreted polysaccharide (EP)	*In vitro*	50, 100, 200 μg/mL	↓ Lipid content in a dose-dependent manner on ox-LDL-treated murine RAW 264.7 macrophage cells. ↓ *cd36* mRNA levels in ox-LDL-treated murine RAW 264.7 macrophage cells at 200 μg/mL of EP.	J. Chen et al. (2014)
	Powdered fruit bodies	*In vivo*	Hypercholesterolemic diet supplemented with 5% mushroom	Female Sprague-Dawley rats; fed with hypercholesterolemic diet supplemented with *P. eryngii* powder (1% cholesterol, 5% *P. eryngii* powder) for 42 days: ↓ Plasma triacylglycerol, LDL-cholesterol, and total lipid in mice. Hepatocytes appearance almost similar to normal mice (not lipid-laden).	Alam et al. (2011)
Pleurotus salmoneo-stramineus	Powdered fruit bodies	*In vivo*	Hypercholesterolemic diet supplemented with 5% mushroom	Female Sprague-Dawley rats; fed with hypercholesterolemic diet supplemented with *P. salmoneostramineus* powder (1% cholesterol, 5% *P. salmoneostramineus* powder) for 42 days: ↓ Plasma triacylglycerol, LDL-cholesterol, and total lipid in mice. Hepatocytes appearance almost similar to normal mice (not lipid-laden).	Yoon et al. (2012)
Grifola frondosa	Powdered fruit bodies	*In vivo*	Hypercholesterolemic diet supplemented with 10% mushroom	Male ICR mice; fed with hypercholesterolemic diet supplemented with *G. frondosa* powder (1% cholesterol, 10% *G. frondosa* powder) for 4 weeks: ↑ *ABCG5* and *ABCG8* expressions. ↓ *SAA* expression.	Sato et al. (2013)

Symbols: ↑, increase; ↓ decrease. Abbreviations: ABCG5, ATP-binding cassette sub-family G member 5; ABCG8, ATP-binding cassette sub-family G member 8; CD36, cluster of differentiation 36; HDL, high-density lipoprotein; LXR, liver X protein; LDL, low-density lipoprotein; LDLr, low-density lipoprotein receptor; MDA, malondialdehyde; ox-LDL, oxidized LDL; PPAR-α, peroxisome proliferator-activated receptor-α; SAA, serum amyloid A; SOD, superoxide dismutase.

Table 5
The *in vitro* and *in vivo* antiplatelet effects of various mushroom species.

Species	Mushroom constituent (s)	*In vitro*/ *in vivo*	Extract dose(s)	*In vitro* and/or *in vivo* effects	Reference
Antrodia camphorata	Crude extracts	*In vitro*	56, 112, 224 μg/ mL	↓ collagen-induced aggregation. ↓ collagen-induced Ca^{2+} mobilization in washed platelets. ↓ phosphorylation of p47 and Akt.	(Lu et al., 2014)
Paxillus curtisii	Curtisian E (CE)	*In vitro*	12.5, 25, 50, 100 200 μg/mL	↓ collagen, thrombin, and ADP-induced platelet aggregation in dose dependent manner. ↓ intracellular Ca^{2+} levels. ↓ ATP release. ↓ phosphorylation of ERK, p38, and Akt ↑ cAMP in platelets, p-VASP. ↓ fibrinogen binding to integrin $\propto_{iib}\beta_3$. ↓fibronectin binding to platelets.	(Kamruzzaman et al., 2013)
Phellinus baumii	*P. baumii* methanol extract (PBME)	*In vitro*	12.5, 25, 50, 100 200 μg/mL	↓ collagen-, thrombin-, and ADP-induced aggregation. ↓ Ca^{2+} concentration and ATP release. ↓ fibrinogen binding in collagen-activated platelets. ↓ phosphorylation of ERK2 and JNK1, but not p38.	(Kamruzzaman et al., 2011)
Hypsizygus marmoreus	*H. marmoreus* methanol extract (HMME)	*In vitro*	0–400 μg/mL 25, 100 μg/mL 50, 100, 200 μg/ mL	Inhibit aggregation induced by collagen, but not thrombin and ADP. ↓ Ca^{2+} elevation in washed platelets. ↓ ATP release in collagen-activated platelets. ↓ fibrinogen binding to integrin $\propto_{iib}\beta_3$ in collagen-activated platelets at 200 μg/mL.	(J. Y. Park et al., 2011)
Hericium erinaceus	Hericenone B	*In vitro*	0.3–100 μM	Inhibited collagen-induced platelet aggregation in a dose-dependent manner in rabbit and human platelets, but not U46619 (TXA_2 analogue), ADP, thrombin, or adrenaline, arachidonic acid, or convulxin (GPVI agonist).	(Mori et al., 2010)

Symbols: ↑, increase; ↓ decrease. Abbreviations: JNK-1, c-Jun N-terminal kinase-1; cAMP, cyclic adenosine monophosphate; ERK, extracellular signal–regulated kinase; GPVI, glycoprotein VI; TXA_2, thromboxane A_2; p-VASP, phosphorylated vasodilator-stimulated phosphoprotein.

extract was able to significantly reduce the phosphorylation of p47 and Akt proteins. The phosphorylation of these proteins would eventually lead to platelet activation. These findings suggested that the mushroom extract exerted its antiplatelet activities by inhibiting Ca^{2+} mobilization and PKC cascade and Akt pathway, thus inhibiting platelet activation and subsequent aggregation (Lu et al., 2014).

Another research was conducted by Kamruzzaman et al. (2013) on *Paxillus curtisii*, in which the *p*-terphenyl antioxidant compound Curtisian E (CE) was isolated and shown to have antiplatelet properties. This compound was able to reduce aggregation triggered by collagen, thrombin, and ADP *in vitro* in a dose-dependent fashion. Even at the low dose of 50 μM, CE was able to reduce ATP release by platelets. The compound was also able to reduce the phosphorylation of ERK, p38, and Akt in a dose-dependent manner, and it was able to increase cyclic adenosine monophosphate (cAMP) levels in platelets. At 200 μM, CE was able to increase the phosphorylation of vasodilator-stimulated-phosphoprotein (VASP). Cyclic nucleotide monoamine phosphates such cAMP has been shown to have a broad antiplatelet effects through VASP, thus an increase in concentration and/or activity of these factors would contribute to increasing antiplatelet activities (Wentworth, Pula, & Poole, 2006). However, when CE was incubated with H-89 (a PKA inhibitor), the phosphorylation of VASP was reduced. This observation suggested that CE may exert its antiplatelet effects *via* the cAMP-PKA-VASP pathway. CE was also shown to reduce fibrinogen binding to integrin $\alpha_{IIb}\beta_3$ and fibronectin adhesion. These findings showed that CE from *P. curtisii* did have potent antiplatelet activities by targeting several possible mechanisms in the aggregation process (Kamruzzaman et al., 2013). Besides that, Kamruzzaman et al. (2011) also did a study on the antiplatelet activities of the methanol extract of *Phellinus baumii* (PBME). The extract was able to reduce platelet aggregation activated by collage, thrombin, and ADP. PBME was also able to reduce Ca^{2+} levels and ATP secretion respectively. It was able to decrease fibrinogen binding in collagen-activated platelets, and increase cAMP, leading to reduced $\alpha_{IIb}\beta_3$ activation. PBME lowered the phosphorylation of ERK2 and JNK1, but not p38. These findings proved that PBME had various antiplatelet potential due to its ability to influence several components involved in the platelet aggregation reactions. However, the composition of PBME was not examined, thus no specific compounds could be attributed to the antiplatelet aggregation activity (Kamruzzaman et al., 2011).

In another study, the anti-platelet activity of *H. marmoreus* methanolic extract (HMME) was studied. HMME was able to inhibit aggregation induced by collagen, but not by thrombin and ADP. It was also able to reduce Ca^{2+} elevation in washed platelets in a dose-dependent manner. HMME also lowered ATP release in collagen-activated platelets. At 200 μg/mL, HMME was able to decrease the fibrinogen binding to integrin $\alpha_{IIb}\beta_3$ in stimulated platelets. However, it did not have any effect on the phosphorylation of ERK2. The ERK pathway is complex, thus its role in platelet aggregation is not necessarily straightforward. Thus, even though the HMME generally exhibited antiplatelet aggregation abilities by inhibiting the classical pathway, it is not surprising that HMME did not affect collagen-stimulated ERK activation. Further studies are needed to understand the signaling molecules involved in the pathway to resolve the discrepancies observed (Park et al., 2011).

In a different research, Mori et al. (2010) isolated the aromatic compound hericenone B from *H. erinaceus*, which proved to have antiplatelet properties. Hericenone B was able to inhibit collagen-induced platelet aggregation in rabbit and human platelets, but not aggregation stimulated by U46619, ADP, thrombin, or adrenaline. Further investigation was carried out to examine the possibility that hericenone B may inhibit aggregation due to arachidonic acid synthesis of TXA_2 and GPVI (using convulxin, a GPVI agonist). However, hericenone B did not inhibit aggregation induced by arachidonic acid and convulxin, suggesting that hericenone B may inhibit platelet aggregation through a mechanism upstream of arachidonic acid metabolism (Mori et al., 2010).

These findings show that various mushrooms have antiplatelet potential, but the mechanism of action for each extract or compound may be different. Some compounds have antiplatelet activities due to their ability to inhibit or decrease multiple pathways in the aggregation process. On the other hand, some other compounds may exert their aggregation-inhibition activities by inhibiting specific pathways. As such, it can be seen that mushrooms possess antiplatelet activities, and

Table 6
The fibrinolytic effects of several enzymes isolated from mushrooms.

Species	Mushroom constituent(s)	*In vitro/in vivo*	Extract dose(s)	*In vitro* and/or *in vivo* effects	Reference
Cordyceps militaris	Plasmin-like protein	*In vitro*	0.075 mg/mL	Enzyme had molecular weight of 32 kDa as determined by SDS-PAGE. The optimal pH and temperature were 7.4 and 37 °C respectively. Enzyme activity was inhibited by Fe^{2+}, PMSF, aprotinin, and pepstatin, but not TPCK and EDTA. Enzyme could cleave fibrin(ogen) directly and it cleaved the α-chain most effectively. Enzyme could degrade thrombin.	(X. Liu et al., 2015)
Pleurotus ostreatus	Purified fibrinolytic enzyme (metalloprotease)	*In vitro*		Enzyme purified by a combination of freeze-thaw treatment, ammonium sulphate precipitation, hydrophobic interaction, and gel filtration chromatographies. The molecular masses of the enzyme as determined by gel filtration and SDS- PAGE were 13.6 and 18.2 kDa.	(X. Liu et al., 2014)
			0.051 mg/mL	Cleaved the α- and β-chains of fibrinogen followed by the γ-chains, and also activated plasminogen into plasmin. Enzyme was optimally active at 45 °C and pH 7.4. Enzyme activity inhibited by EDTA. Partial amino acid sequences were ATFVGCSATR, GGTLIHESSHFTR, and YTTWFGTFVTSR.	
Lyophyllum shimeji	Chymotrypsin-like Serine metalloprotease	*In vitro*		Enzyme purified using anion exchange chromatography and size exclusion gel filtration chromatography Enzyme estimated to be 21 kDa by SDS-PAGE and size exclusion gel filtration. N-terminal amino acid sequence was ITFQSASP. A neutral protease with an optimal reaction pH and temperature of 8.0 and 37 °C. Activity inhibited by Cu^{2+} and Co^{2+}. Inhibited by PMSF, TPCK, and EDTA.	(Moon et al., 2014)
			5 μg 1 unit/2μL	Two fold more activity than 1 unit of plasmin on fibrin plate. Preferentially hydrolysed the Aa-chain followed by the Bb- and γ-chain of fibrinogen.	
Hericium erinaceus	Herinase (metalloprotease)	*In vitro*		Molecular mass of 51 kDa. The N-terminal sequence of herinase: VPSSFRTTITDAQLRG. Enzyme activity was strongly inhibited by EDTA and EGTA.	(Choi et al., 2013)
			0.1 mg/mL	It was able to degrade fibrin clot directly and activate plasminogen. Rapid degradation of fibrin and fibrinogen α-chains and slower degradation of γ-chains. It had no activity on the β-chains of fibrin and fibrinogen. Maximum activity at 30 °C and pH 7.0.	
Schizophyllum commune	Mushrokinase (MsK) (metalloprotease)	*In vitro*	–	Enzyme purified using anion-exchange column and gel filtrations columns. Enzyme was a monomeric subunit and was estimated to be 17 kDa. The N-terminal amino acid sequence of the purified enzyme was identified as HYNIXNSWSSFID. Reduced activity due to EDTA. The optimum temperature for activity 45 °C, and over 87% of the enzymatic activity was maintained at pH range 4.0 to 6.0. Enzyme has higher activity in plasminogen-rich fibrin plate than plasminogen-free plate.	(I. S. Park et al., 2010)

Symbols: ↑, increase; ↓ decrease. Abbreviations: PMSF, phenylmethylsulfonyl fluoride; TPCK, tosyl phenylalanyl chloromethyl ketone; EDTA, ethylenediaminetetraacetic acid; EGTA, ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid.

they are a valuable potential source for handling aggregation implicated in atherosclerosis. Table 5 shows the various mushroom species and their antiplatelet effects.

6. Anti-thrombotic effects of mushrooms

At present, pathologic thrombus formation could be managed using intravenous insertion of thrombolytic agents. Some examples of such agents include plasminogen activators such as recombinant tPA (r-TPA) and uPA, urokinase, streptokinase, and anisoylated plasminogen streptokinase-activator complex. These agents have been shown to be successful in restoring blood flow in occluded arteries and veins (Liu et al., 2005). However, these fibrinolytic agents can be expensive and there is the possibility of causing rapid degradation leading to uncontrollable acceleration of fibrinolysis and hemorrhage. Thus, there is a need to find fibrinolytic agents from other sources. Some findings include fibrinolytic enzymes found in food grade microorganism (Deepak et al., 2008; Wong & Mine, 2004), insects (Ahn et al., 2003), earthworm secretions (Wang et al., 2005), and various fermented food products like the Chinese “douchi” (Wang et al., 2006), Japanese “natto” (Sumi, Yanagisawa, Yatagai, & Saito, 2004), and Korean “chunkookjang” (Kim et al., 1996).

In recent years, many fibrin(ogen)olytic enzymes have been isolated and characterized from several mushroom species. Recently a fibrinolytic enzyme purified from *Cordyceps militaris* was studied (Liu et al., 2015). This particular enzyme was able to directly degrade fibrin and fibrinogen, suggesting that it might work more like plasmin. There was no difference in terms of the cleaving area caused by the enzyme in plasminogen-free and plasminogen-rich fibrin plates, implying that the enzyme did not act like a plasminogen activator. Interestingly, Liu and colleagues also showed the enzyme's anticoagulant activity, since it was shown to also degrade human thrombin. The authors suggested that this particular enzyme could act as both an anticoagulant agent and a fibrinolytic agent (Liu et al., 2015). In a different study, a fibrinolytic enzyme was isolated from *P. ostreatus*. Since this enzyme was greatly inhibited by EDTA, it was assumed to be a metalloprotease. This particular enzyme was able to cleave the α- and β- chains of fibrinogen effectively, followed by the γ-chain. Added to that, this enzyme was able to degrade fibrin in both plasminogen-free and plasminogen-rich plates. The results suggested that it could directly cleave fibrin and also activate plasminogen into becoming plasmin (Liu et al., 2014).

Moon et al. (2014) isolated a novel fibrinolytic enzyme from *L. shimeji* with properties similar to α chymotrypsin. The activity of this particular enzyme was significantly inhibited by PMSF, TPCK, and EDTA. PMSF and TPCK are well known Serine protease inhibitors, while EDTA is a metalloprotease inhibitor. This result implied that the enzyme purified from *L. shimeji* is a Serine metalloprotease. At 5 μg, the fibrinolytic enzyme exhibited two-fold higher activity on a fibrin plate than plasmin (Moon et al., 2014).

Choi et al. (2013) also managed to isolate a fibrinolytic enzyme that could act on both fibrin and plasminogen from the medicinal mushroom *H. erinaceus*. The enzyme, which is called herinase, was inhibited by EDTA and EGTA, suggesting that it was a metalloprotease. However, herinase did not show any ability to cleave the β-chain of fibrin. Instead, it was able to cleave the α- and γ- chains, suggesting that it had different activity and may even have specific activity for the α-chain (Choi et al., 2013).

Park et al. (2010) on the other hand isolated a fibrinolytic enzyme from *S. commune*. This enzyme was believed to be a metalloprotease, as it was inhibited by EDTA, Phophoramidon, and Bestatin. However, the enzyme from *S. commune* was only able to degrade fibrin in plasminogen-rich plates, indicating that it acts more on plasminogen than on fibrin itself (Park et al., 2010).

These findings show that different mushroom species have the potential to produce various types of fibrinolytic agents. The agents are varied in their properties and activities. Some purified enzymes from mushrooms are Serine proteases, while others are metalloprotease, and still some are Serine metalloproteases. The fibrinolytic enzymes from mushrooms can sometimes have direct lysis activity on fibrin by cleaving fibrin chains directly. However, there are also enzymes that act more like plasminogen activators, in which they can only exert their fibrinolytic activities in the presence of plasminogen. Fibrinolytic agents from mushroom sources are hoped to be safer and more specific in their activities. Thus, further research needs to be carried out to see how these enzymes may exert their effects, especially in *in vivo* settings. Some fibrinolytic enzymes from mushrooms and their antithrombotic effects are summarized in Table 6.

7. Conclusion

Atherosclerosis is a complex pathology that involves numerous factors in its initiation and progress. Some of the factors involved include oxidative stress, inflammation, hyperlipidemia, platelet aggregation and thrombus formation. As such, there are multiple ways in which the development of the lesion could be slowed down or completely halted. Mushrooms of various species are rich in anti-oxidative, anti-inflammatory and cholesterol lowering compounds that have the potential to alleviate some aspects of atherosclerosis development. These possible anti-atheroscloretic effects could be exhibited by different mushroom species through the use of their crude extracts, or through their isolated bioactive compounds. As such, it is clear that mushrooms are a potential source for several biocompounds that could be studied and utilized for handling the myriads of facets of atherosclerosis.

Acknowledgements

This work was supported by the University of Malaya Research Grant (UMRG) RP014A-13AFR.

References

Adam, F., Kauskot, A., Rosa, J.-P., & Bryckaert, M. (2008). Mitogen-activated protein kinases in hemostasis and thrombosis. *Journal of Thrombosis and Haemostasis, 6*(12), 2007–2016. http://dx.doi.org/10.1111/j.1538-7836.2008.03169.x.

Ahn, M. Y., Hahn, B.-S., Ryu, K. S., Kim, J. W., Kim, I., & Kim, Y. S. (2003). Purification and characterization of a serine protease with fibrinolytic activity from the dung beetles, *Catharsius molossus*. *Thrombosis Research, 112*(5–6), 339–347. http://dx.doi.org/10.1016/j.thromres.2004.01.005.

Ahn, W.-S., Kim, D.-J., Chae, G.-T., Lee, J.-M., Bae, S.-M., Sin, J.-I., ... Lee, I. P. (2004). Natural killer cell activity and quality of life were improved by consumption of a mushroom extract, *Agaricus blazei* Murill Kyowa, in gynecological cancer patients undergoing chemotherapy. *International Journal of Gynecological Cancer, 14*(4), 589–594. http://dx.doi.org/10.1111/j.1048-891X.2004.14403.x.

Alam, N., Yoon, K. N., Lee, J. S., Cho, H. J., Shim, M. J., & Lee, T. S. (2011). Dietary effect of *Pleurotus eryngii* on biochemical function and histology in hypercholesterolemic rats. *Saudi Journal of Biological Sciences, 18*(4), 403–409. http://dx.doi.org/10.1016/j.sjbs.2011.07.001.

Alberts, A. W. (1990). Lovastatin and simvastatin—Inhibitors of HMG CoA reductase and cholesterol biosynthesis. *Cardiology, 77*(Suppl. 4), 14–21. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2073667.

Askenasy, N., Kaminitz, A., & Yarkoni, S. (2008). Mechanisms of T regulatory cell function. *Autoimmunity Reviews, 7*(5), 370–375. http://dx.doi.org/10.1016/j.autrev.2008.03.001.

Bae, A. H., Lee, S. W., Ikeda, M., Sano, M., Shinkai, S., & Sakurai, K. (2004). Rod-like architecture and helicity of the poly(C)/schizophyllan complex observed by AFM and SEM. *Carbohydrate Research, 339*(2), 251–258. http://dx.doi.org/10.1016/j.carres.2003.09.032.

Baeuerle, P. A., & Henkel, T. (1994). Function and activation of NF-kappaB in the immune system. *Annual Review of Immunology, 12*(1), 141–179. http://dx.doi.org/10.1146/annurev.iy.12.040194.001041.

Balasundram, N., Sundram, K., & Samman, S. (2006). Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chemistry, 99*(1), 191–203. http://dx.doi.org/10.1016/j.foodchem.2005.07.042.

Barlic, J., Zhang, Y., Foley, J. F., & Murphy, P. M. (2006). Oxidized lipid-driven chemokine receptor switch, CCR2 to CX3CR1, mediates adhesion of human macrophages to coronary artery smooth muscle cells through a peroxisome proliferator-activated receptor gamma-dependent pathway. *Circulation, 114*(8), 807–819. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.602359.

Barros, L., Baptista, P., Correia, D. M., Casal, S., Oliveira, B., & Ferreira, I. C. F. R. (2007). Fatty acid and sugar compositions, and nutritional value of five wild edible

mushrooms from Northeast Portugal. *Food Chemistry, 105*(1), 140–145. http://dx.doi.org/10.1016/j.foodchem.2007.03.052.
Barros, L., Correia, D. M., Ferreira, I. C. F. R., Baptista, P., & Santos-Buelga, C. (2008). Optimization of the determination of tocopherols in *Agaricus* sp. edible mushrooms by a normal phase liquid chromatographic method. *Food Chemistry, 110*(4), 1046–1050. http://dx.doi.org/10.1016/j.foodchem.2008.03.016.
Bartczak, D., Muskens, O. L., Nitti, S., Sanchez-Elsner, T., Millar, T. M., & Kanaras, A. G. (2012). Interactions of human endothelial cells with gold nanoparticles of different morphologies. *Small (Weinheim an Der Bergstrasse, Germany), 8*(1), 122–130. http://dx.doi.org/10.1002/smll.201101422.
Bobek, P., & Galbavý, S. (1999). Hypocholesterolemic and antiatherogenic effect of oyster mushroom (*Pleurotus ostreatus*) in rabbits. *Die Nahrung, 43*(5), 339–342. http://dx.doi.org/10.1002/(SICI)1521-3803(19991001)43:5<339::AID-FOOD339>3.0.CO;2-5.
Bobek, P., Hromadová, M., & Ozdín, L. (1995). Oyster mushroom (*Pleurotus ostreatus*) reduces the activity of 3-hydroxy-3-methylglutaryl CoA reductase in rat liver microsomes. *Experientia, 51*(6), 589–591. http://dx.doi.org/10.1111/j.1574-6968.1995.tb07334.x.
Bobek, P., Kuniak, L., & Ozdín, L. (1993). The mushroom *Pleurotus ostreatus* reduces secretion and accelerates the fractional turnover rate of very-low-density lipoproteins in the rat. *Annals of Nutrition & Metabolism, 37*(3), 142–145.
Bobek, P., Ondreicka, R., Klvanova, J., & Ozdin, L. (1994). Oyster mushroom (*Pleurotus ostreatus*) decreases serum and liver cholesterol and increases cholesterol 7α-hydroxylase activity and fecal excretion of neutral sterols and bile acids in hypercholesterolemic rats. *Nutrition Research, 14*(11), 1683–1688. http://dx.doi.org/10.1016/S0271-5317(05)80323-9.
Bobek, P., Ozdín, L., & Galbavý, Š. (1998). Dose- and time-dependent hypocholesterolemic effect of oyster mushroom (*Pleurotus ostreatus*) in rats. *Nutrition, 14*(3), 282–286. http://dx.doi.org/10.1016/S0899-9007(97)00471-1.
Borchers, A. T., Keen, C. L., & Gershwin, M. E. (2004). Mushrooms, tumors, and immunity: An update. *Experimental Biology and Medicine (Maywood, N.J.), 229*(5), 393–406. http://dx.doi.org/10.1258/ebm.2009.009e01.
Boring, L., Gosling, J., Cleary, M., & Charo, I. F. (1998). Decreased lesion formation in CCR2 −/− mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature, 394*(6696), 894–897. http://dx.doi.org/10.1038/29788.
Cai, H., & Harrison, D. G. (2000). Endothelial dysfunction in cardiovascular diseases: The role of oxidant stress. *Circulation Research, 87*(10), 840–844. http://dx.doi.org/10.1161/01.RES.87.10.840.
Carneiro, A. A. J., Ferreira, I. C. F. R., Dueñas, M., Barros, L., da Silva, R., Gomes, E., & Santos-Buelga, C. (2013). Chemical composition and antioxidant activity of dried powder formulations of *Agaricus blazei* and *Lentinus edodes*. *Food Chemistry, 138*(4), 2168–2173. http://dx.doi.org/10.1016/j.foodchem.2012.12.036.
Chakrabarti, S., Lekontseva, O., & Davidge, S. T. (2008). Estrogen is a modulator of vascular inflammation. *IUBMB Life*. http://dx.doi.org/10.1002/iub.48.
Chang, S. T., & Miles, P. G. (2004). *Mushrooms: Cultivation, nutritional value, medicinal effect, and environmental impact.* CRC Press.
Cheah, I. K., & Halliwell, B. (2012). Ergothioneine; antioxidant potential, physiological function and role in disease. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1822*(5), 784–793. http://dx.doi.org/10.1016/j.bbadis.2011.09.017.
Chen, J., Yong, Y., Xia, X., Wang, Z., Liang, Y., Zhang, S., & Lu, L. (2014). The excreted polysaccharide of *Pleurotus eryngii* inhibits the foam-cell formation via down-regulation of CD36. *Carbohydrate Polymers, 112*, 16–23. http://dx.doi.org/10.1016/j.carbpol.2014.05.068.
Chen, J.-N., de Mejia, E. G., & Wu, J. S.-B. (2011). Inhibitory effect of a glycoprotein isolated from golden oyster mushroom (*Pleurotus citrinopileatus*) on the lipopolysaccharide-induced inflammatory reaction in RAW 264.7 macrophage. *Journal of Agricultural and Food Chemistry, 59*(13), 7092–7097. http://dx.doi.org/10.1021/jf201335g.
Cheung, P. C. K. (2009). Mushrooms as functional foods. *Mushrooms as functional foods*http://dx.doi.org/10.1002/9780470367285.
Cheung, P. C. K. (2010). The nutritional and health benefits of mushrooms. *Nutrition Bulletin, 35*(4), 292–299. http://dx.doi.org/10.1111/j.1467-3010.2010.01859.x.
Choi, B. S., Sapkota, K., Choi, J. H., Shin, C. H., Kim, S., & Kim, S. J. (2013). Herinase: A novel bi-functional fibrinolytic protease from the monkey head mushroom, *Hericium erinaceum*. *Applied Biochemistry and Biotechnology, 170*(3), 609–622. http://dx.doi.org/10.1007/s12010-013-0206-2.
Clarke, M., & Bennett, M. (2006). The emerging role of vascular smooth muscle cell apoptosis in atherosclerosis and plaque stability. *American Journal of Nephrology, 26*(6), 531–535. http://dx.doi.org/10.1159/000097815.
Collen, D. (1999). The plasminogen (fibrinolytic) system. *Thrombosis and Haemostasis, 82*(2), 259–270. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10605712.
Dai, Y.-C., Yang, Z.-L., Cui, B.-K., Yu, C.-J., & Zhou, L.-W. (2009). Species diversity and utilization of medicinal mushrooms and fungi in China (review). *International Journal of Medicinal Mushrooms, 11*(3), 287–302. http://dx.doi.org/10.1615/IntJMedMushr.v11.i3.80.
Deepak, V., Kalishwaralal, K., Ramkumarpandian, S., Babu, S. V., Senthilkumar, S. R., & Sangiliyandi, G. (2008). Optimization of media composition for Nattokinase production by *Bacillus subtilis* using response surface methodology. *Bioresource Technology, 99*(17), 8170–8174. http://dx.doi.org/10.1016/j.biortech.2008.03.018.
Delgado-Lista, J., Garcia-Rios, A., Perez-Martinez, P., Lopez-Miranda, J., & Perez-Jimenez, F. (2011). Olive oil and haemostasis: Platelet function, thrombogenesis and fibrinolysis. *Current Pharmaceutical Design, 17*(8), 778–785. http://dx.doi.org/10.2174/138161211795428876.
Díaz-Reinoso, B., Moure, A., Domínguez, H., & Parajo, J. (2007). Antioxidant extraction by supercritical fluids. *Supercritical fluid extraction of nutraceuticals and bioactive compounds* (pp. 275–305). Boca Raton, FL, USA: CRC Press.
Didukh, M., Wasser, S. P., & Nevo, E. (2003). Medicinal value of species of the family Agaricaceae Cohn (higher basidiomycetes): Current stage of knowledge and future perspectives. *International Journal of Medicinal Mushrooms, 5*, 133–152. http://dx.doi.org/10.1615/InterJMedicMush.v5.i2.30.
Diez, V., & Alvarez, A. (2001). Compositional and nutritional studies on two wild edible mushrooms from northwest Spain. *Food Chemistry*. http://dx.doi.org/10.1016/S0308-8146(01)00229-1.
Doll, R., Peto, R., Boreham, J., & Sutherland, I. (2005). Mortality from cancer in relation to smoking: 50 years observations on British doctors. *British Journal of Cancer, 92*(3), 426–429. http://dx.doi.org/10.1038/sj.bjc.6602359.
El-Fakharany, E. M., Haroun, B. M., Ng, T. B., & Redwan, E. R. (2010). Oyster mushroom laccase inhibits hepatitis C virus entry into peripheral blood cells and hepatoma cells. *Protein and Peptide Letters, 17*(8), 1031–1039. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20156183.
El-Mekkawy, S., Meselhy, M. R., Nakamura, N., Tezuka, Y., Hattori, M., Kakiuchi, N., ... Otake, T. (1998). Anti-HIV-1 and anti-HIV-1-protease substances from *Ganoderma lucidum*. *Phytochemistry, 49*(6), 1651–1657. http://dx.doi.org/10.1016/S0031-9422(98)00254-4.
Elsayed, E. A., El Enshasy, H., Wadaan, M. A. M., & Aziz, R. (2014). Mushrooms: A potential natural source of anti-inflammatory compounds for medical applications. *Mediators of Inflammation,* 1–15. http://dx.doi.org/10.1155/2014/805841.
Erjavec, J., Kos, J., Ravnikar, M., Dreo, T., & Sabotič, J. (2012). Proteins of higher fungi — From forest to application. *Trends in Biotechnology*. http://dx.doi.org/10.1016/j.tibtech.2012.01.004.
Falch, B. H., Espevik, T., Ryan, L., & Stokke, B. T. (2000). The cytokine stimulating activity of (1 → 3)-β-d-glucans is dependent on the triple helix conformation. *Carbohydrate Research, 329*(3), 587–596. http://dx.doi.org/10.1016/S0008-6215(00)00222-6.
Ferreira, I. C. F. R., Barros, L., & Abreu, R. M. V. (2009). Antioxidants in wild mushrooms. *Current Medicinal Chemistry, 16*(12), 1543–1560. http://dx.doi.org/10.2174/092986709787909587.
Finkel, T., & Holbrook, N. J. (2000). Oxidants, oxidative stress and the biology of ageing. *Nature, 408*(6809), 239–247. http://dx.doi.org/10.1038/35041687.
Finley, J. W., Kong, A.-N., Hintze, K. J., Jeffery, E. H., Ji, L. L., & Lei, X. G. (2011). Antioxidants in foods: State of the science important to the food industry. *Journal of Agricultural and Food Chemistry, 59*(13), 6837–6846. http://dx.doi.org/10.1021/jf2013875.
Førland, D. T., Johnson, E., Saetre, L., Lyberg, T., Lygren, I., & Hetland, G. (2011). Effect of an extract based on the medicinal mushroom *Agaricus blazei* Murill on expression of cytokines and calprotectin in patients with ulcerative colitis and Crohn's disease. *Scandinavian Journal of Immunology, 73*(1), 66–75. http://dx.doi.org/10.1111/j.1365-3083.2010.02477.x.
Fu, L., Wang, Y., Wang, J., Yang, Y., & Hao, L. (2013). Evaluation of the antioxidant activity of extracellular polysaccharides from *Morchella esculenta*. *Food & Function, 4*(6), 871–879. http://dx.doi.org/10.1039/c3fo60033e.
Gao, Y., Chan, E., & Zhou, S. (2004). Immunomodulating activities of Ganoderma, a mushroom with medicinal properties. *Food Reviews International, 20*(2), 123–161. http://dx.doi.org/10.1081/fri-120037158.
Gao, Y., Lan, J., Dai, X., Ye, J., & Zhou, S. (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. *International Journal of Medicinal Mushrooms, 6*(1), 8. http://dx.doi.org/10.1615/IntJMedMushr.v6.i1.30.
Gao, Y., Zhou, S., Huang, M., & Xu, A. (2003). Antibacterial and antiviral value of the genus Ganoderma P. Karst. Species (*Aphyllophoromycetideae*): A review. *International Journal of Medicinal Mushrooms, 5*. http://dx.doi.org/10.1615/InterJMedicMush.v5.i3.20.
Garcia, M. J., McNamara, P. M., Gordon, T., & Kannel, W. B. (1974). Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes, 23*(2), 105–111. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4359625.
George, S. J., & Beeching, C.a. (2006). Cadherin: Catenin complex: A novel regulator of vascular smooth muscle cell behaviour. *Atherosclerosis, 188*(1), 1–11. http://dx.doi.org/10.1016/j.atherosclerosis.2005.12.017.
George, S. J., & Dwivedi, A. (2004). MMPs, cadherins, and cell proliferation. *Trends in Cardiovascular Medicine, 14*(3), 100–105. http://dx.doi.org/10.1016/j.tcm.2003.12.008.
George, S. J., & Johnson, J. (Eds.). (2010). *Atherosclerosis: Molecular and cellular mechanisms*. Weinheim, Federal Republic of Germany: WILEY-VCH Verlag GmbH & Co.
Ghosh, S., May, M. J., & Kopp, E. B. (1998). NF- κ B AND REL PROTEINS: Evolutionarily conserved mediators of immune responses. *Annual Review of Immunology, 16*, 225–260. http://dx.doi.org/10.1146/annurev.immunol.16.1.225.
Gloire, G., Legrand-Poels, S., & Piette, J. (2006). NF-κB activation by reactive oxygen species: Fifteen years later. *Biochemical Pharmacology, 72*(11), 1493–1505. http://dx.doi.org/10.1016/j.bcp.2006.04.011.
Gosling, J., Slaymaker, S., Gu, L., Tseng, S., Zlot, C. H., Young, S. G., ... Charo, I. F. (1999). MCP-1 deficiency reduces susceptibility to atherosclerosis in mice that overexpress human apolipoprotein B. *Journal of Clinical Investigation, 103*(6), 773–778. http://dx.doi.org/10.1172/JCI5624.
Grotto, D., Bueno, D. C. R., Ramos, G. K., de A, da Costa, S. R., Spim, S. R. V., & Gerenutti, M. (2016). Assessment of the safety of the shiitake culinary-medicinal mushroom, *Lentinus edodes* (Agaricomycetes), in rats: Biochemical, hematological, and antioxidative parameters. *International Journal of Medicinal Mushrooms, 18*(10), 861–870. http://dx.doi.org/10.1615/IntJMedMushrooms.v18.i10.20.
Guillamón, E., García-Lafuente, A., Lozano, M., D'Arrigo, M., Rostagno, M. A., Villares, A., & Martínez, J. A. (2010). Edible mushrooms: Role in the prevention of cardiovascular diseases. *Fitoterapia, 81*(7), 715–723. http://dx.doi.org/10.1016/j.fitote.2010.06.

005.
Gunde-Cimerman, N. (1999). Medicinal value of the genus *Pleurotus* (Fr.) P.Karst. (Agaricales s.l., basidiomycetes). *International Journal of Medicinal Mushrooms, 1*(1), 69–80. http://dx.doi.org/10.1615/IntJMedMushrooms.v1.i1.50.
Guo, C. Y., Ji, S. Z., & Ping, C. X. (2009). Modulatory effect of *Ganoderma lucidum* polysaccharides on serum antioxidant enzymes activities in ovarian cancer rats. *Carbohydrate Polymers, 78*(2), 258–262. http://dx.doi.org/10.1016/j.carbpol.2009.03.030.
Hamilton, C. A., Miller, W. H., Al-benna, S., Brosnan, M. J., Drummond, R. D., Bride, M. W. M. C., & Dominiczak, A. F. (2004). *Strategies to reduce oxidative stress in cardiovascular disease. 234*, 219–234.
Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine, 352*(16), 1685–1695. http://dx.doi.org/10.1056/NEJMra043430.
Harada, E., D'Alessandro-Gabazza, C. N., Toda, M., Morizono, T., Chelakkot-Govindalayathil, A.-L., Roeen, Z., ... Gabazza, E. C. (2015). Amelioration of atherosclerosis by the new medicinal mushroom *Grifola gargal* singer. *Journal of Medicinal Food, 18*(8), 872–881. http://dx.doi.org/10.1089/jmf.2014.3315.
Heleno, S. A., Barros, L., Martins, A., Queiroz, M. J. R. P., Santos-Buelga, C., & Ferreira, I. C. F. R. (2012). Phenolic, polysaccharidic, and lipidic fractions of mushrooms from Northeastern Portugal: Chemical compounds with antioxidant properties. *Journal of Agricultural and Food Chemistry, 60*(18), 4634–4640. http://dx.doi.org/10.1021/jf300739m.
Hensley, K., Benaksas, E. J., Bolli, R., Comp, P., Grammas, P., Hamdheydari, L., ... Floyd, R. A. (2004). New perspectives on vitamin E: γ-Tocopherol and carboxyethylhydroxychroman metabolites in biology and medicine. *Free Radical Biology and Medicine, 36*(1), 1–15. http://dx.doi.org/10.1016/j.freeradbiomed.2003.10.009.
Hsu, C.-H., Hwang, K.-C., Chiang, Y.-H., & Chou, P. (2008). The mushroom *Agaricus blazei* murill extract normalizes liver function in patients with chronic hepatitis B. *The Journal of Alternative and Complementary Medicine, 14*(3), 299–301. http://dx.doi.org/10.1089/acm.2006.6344.
Huo, Y., & Ley, K. (2001). Adhesion molecules and atherogenesis. *Acta Physiologica Scandinavica, 173*(1), 35–43. http://dx.doi.org/10.1046/j.1365-201X.2001.00882.x.
Ichinohe, T., Ainai, A., Nakamura, T., Akiyama, Y., Maeyama, J., Odagiri, T., ... Hasegawa, H. (2010). Induction of cross-protective immunity against influenza A virus H5N1 by an intranasal vaccine with extracts of mushroom mycelia. *Journal of Medical Virology, 82*(1), 128–137. http://dx.doi.org/10.1002/jmv.21670.
Inoue, O., Suzuki-Inoue, K., Dean, W. L., Frampton, J., & Watson, S. P. (2003). Integrin alpha2beta1 mediates outside-in regulation of platelet spreading on collagen through activation of Src kinases and PLCgamma2. *The Journal of Cell Biology, 160*(5), 769–780. http://dx.doi.org/10.1083/jcb.200208043.
Ishibashi, K., Miura, N. N., Adachi, Y., Ohno, N., & Yadomae, T. (2001). Relationship between solubility of grifolan, a fungal 1,3-beta-D-glucan, and production of tumor necrosis factor by macrophages in vitro. *Bioscience, Biotechnology, and Biochemistry, 65*(9), 1993–2000. http://dx.doi.org/10.1271/bbb.65.1993.
Jackson, S. P., Nesbitt, W. S., & Kulkarni, S. (2003). Signaling events underlying thrombus formation. *Journal of Thrombosis and Haemostasis*. http://dx.doi.org/10.1046/j.1538-7836.2003.00267.x.
Jayakumar, T. (2010). An extract of the oyster mushroom, *Pleurotus ostreatus*, increases catalase gene expression and reduces protein oxidation during aging in rats. *Journal of Chinese Integrative Medicine,* 774–780. http://dx.doi.org/10.3736/jcim20100808.
Jedinak, A., Dudhgaonkar, S., Wu, Q.-L., Simon, J., & Sliva, D. (2011). Anti-inflammatory activity of edible oyster mushroom is mediated through the inhibition of NF-κB and AP-1 signaling. *Nutrition Journal, 10*(1), 52. http://dx.doi.org/10.1186/1475-2891-10-52.
Jeurink, P. V., Noguera, C. L., Savelkoul, H. F. J., & Wichers, H. J. (2008). Immunomodulatory capacity of fungal proteins on the cytokine production of human peripheral blood mononuclear cells. *International Immunopharmacology, 8*(8), 1124–1133. http://dx.doi.org/10.1016/j.intimp.2008.04.004.
Jia, J., Zhang, X., Hu, Y. S., Wu, Y., Wang, Q. Z., Li, N. N., ... Dong, X. C. (2009). Evaluation of in vivo antioxidant activities of *Ganoderma lucidum* polysaccharides in STZ-diabetic rats. *Food Chemistry, 115*(1), 32–36. http://dx.doi.org/10.1016/j.foodchem.2008.11.043.
Johnson, E., Førland, D. T., Saetre, L., Bernardshaw, S. V., Lyberg, T., & Hetland, G. (2009). Effect of an extract based on the medicinal mushroom *Agaricus blazei* murill on release of cytokines, chemokines and leukocyte growth factors in human blood ex vivo and in vivo. *Scandinavian Journal of Immunology, 69*(3), 242–250. http://dx.doi.org/10.1111/j.1365-3083.2008.02218.x.
Johnson, J. L., Jackson, C. L., Angelini, G. D., & George, S. J. (1998). Activation of matrix-degrading metalloproteinases by mast cell proteases in atherosclerotic plaques. *Arteriosclerosis, Thrombosis, and Vascular Biology, 18*(11), 1707–1715. http://dx.doi.org/10.1161/01.ATV.18.11.1707.
Jong, S. C., & Birmingham, J. M. (1992). Medicinal benefits of the mushroom Ganoderma. *Advances in Applied Microbiology, 37*, 101–134. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1642155.
Kabir, Y., Kimura, S., & Tamura, T. (1988). Dietary effect of *Ganoderma lucidum* mushroom on blood pressure and lipid levels in spontaneously hypertensive rats (SHR). *Journal of Nutritional Science and Vitaminology, 34*(4), 433–438. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3236086.
Kabir, Y., Yamaguchi, M., & Kimura, S. (1987). Effect of shiitake (*Lentinus edodes*) and maitake (*Grifola frondosa*) mushrooms on blood pressure and plasma lipids of spontaneously hypertensive rats. *Journal of Nutritional Science and Vitaminology, 33*(5), 341–346. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3443885.
Kajimoto, O., Ikeda, Y., Yabune, M., Sakamoto, A., & Kajimoto, Y. (2006). *The safety of extended consumption of freezing dryness Agaricus blazei (lwade strain 101) himematsutake. Yakuri to Chiryo. Yakuri to Chiryo. Vol. 34*Tokyo, Japan: Life Science. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=17649377.
Kalač, P. (2013). A review of chemical composition and nutritional value of wild-growing and cultivated mushrooms. *Journal of the Science of Food and Agriculture, 93*(2), 209–218. http://dx.doi.org/10.1002/jsfa.5960.
Kamruzzaman, S. M., Endale, M., Oh, W. J., Park, S. C., Kim, T. H., Lee, I. K., ... Rhee, M. H. (2011). Antiplatelet activity of *Phellinus baummii* methanol extract is mediated by cyclic AMP elevation and inhibition of collagen-activated integrin- α iibβ 3 and MAP kinase. *Phytotherapy Research, 25*(11), 1596–1603. http://dx.doi.org/10.1002/ptr.3450.
Kamruzzaman, S. M., Yayeh, T., Ji, H. D., Park, J. Y., Kwon, Y. S., Lee, I. K., ... Rhee, M. H. (2013). P-Terphenyl curtisian E inhibits in vitro platelet aggregation via cAMP elevation and VASP phosphorylation. *Vascular Pharmacology, 59*(3–4), 83–89. http://dx.doi.org/10.1016/j.vph.2013.07.002.
Kaneda, T., & Tokuda, S. (1966). Effect of various mushroom preparations on cholesterol levels in rats. *The Journal of Nutrition, 90*(4), 371–376. Retrieved from http://jn.nutrition.org/cgi/content/abstract/90/4/371.
Karácsonyi, Š., & Kuniak, Ľ. (1994). Polysaccharides of *Pleurotus ostreatus*: Isolation and structure of pleuran, an alkali-insoluble β-D-glucan. *Carbohydrate Polymers, 24*(2), 107–111. http://dx.doi.org/10.1016/0144-8617(94)90019-1.
Karin, M., Cao, Y., Greten, F. R., & Li, Z.-W. (2002). NF-κB in cancer: From innocent bystander to major culprit. *Nature Reviews Cancer, 2*(4), 301–310. http://dx.doi.org/10.1038/nrc780.
Kataoka, K., Muta, T., Yamazaki, S., & Takeshige, K. (2002). Activation of macrophages by linear (1 → 3)-β-D-glucans. Impliations for the recognition of fungi by innate immunity. *The Journal of Biological Chemistry, 277*(39), 36825–36831. http://dx.doi.org/10.1074/jbc.M206756200.
Kauskot, A., Adam, F., Mazharian, A., Ajzenberg, N., Berrou, E., Bonnefoy, A., ... Bryckaert, M. (2007). Involvement of the mitogen-activated protein kinase c-Jun NH2-terminal kinase 1 in thrombus formation. *Journal of Biological Chemistry, 282*(44), 31990–31999. http://dx.doi.org/10.1074/jbc.M701596200.
Khan, M. A., Tania, M., Liu, R., & Rahman, M. M. (2013). *Hericium erinaceus*: An edible mushroom with medicinal values. *Journal of Complementary and Integrative Medicine, 10*(1), http://dx.doi.org/10.1515/jcim-2013-0001.
Kim, H. W., & Kim, B. K. (1999). Biomedicinal triterpenoids of *Ganoderma lucidum* (Curt.: Fr.) P. Karst. (*Aphyllophoromycetideae*). *International Journal of Medicinal Mushrooms, 1*(2), 121–138. http://dx.doi.org/10.1615/IntJMedMushrooms.v1.i2.20.
Kim, M.-Y., Seguin, P., Ahn, J.-K., Kim, J.-J., Chun, S.-C., Kim, E.-H., ... Chung, I.-M. (2008). Phenolic compound concentration and antioxidant activities of edible and medicinal mushrooms from Korea. *Journal of Agricultural and Food Chemistry, 56*(16), 7265–7270. http://dx.doi.org/10.1021/jf8008553.
Kim, W., Choi, K., Kim, Y., Park, H., Choi, J., Lee, Y., ... Lee, S. (1996). Purification and characterization of a fibrinolytic enzyme produced from *Bacillus* sp. strain CK 11-4 screened from Chungkook-Jang. *Applied and Environmental Microbiology, 62*(7), 2482–2488.
Kim, Y.-O., Lee, S.-W., Oh, C.-H., & Rhee, Y.-H. (2012). *Hericium erinaceus* suppresses LPS-induced pro-inflammation gene activation in RAW264.7 macrophages. *Immunopharmacology and Immunotoxicology, 34*(3), 504–512. http://dx.doi.org/10.3109/08923973.2011.633527.
Ko, J. L., Hsu, C. I., Lin, R. H., Kao, C. L., & Lin, J. Y. (1995). A new fungal immunomodulatory protein, FIP-fve isolated from the edible mushroom, *Flammulina velutipes* and its complete amino acid sequence. *European Journal of Biochemistry, 228*(2), 244–249. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7705335.
Kodama, K., Suzuki, M., Toyosawa, T., & Araki, S. (2005). Inhibitory mechanisms of highly purified vitamin B2 on the productions of proinflammatory cytokine and NO in endotoxin-induced shock in mice. *Life Sciences, 78*(2), 134–139. http://dx.doi.org/10.1016/j.lfs.2005.04.037.
Kokubo, T., Taniguchi, Y., Kanayama, M., Shimura, M., Konishi, Y., Kawagishi, H., ... Yoshida, A. (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 Chemistry, 129*(1), 92–99. http://dx.doi.org/10.1016/j.foodchem.2011.04.031.
Kolodgie, F. D., Burke, A. P., Wight, T. N., & Virmani, R. (2004). The accumulation of specific types of proteoglycans in eroded plaques: A role in coronary thrombosis in the absence of rupture. *Current Opinion in Lipidology, 15*(5), 575–582. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15361794.
Komoda, Y., Shimizu, M., Sonoda, Y., & Sato, Y. (1989). Ganoderic acid and its derivatives as cholesterol synthesis inhibitors. *Chemical & Pharmaceutical Bulletin, 37*(2), 531–533. http://dx.doi.org/10.1248/cpb.37.531.
Kozarski, M. S., Klaus, A., Jakovljevic, D., Todorovic, N., Vunduk, J., Petrović, P., ... Van Griensven, L. (2015). Antioxidants of edible mushrooms. *Molecules, 20*(10), 19489–19525. http://dx.doi.org/10.3390/molecules201019489.
Kuijpers, M. J. E., Schulte, V., Oury, C., Lindhout, T., Broers, J., Hoylaerts, M. F., ... Heemskerk, J. W. M. (2004). Facilitating roles of murine platelet glycoprotein Ib and alphaIIbbeta3 in phosphatidylserine exposure during vWF-collagen-induced thrombus formation. *The Journal of Physiology*. http://dx.doi.org/10.1113/jphysiol.2004.062414.
Kuroiwa, Y., Nishikawa, A., Imazawa, T., Kanki, K., Kitamura, Y., Umemura, T., & Hirose, M. (2005). Lack of subchronic toxicity of an aqueous extract of *Agaricus blazei* Murrill in F344 rats. *Food and Chemical Toxicology, 43*(7), 1047–1053. http://dx.doi.org/10.1016/j.fct.2005.02.007.
Lam, S. K., & Ng, T. B. (2001a). First simultaneous isolation of a ribosome inactivating protein and an antifungal protein from a mushroom (*Lyophyllum shimeji*) together with evidence for synergism of their antifungal effects. *Archives of Biochemistry and Biophysics, 393*(2), 271–280. http://dx.doi.org/10.1006/abbi.2001.2506.
Lam, S. K., & Ng, T. B. (2001b). Hypsin, a novel thermostable ribosome-inactivating protein with antifungal and antiproliferative activities from fruiting bodies of the

edible mushroom *Hypsizygus marmoreus*. *Biochemical and Biophysical Research Communications, 285*(4), 1071–1075. http://dx.doi.org/10.1006/bbrc.2001.5279.
Langer, H. F., & Gawaz, M. (2008). Platelet-vessel wall interactions in atherosclerotic disease. *Thrombosis and Haemostasis, 99*(3), 480–486. http://dx.doi.org/10.1160/TH07-11-0685.
Lee, M.-K., Park, Y. B., Moon, S.-S., Bok, S. H., Kim, D.-J., Ha, T.-Y., ... Choi, M.-S. (2007). Hypocholesterolemic and antioxidant properties of 3-(4-hydroxyl)propanoic acid derivatives in high-cholesterol fed rats. *Chemico-Biological Interactions, 170*(1), 9–19. http://dx.doi.org/10.1016/j.cbi.2007.06.037.
Levine, T. B., & Levine, A. B. (2012). Inflammation. *Metabolic syndrome and cardiovascular disease* (pp. 192–227). Oxford, UK: Blackwell Publishing Ltd. http://dx.doi.org/10.1002/9781118480045.ch9.
Li, A. C., & Glass, C. K. (2002). The macrophage foam cell as a target for therapeutic intervention. *Nature Medicine, 8*(11), 1235–1242. http://dx.doi.org/10.1038/nm1102-1235.
Li, I.-C., Chen, Y.-L., Lee, L.-Y., Chen, W.-P., Tsai, Y.-T., Chen, C.-C., & Chen, C.-S. (2014). Evaluation of the toxicological safety of erinacine A-enriched *Hericium erinaceus* in a 28-day oral feeding study in Sprague–Dawley rats. *Food and Chemical Toxicology, 70*, 61–67. http://dx.doi.org/10.1016/j.fct.2014.04.040.
Li, M., Zhang, G., Wang, H., & Ng, T. (2010a). Purification and characterization of a laccase from the edible wild mushroom Tricholoma mongolicum. *Journal of Microbiology and Biotechnology, 20*(7), 1069–1076. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20668399.
Li, Y., Zhang, G., Ng, T. B., & Wang, H. (2010b). A novel lectin with antiproliferative and HIV-1 reverse transcriptase inhibitory activities from dried fruiting bodies of the monkey head mushroom *Hericium erinaceum*. *Journal of Biomedicine and Biotechnology, 2010*, 1–9. http://dx.doi.org/10.1155/2010/716515.
Libby, P. (2002). Atherosclerosis: The new view. *Scientific American, 286*(5), 46–55. http://dx.doi.org/10.1038/scientificamerican0502-46.
Libby, P. (2009). Molecular and cellular mechanisms of the thrombotic complications of atherosclerosis. *Journal of Lipid Research, 50*, 352–357. http://dx.doi.org/10.1194/jlr.R800099-JLR200.
Libby, P., Ridker, P. M., & Hansson, G. K. (2011). Progress and challenges in translating the biology of atherosclerosis. *Nature, 473*(7347), 317–325. http://dx.doi.org/10.1038/nature10146.
Lin, C.-H., Sheu, G.-T., Lin, Y.-W., Yeh, C.-S., Huang, Y.-H., Lai, Y.-C., ... Ko, J.-L. (2010). A new immunomodulatory protein from Ganoderma microsporum inhibits epidermal growth factor mediated migration and invasion in A549 lung cancer cells. *Process Biochemistry, 45*(9), 1537–1542. http://dx.doi.org/10.1016/j.procbio.2010.06.006.
Liu, J., Jia, L., Kan, J., & Jin, C. (2012). In vitro and in vivo antioxidant activity of ethanolic extract of white button mushroom (*Agaricus bisporus*). *Food and Chemical Toxicology, 51*, 310–316. http://dx.doi.org/10.1016/j.fct.2012.10.014.
Liu, J., Yao, Y., Xu, R., Xu, W., Zhang, W., Kuang, R., & Gao, M. (2005). Study on early fibrinolytic therapy to avoid acute myocardial infarction. *Zhonghua Xin Xue Guan Bing Za Zhi, 33*(9), 782–784. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16266450.
Liu, X., Kopparapu, N., Shi, X., Deng, Y., Zheng, X., & Wu, J. (2015). Purification and biochemical characterization of a novel fibrinolytic enzyme from culture supernatant of *Cordyceps militaris*. *Journal of Agricultural and Food Chemistry, 63*(8), 2215–2224. http://dx.doi.org/10.1021/jf505717e.
Liu, X., Zheng, X., Qian, P.-Z., Kopparapu, N.-K., Deng, Y., Nonaka, M., & Harada, N. (2014). Purification and characterization of a novel fibrinolytic enzyme from culture supernatant of *Pleurotus ostreatus*. *Journal of Microbiology and Biotechnology, 24*(2), 245–253. http://dx.doi.org/10.1021/jf505717e.
Longvah, T., & Deosthale, Y. G. (1998). Compositional and nutritional studies on edible wild mushroom from northeast India. *Food Chemistry, 63*(3), 331–334. http://dx.doi.org/10.1016/S0308-8146(98)00026-0.
Lu, W. J., Lin, S. C., Lan, C. C., Lee, T. Y., Hsia, C. H., Huang, Y. K., ... Sheu, J. R. (2014). Effect of *Antrodia camphorata* on inflammatory arterial thrombosis-mediated platelet activation: The pivotal role of protein kinase C. *Scientific World Journal,* 2014. http://dx.doi.org/10.1155/2014/745802.
Lull, C., Wichers, H. J., & Savelkoul, H. F. J. (2005). Antiinflammatory and immunomodulating properties of fungal. *Metabolites, 2*, 63–80. http://dx.doi.org/10.1155/MI.2005.63.
Lusis, A. J. (2000). Atherosclerosis. *Nature, 407*(6801), 233–241. http://dx.doi.org/10.1038/35025203.
Martin, K. R. (2010a). 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. *Nutrition Journal, 9*, 29. http://dx.doi.org/10.1186/1475-2891-9-29.
Martin, K. R. (2010b). The bioactive agent ergothioneine, a key component of dietary mushrooms, inhibits monocyte binding to endothelial cells characteristic of early cardiovascular disease. *Journal of Medicinal Food, 13*(6), 1340–1346. http://dx.doi.org/10.1089/jmf.2009.0194.
Massberg, S., Brand, K., Gruner, S., Page, S., Muller, E., Muller, I., ... Gawaz, M. (2002). A critical role of platelet adhesion in the initiation of atherosclerotic lesion formation. *Journal of Experimental Medicine, 196*(7), 887–896. http://dx.doi.org/10.1084/jem.20012044.
Masuko, T., Minami, A., Iwasaki, N., Majima, T., Nishimura, S. I., & Lee, Y. C. (2005). Carbohydrate analysis by a phenol-sulfuric acid method in microplate format. *Analytical Biochemistry, 339*(1), 69–72. http://dx.doi.org/10.1016/j.ab.2004.12.001.
Mattila, P., Könkö, K., Eurola, M., Pihlava, J. M., Astola, J., Vahteristo, L., ... Piironen, V. (2001). Contents of vitamins, mineral elements, and some phenolic compounds in cultivated mushrooms. *Journal of Agricultural and Food Chemistry, 49*(5), 2343–2348. http://dx.doi.org/10.1021/jf001525d.
Mattila, P., Suonpää, K., & Piironen, V. (2000). Functional properties of edible mushrooms. *Nutrition, 16*(7–8), 694–696. http://dx.doi.org/10.1016/S0899-9007(00)00341-5.
Mau, J.-L., Lin, H.-C., Ma, J.-T., & Song, S.-F. (2001). Non-volatile taste components of several speciality mushrooms. *Food Chemistry, 73*(4), 461–466. http://dx.doi.org/10.1016/S0308-8146(00)00330-7.
Medved, L., & Nieuwenhuizen, W. (2003). Molecular mechanisms of initiation of fibrinolysis by fibrin. *Thrombosis and Haemostasis*. http://dx.doi.org/10.1267/THRO03030409.
Meng, F., Zhou, B., Lin, R., Jia, L., Liu, X., Deng, P., ... Zhang, J. (2010). Extraction optimization and in vivo antioxidant activities of exopolysaccharide by *Morchella esculenta* SO-01. *Bioresource Technology, 101*(12), 4564–4569. http://dx.doi.org/10.1016/j.biortech.2010.01.113.
Mensink, R. P., Aro, A., Den Hond, E., German, J. B., Griffin, B.a., Ter Meer, H. U., ... Stahl, W. (2003). PASSCLAIM — Diet-related cardiovascular disease. *European Journal of Nutrition, 42*, 6–27. http://dx.doi.org/10.1007/s00394-003-1102-2.
Mine, Y., Kwan Wong, A. H., & Jiang, B. (2005). Fibrinolytic enzymes in Asian traditional fermented foods. *Food Research International, 38*(3), 243–250. http://dx.doi.org/10.1016/j.foodres.2004.04.008.
de Miranda, A. M., Rossoni Júnior, J. V., Souza e Silva, L., dos Santos, R. C., Silva, M. E., & Pedrosa, M. L. (2016). *Agaricus brasiliensis* (sun mushroom) affects the expression of genes related to cholesterol homeostasis. *European Journal of Nutrition*. http://dx.doi.org/10.1007/s00394-016-1217-x.
Miyazawa, N., Okazaki, M., & Ohga, S. (2008). Antihypertensive effect of *Pleurotus nebrodensis* in spontaneously hypertensive rats. *Journal of Oleo Science, 57*(12), 675–681. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19001780.
Moon, S. M., Kim, J. S., Kim, H. J., Choi, M. S., Park, B. R., Kim, S. G., ... Kim, C. S. (2014). Purification and characterization of a novel fibrinolytic α chymotrypsin like serine metalloprotease from the edible mushroom, *Lyophyllum shimeji*. *Journal of Bioscience and Bioengineering, 117*(5), 544–550. http://dx.doi.org/10.1016/j.jbiosc.2013.10.019.
Moore, K. J., & Rayner, K. (2010). Macrophage foam cell formation: The pathways to cholesterol engorgement. In S. J. George, & J. Johnson (Eds.). *Atherosclerosis: Molecular and cellular mechanisms* (pp. 231–254). Weinheim, Federal Republic of Germany: WILEY-VCH Verlag GmbH & Co.
Mor, A., Planer, D., Luboshits, G., Afek, A., Metzger, S., Chajek-Shaul, T., ... George, J. (2007). Role of naturally occurring CD4 + CD25 + regulatory T cells in experimental atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 27*(4), 893–900.
Mori, K., Kikuchi, H., Obara, Y., Iwashita, M., Azumi, Y., Kinugasa, S., ... Nakahata, N. (2010). Inhibitory effect of hericenone B from *Hericium erinaceus* on collagen-induced platelet aggregation. *Phytomedicine, 17*(14), 1082–1085. http://dx.doi.org/10.1016/j.phymed.2010.05.004.
Mori, K., Kobayashi, C., Tomita, T., Inatomi, S., & Ikeda, M. (2008). Antiatherosclerotic effect of the edible mushrooms *Pleurotus eryngii* (Eringi), *Grifola frondosa* (Maitake), and *Hypsizygus marmoreus* (Bunashimeji) in apolipoprotein E-deficient mice. *Nutrition Research (New York, N.Y.), 28*(5), 335–342. http://dx.doi.org/10.1016/j.nutres.2008.03.010.
Morigiwa, A., Kitabake, K., Fujimoto, Y., & Ikekawa, N. (1986). Angiotensin converting enzyme-inhibitory triterpenes from *Ganoderma lucidum*. *Chemical & Pharmaceutical Bulletin, 34*(7), 3025–3028. http://dx.doi.org/10.1248/cpb.34.3025.
Moro, C., Palacios, I., Lozano, M., D'Arrigo, M., Guillamón, E., Villares, A., ... García-Lafuente, A. (2012). Anti-inflammatory activity of methanolic extracts from edible mushrooms in LPS activated RAW 264.7 macrophages. *Food Chemistry, 130*(2), 350–355. http://dx.doi.org/10.1016/j.foodchem.2011.07.049.
Mukai, H., Watanabe, T., Ando, M., & Katsumata, N. (2006). An alternative medicine, *Agaricus blazei*, may have induced severe hepatic dysfunction in cancer patients. *Japanese Journal of Clinical Oncology, 36*(12), 808–810. http://dx.doi.org/10.1093/jjco/hyl108.
Muzaffar, S., Shukla, N., & Jeremy, J. Y. (2005). Nicotinamide adenine dinucleotide phosphate oxidase: A promiscuous therapeutic target for cardiovascular drugs? *Trends in Cardiovascular Medicine, 15*(8), 278–282. http://dx.doi.org/10.1016/j.tcm.2005.09.001.
Nanba, H., Hamaguchi, A., & Kuroda, H. (1987). The chemical structure of an antitumor polysaccharide in fruit bodies of *Grifola frondosa* (maitake). *Chemical & Pharmaceutical Bulletin, 35*(3), 1162–1168. http://dx.doi.org/10.1248/cpb.35.1162.
Nelson, D. L., Lehninger, A. L., Cox, M. M., & Freeman, W. H. (2008). Lehninger principles of biochemistry. Retrieved from https://books.google.com.my/books?id=5Ek9J4p3NfkC.
Newby, A. C. (2006). Matrix metalloproteinases regulate migration, proliferation, and death of vascular smooth muscle cells by degrading matrix and non-matrix substrates. *Cardiovascular Research, 69*(3), 614–624. http://dx.doi.org/10.1016/j.cardiores.2005.08.002.
Newman, T. B., & Maisels, M. J. (1992). Evaluation and treatment of jaundice in the term newborn: A kinder, gentler approach. *Pediatrics, 89*(5 Pt 1), 809–818. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1579380.
Ng, T. B., Lam, Y. W., & Wang, H. (2003). Calcaelin, a new protein with translation-inhibiting, antiproliferative and antimitogenic activities from the mosaic puffball mushroom *Calvatia caelata*. *Planta Medica, 69*(3), 212–217. http://dx.doi.org/10.1055/s-2003-38492.
Ouimet, M., Wang, M.-D., Cadotte, N., Ho, K., & Marcel, Y. L. (2008). Epoxycholesterol impairs cholesteryl ester hydrolysis in macrophage foam cells, resulting in decreased cholesterol efflux. *Arteriosclerosis, Thrombosis, and Vascular Biology, 28*(6), 1144–1150. http://dx.doi.org/10.1161/ATVBAHA.107.157115.
Pacheco-Sánchez, M., Boutin, Y., Angers, P., Gosselin, A., & Tweddell, R. J. (2007). Inhibitory effect of CDP, a polysaccharide extracted from the mushroom *Collybia dryophila*, on nitric oxide synthase expression and nitric oxide production in macrophages. *European Journal of Pharmacology, 555*(1), 61–66. http://dx.doi.org/10.

1016/j.ejphar.2006.10.015.
Palacios, I., Lozano, M., Moro, C., Dapos Arrigo, M., Rostagno, M. A., Martínez, J. A., ... Villares, A. (2011). Antioxidant properties of phenolic compounds occurring in edible mushrooms. *Food Chemistry, 128*(3), 674–678. http://dx.doi.org/10.1016/j.foodchem.2011.03.085.
Park, I. S., Park, J. U., Seo, M. J., Kim, M. J., Lee, H. H., Kim, S. R., ... Jeong, Y. K. (2010). Purification and biochemical characterization of a 17 kDa fibrinolytic enzyme from *Schizophyllum commune*. *Journal of Microbiology, 48*(6), 836–841. http://dx.doi.org/10.1007/s12275-010-0384-3.
Park, J. Y., Oh, W.-J., Kwak, D.-M., Kim, M.-G., Seo, G.-S., Hong, S.-B., & Rhee, M. H. (2011). The anti-platelet activity of *Hypsizygus marmoreus* extract is involved in the suppression of intracellular calcium mobilization and integrin α IIbβ 3 activation. *Journal of Medicinal Plant Research, 5*(11), 2369–2377. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-79959822895&partnerID=40&md5=2be0c0caaaf5ac7122ff4b2fb6df51c2.
Paterson, R. R. M., & Lima, N. (2014). Biomedical effects of mushrooms with emphasis on pure compounds. *Biomedical Journal, 37*(6), 357. http://dx.doi.org/10.4103/2319-4170.143502.
Ping, C. X., Yan, C., Bing, L. S., Guo, C. Y., Yun, L. J., & Ping, L. L. (2009). Free radical scavenging of *Ganoderma lucidum* polysaccharides and its effect on antioxidant enzymes and immunity activities in cervical carcinoma rats. *Carbohydrate Polymers, 77*(2), 389–393. http://dx.doi.org/10.1016/j.carbpol.2009.01.009.
Poder, R. (2005). The ice man's fungi: Facts and mysteries. *International Journal of Medicinal Mushrooms, 7*(3), http://dx.doi.org/10.1615/IntJMedMushrooms.v7.i3.190.
Ramberg, J. E., Nelson, E. D., & Sinnott, R. A. (2010). Immunomodulatory dietary polysaccharides: A systematic review of the literature. *Nutrition Journal, 9*(1), 54. http://dx.doi.org/10.1186/1475-2891-9-54.
Rauch, U., Osende, J. I., Fuster, V., Badimon, J. J., Fayad, Z., & Chesebro, J. H. (2001). Thrombus formation on atherosclerotic plaques: Pathogenesis and clinical consequences. *Annals of Internal Medicine*. http://dx.doi.org/10.1059/0003-4819-156-2-201201170-02011.
Reis, F. S., Martins, A., Barros, L., & Ferreira, I. C. F. R. (2012). Antioxidant properties and phenolic profile of the most widely appreciated cultivated mushrooms: A comparative study between in vivo and in vitro samples. *Food and Chemical Toxicology, 50*(5), 1201–1207. http://dx.doi.org/10.1016/j.fct.2012.02.013.
Reshetnikov, S. V., Wasser, S. P., & Tan, K. K. (2001). Higher *Basidiomycota* as a source of antitumor and immunostimulating polysaccharides (review). *International Journal of Medicinal Mushrooms, 3*(4), 361–394. http://dx.doi.org/10.1615/IntJMedMushr.v3.i4.80.
Ridker, P. M. (2003). High-sensitivity C-reactive protein and cardiovascular risk: Rationale for screening and primary prevention. *The American Journal of Cardiology, 92*(4B), 17K–22K. http://dx.doi.org/10.1016/S0002-9149(03)00774-4.
Rony, K. A., Ajith, T. A., Nima, N., & Janardhanan, K. K. (2014). Hypolipidemic activity of *Phellinus rimosus* against triton WR-1339 and high cholesterol diet induced hyperlipidemic rats. *Environmental Toxicology and Pharmacology, 37*(2), 482–492. http://dx.doi.org/10.1016/j.etap.2014.01.004.
Ross, R. (1999). Atherosclerosis—An inflammatory disease. *The New England Journal of Medicine, 340*(2), 115–126. http://dx.doi.org/10.1016/S1053-0770(99)90233-1.
Ross, R., Glomset, J., & Harker, L. (1977). Response to injury and atherogenesis. *The American Journal of Pathology, 86*(3), 675–684. http://dx.doi.org/PMC2032127.
Rowan, N., Smith, J., & Sullivan, R. (2003). Immunomodulatory activities of mushroom glucans and polysaccharide–protein complexes in animals and humans (a review). *International Journal of Medicinal Mushrooms, 5*(2), http://dx.doi.org/10.1615/InterJMedicMush.v5.i2.10.
RP, A., Chopra, A., GS, L., MM, P., Srikanth, N., Ota, S., & Jain, S. (2010). Effect of oyster mushroom on glycemia, lipid profile and quality of life in type 2 diabetic patients. *Australian Journal of Medical Herbalism, 22*(2), 50–54. 5 pp. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=105032681&site=ehost-live.
Saarinen, J., Kalkkinen, N., Welgus, H. G., & Kovanen, P. T. (1994). Activation of human interstitial procollagenase through direct cleavage of the Leu83-Thr84 bond by mast cell chymase. *The Journal of Biological Chemistry, 269*(27), 18134–18140. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8027075.
Sachs, U. J. H., & Nieswandt, B. (2007). In vivo thrombus formation in murine models. *Circulation Research*. http://dx.doi.org/10.1161/01.RES.0000261936.85776.5f.
Sánchez, C. (2017). Bioactives from mushroom and their application. *Food bioactives* (pp. 23–57). Cham: Springer International Publishing. http://dx.doi.org/10.1007/978-3-319-51639-4_2.
Sasaki, N., Yamashita, T., Takeda, M., & Hirata, K. (2012). Regulatory T cells in atherogenesis. *Journal of Atherosclerosis and Thrombosis, 19*(6), 503–515. http://dx.doi.org/10.5551/jat.10934.
Sasaki, T., & Takasuka, N. (1976). Further study of the structure of lentinan, an antitumor polysaccharide from *Lentinus edodes*. *Carbohydrate Research, 47*(1), 99–104. http://dx.doi.org/10.1016/S0008-6215(00)83552-1.
Sato, M., Tokuji, Y., Yoneyama, S., Fujii-Akiyama, K., Kinoshita, M., Chiji, H., & Ohnishi, M. (2013). Effect of dietary maitake (*Grifola frondosa*) mushrooms on plasma cholesterol and hepatic gene expression in cholesterol-fed mice. *Journal of Oleo Science, 62*(12), 1049–1058. http://dx.doi.org/10.5650/jos.62.1049.
Saxena, R. N., Pendse, V. K., & Khanna, N. K. (1984). Anti-inflammatory and analgesic properties of four amino-acids. *Indian Journal of Physiology and Pharmacology, 28*(4), 299–305. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6335992.
Schneider, I., Kressel, G., Meyer, A., Krings, U., Berger, R. G., & Hahn, A. (2010). Lipid lowering effects of oyster mushroom (*Pleurotus ostreatus*) in humans. *Journal of Functional Foods, 3*(1), 17–24. http://dx.doi.org/10.1016/j.jff.2010.11.004.
Shamamian, P., Schwartz, J. D., Pocock, B. J., Monea, S., Whiting, D., Marcus, S. G., & Mignatti, P. (2001). Activation of progelatinase A (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: A role for inflammatory cells in tumor invasion and angiogenesis. *Journal of Cellular Physiology, 189*(2), 197–206. http://dx.doi.org/10.1002/jcp.10014.
Shimada, K. (2009). Immune system and atherosclerotic disease: Heterogeneity of leukocyte subsets participating in the pathogenesis of atherosclerosis. *Circulation Journal: Official Journal of the Japanese Circulation Society, 73*(6), 994–1001. http://dx.doi.org/10.1253/circj.CJ-09-0277.
Silverman, N., & Maniatis, T. (2001). NF-kappaB signaling pathways in mammalian and insect innate immunity. *Genes & Development*. http://dx.doi.org/10.1101/gad.909001.
Smith, J. E., Rowan, N. J., & Sullivan, R. (2002). Medicinal mushrooms: A rapidly developing area of biotechnology for cancer therapy and other bioactivities. *Biotechnology Letters, 24*(22), 1839–1845. http://dx.doi.org/10.1023/A:1020994628109.
Steinberg, D. (2002). Atherogenesis in perspective: Hypercholesterolemia and inflammation as partners in crime. *Nature Medicine, 8*(11), 1211–1217. http://dx.doi.org/10.1038/nm1102-1211.
Steinberg, D. (2009). The LDL modification hypothesis of atherogenesis: An update. *Journal of Lipid Research, 50*(Supplement), S376–S381. http://dx.doi.org/10.1194/jlr.R800087-JLR200.
Strehlow, K., Rotter, S., Wassmann, S., Adam, O., Grohe, C., Laufs, K., ... Nickenig, G. (2003). Modulation of antioxidant enzyme expression and function by estrogen. *Circulation Research, 93*(2), 170–177. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12816884.
Su, C.-Y., Shiao, M.-S., & Wang, C.-T. (1999). Predominant inhibition of ganodermic acid S on the thromboxane A2-dependent pathway in human platelets response to collagen. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 1437*(2), 223–234. http://dx.doi.org/10.1016/S1388-1981(98)00012-2.
Sullivan, R., Smith, J. E., & Rowan, N. J. (2006). Medicinal mushrooms and cancer therapy: Translating a traditional practice into Western medicine. *Perspectives in Biology and Medicine, 49*(2), 159–170. http://dx.doi.org/10.1353/pbm.2006.0034.
Sumi, H., Yanagisawa, Y., Yatagai, C., & Saito, J. (2004). Natto Bacillus as an oral fibrinolytic agent: Nattokinase activity and the ingestion effect of *Bacillus subtilis* natto. *Food Science and Technology Research, 10*(1), 17–20. http://dx.doi.org/10.3136/fstr.10.17.
Sun, Y., Ma, Y., Xu, Z., Yang, W., Mariga, A. M., Pang, G., ... Hu, Q. (2014). Immunoregulatory role of *Pleurotus eryngii* superfine powder through intercellular communication of cytokines. *Food and Agricultural Immunology, 25*(4), 586–599. http://dx.doi.org/10.1080/09540105.2013.858662.
Tabas, I. (2010). Macrophage death and defective inflammation resolution in atherosclerosis. *Nature Reviews Immunology, 10*, 36–46. http://dx.doi.org/10.1038/nri2675.
Tabas, I., García-Cardeña, G., & Owens, G. K. (2015). Recent insights into the cellular biology of atherosclerosis. *The Journal of Cell Biology, 209*(1), 13–22. http://dx.doi.org/10.1083/jcb.201412052.
Tabas, I., Williams, K. J., & Borén, J. (2007). *Subendothelial lipoprotein retention as the initiating process in atherosclerosis update and therapeutic implications.* 1832–1845. http://dx.doi.org/10.1161/CIRCULATIONAHA.106.676890.
Tak, P. P., & Firestein, G. S. (2001). NF-κB: A key role in inflammatory diseases. *Journal of Clinical Investigation, 107*(1), 7–11. http://dx.doi.org/10.1172/JCI11830.
Tedgui, A., & Mallat, Z. (2006). Cytokines in atherosclerosis: Pathogenic and regulatory pathways. *Physiological Reviews, 86*(2), 515–581. http://dx.doi.org/10.1152/physrev.00024.2005.
Tortora, G. J., & Derrickson, B. H. (2011). *Principles of anatomy and physiology, 13th edition* (13th ed.). John Wiley Sons, Inc.
Toyosawa, T., Suzuki, M., Kodama, K., & Araki, S. (2004). Effects of intravenous infusion of highly purified vitamin B 2 on lipopolysaccharide-induced shock and bacterial infection in mice. *European Journal of Pharmacology, 492*(2–3), 273–280. http://dx.doi.org/10.1016/j.ejphar.2004.04.004.
Valverde, M. E., Hernández-Pérez, T., & Paredes-López, O. (2015). Edible mushrooms: Improving human health and promoting quality life. *International Journal of Microbiology, 2015*, 1–14. http://dx.doi.org/10.1155/2015/376387.
Van Griensven, L. J. L. D. (2009). Culinary-medicinal mushrooms: Must action be taken? *International Journal of Medicinal Mushrooms, 11*(3), 281–286. http://dx.doi.org/10.1615/IntJMedMushr.v11.i3.70.
Varga-Szabo, D., Pleines, I., & Nieswandt, B. (2008). Cell adhesion mechanisms in platelets. *Arteriosclerosis, Thrombosis, and Vascular Biology*. http://dx.doi.org/10.1161/ATVBAHA.107.150474.
Verma, I. M., Stevenson, J. K., Schwarz, E. M., Van Antwerp, D., & Miyamoto, S. (1995). Rel/NF-kappa B/I kappa B family: Intimate tales of association and dissociation. *Genes & Development, 9*(22), 2723–2735. http://dx.doi.org/10.1101/gad.9.22.2723.
Vetvicka, V., & Yvin, J.-C. (2004). Effects of marine β − 1,3 glucan on immune reactions. *International Immunopharmacology, 4*(6), 721–730. http://dx.doi.org/10.1016/j.intimp.2004.02.007.
Vickers, A. (2002). Botanical medicines for the treatment of cancer: Rationale, overview of current data, and methodological considerations for phase I and II trials. *Cancer Investigation, 20*(7–8), 1069–1079. http://dx.doi.org/10.1081/CNV-120005926.
van der Wal, A., & Becker, A. E. (1999). Atherosclerotic plaque rupture – Pathologic basis of plaque stability and instability. *Cardiovascular Research, 41*(2), 334–344. http://dx.doi.org/10.1016/S0008-6363(98)00276-4.
Wang, C. T., Ji, B. P., Li, B., Nout, R., Li, P. L., Ji, H., & Chen, L. F. (2006). Purification and characterization of a fibrinolytic enzyme of *Bacillus subtilis* DC33, isolated from Chinese traditional Douchi. *Journal of Industrial Microbiology & Biotechnology, 33*(9), 750–758. http://dx.doi.org/10.1007/s10295-006-0111-6.
Wang, F., Wang, C., Li, M., Zhang, J.-P., Gui, L.-L., An, X.-M., & Chang, W.-R. (2005).

Crystal structure of earthworm fibrinolytic enzyme component B: A novel, glycosylated two-chained trypsin. *Journal of Molecular Biology, 348*(3), 671–685. http://dx.doi.org/10.1016/j.jmb.2005.02.055.

Wang, H. X., & Ng, T. B. (2001). Isolation of pleuturegin, a novel ribosome-inactivating protein from fresh sclerotia of the edible mushroom pleurotus tuber-regium. *Biochemical and Biophysical Research Communications, 288*(3), 718–721. http://dx.doi.org/10.1006/bbrc.2001.5816.

Wang, H. X., & Ng, T. B. (2006). Purification of a laccase from fruiting bodies of the mushroom *Pleurotus eryngii*. *Applied Microbiology and Biotechnology, 69*(5), 521–525. http://dx.doi.org/10.1007/s00253-005-0086-7.

Wasser, S. P. (2002). Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Applied Microbiology and Biotechnology, 60*(3), 258–274. http://dx.doi.org/10.1007/s00253-002-1076-7.

Wasser, S. P. (2010). Medicinal mushroom science: History, current status, future trends, and unsolved problems. *International Journal of Medicinal Mushrooms, 12*(1), 1–16. http://dx.doi.org/10.1615/IntJMedMushr.v12.i1.10.

Wasser, S. P. (2011). Current findings, future trends, and unsolved problems in studies of medicinal mushrooms. *Applied Microbiology and Biotechnology, 89*(5), 1323–1332. http://dx.doi.org/10.1007/s00253-010-3067-4.

Wasser, S. P., & Weis, A. L. (1999). Therapeutic effects of substances occurring in higher *Basidiomycetes* mushrooms: A modern perspective. *Critical Reviews in Immunology*. http://dx.doi.org/10.1615/CritRevImmunol.v19.i1.30.

Wasson, R. G. (1968). *Soma: Divine mushroom of immortality*. New York, NY: Harcourt Brace Jovanovich.

Watson, S. P., Auger, J. M., McCarty, O. J. T., & Pearce, A. C. (2005). GPVI and integrin alphaIIb beta3 signaling in platelets. *Journal of Thrombosis and Haemostasis, 3*(8), 1752–1762. http://dx.doi.org/10.1111/j.1538-7836.2005.01429.x.

Wen, C.-L., Chang, C.-C., Huang, S.-S., Kuo, C.-L., Hsu, S.-L., Deng, J.-S., & Huang, G.-J. (2011). Anti-inflammatory effects of methanol extract of *Antrodia cinnamomea* mycelia both in vitro and in vivo. *Journal of Ethnopharmacology, 137*(1), 575–584. http://dx.doi.org/10.1016/j.jep.2011.06.009.

Wentworth, J. K. T., Pula, G., & Poole, A. W. (2006). Vasodilator-stimulated phosphoprotein (VASP) is phosphorylated on Ser 157 by protein kinase C-dependent and -independent mechanisms in thrombin-stimulated human platelets. *Biochemical Journal, 393*(2), 555–564. http://dx.doi.org/10.1042/BJ20050796.

Witztum, J., & Steinberg, D. (2001). The oxidative modification hypothesis of atherosclerosis does it hold for humans? *Trends in Cardiovascular Medicine, 11*(3–4), 93–102. http://dx.doi.org/10.1016/S1050-1738(01)00111-6.

Wong, A. H. K., & Mine, Y. (2004). Novel fibrinolytic enzyme in fermented shrimp paste, a traditional asian fermented seasoning. *Journal of Agricultural and Food Chemistry, 52*(4), 980–986. http://dx.doi.org/10.1021/jf034535y.

World Health Organization (2002). *The world health report 2002 — Reducing risks*. Geneva: Promoting Healthy Life.

World Health Organization (2017). Cardiovascular diseases (CVDs). Retrieved September 15, 2017, from http://www.who.int/mediacentre/factsheets/fs317/en/.

Wu, D., Duan, W., Liu, Y., & Cen, Y. (2010). Anti-inflammatory effect of the polysaccharides of golden needle mushroom in burned rats. *International Journal of Biological Macromolecules, 46*(1), 100–103. http://dx.doi.org/10.1016/j.ijbiomac.2009.10.013.

Xu, C., HaiYan, Z., JianHong, Z., & 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. *Carbohydrate Polymers, 74*(3), 445–450. http://dx.doi.org/10.1016/j.carbpol.2008.03.018.

Xu, X., Yan, H., Chen, J., & Zhang, X. (2011). Bioactive proteins from mushrooms. *Biotechnology Advances, 29*(6), 667–674. http://dx.doi.org/10.1016/j.biotechadv.2011.05.003.

Yamaguchi, Y., Miyahara, E., & Hihara, J. (2011). Efficacy and safety of orally administered lentinula edodes mycelia extract for patients undergoing cancer chemotherapy: A pilot study. *The American Journal of Chinese Medicine, 39*(3), 451–459. http://dx.doi.org/10.1142/S0192415X11008956.

Ye, N., Ding, Y., Wild, C., Shen, Q., & Zhou, J. (2014). Small molecule inhibitors targeting activator protein 1 (AP-1). *Journal of Medicinal Chemistry, 57*(16), 6930–6948. http://dx.doi.org/10.1021/jm5004733.

Yoon, K. N., Alam, N., Shim, M. J., & Lee, T. S. (2012). Hypolipidemic and antiatherogenesis effect of culinary-medicinal pink oyster mushroom, *Pleurotus salmoneostramineus* L. Vass. (higher basidiomycetes), in hypercholesterolemic rats. *International Journal of Medicinal Mushrooms, 14*(1), 27–36. http://dx.doi.org/10.1615/IntJMedMushr.v14.i1.30.

Yuen, M.-F., Ip, P., Ng, W.-K., & Lai, C.-L. (2004). Hepatotoxicity due to a formulation of *Ganoderma lucidum* (lingzhi). *Journal of Hepatology, 41*(4), 686–687. http://dx.doi.org/10.1016/j.jhep.2004.06.016.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., ... INTERHEART Study Investigators (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet (London, England), 364*(9438), 937–952. http://dx.doi.org/10.1016/S0140-6736(04)17018-9.

Zhang, G., Sun, J., Wang, H., & Ng, T. B. (2010). First isolation and characterization of a novel lectin with potent antitumor activity from a *Russula* mushroom. *Phytomedicine, 17*(10), 775–781. http://dx.doi.org/10.1016/j.phymed.2010.02.001.

Zhang, G. Q., Sun, J., Wang, H. X., & Ng, T. B. (2009). A novel lectin with antiproliferative activity from the medicinal mushroom *Pholiota adiposa*. *Acta Biochimica Polonica, 56*(3), 415–421. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19636442.

Zhang, G.-Q., Wang, Y.-F., Zhang, X.-Q., Ng, T. B., & Wang, H.-X. (2010). Purification and characterization of a novel laccase from the edible mushroom *Clitocybe maxima*. *Process Biochemistry, 45*(5), 627–633. http://dx.doi.org/10.1016/j.procbio.2009.12.010.

Zhang, M., Cui, S. W., Cheung, P. C. K., & Wang, Q. (2007). Antitumor polysaccharides from mushrooms: A review on their isolation process, structural characteristics and antitumor activity. *Trends in Food Science & Technology, 18*(1), 4–19. http://dx.doi.org/10.1016/j.tifs.2006.07.013.