Anti-inflammatory potential of mushroom extracts and isolated metabolites

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Abstract

Background: In the recent years natural resources are being in focus due to their great potential to be exploited in the discovery/development of novel bioactive compounds and, among them, mushrooms can be highlighted as alternative sources of anti-inflammatory agents.

Scope and approach: The present review reports the anti-inflammatory activity of mushroom extracts and of their bioactive metabolites involved in this bioactive action. Additionally the most common assays used to evaluate mushrooms anti-inflammatory activity were also reviewed, including *in vitro* studies in cell lines, as well as in animal models *in vivo*.

Key findings and conclusions: The anti-inflammatory compounds identified in mushrooms include polysaccharides, terpenes, phenolic acids, steroids, fatty acids and other metabolites. Among them, polysaccharides, terpenoids and phenolic compounds seem to be the most important contributors to the anti-inflammatory activity of mushrooms as demonstrated by numerous studies. However, clinical trials need to be conducted in order to confirm the effectiveness of some of these mushroom compounds namely, inhibitors of NF-κB pathway and of cyclooxygenase related with the expression of many inflammatory mediators.

Keywords: Inflammation; NSAIDs; Mushrooms; Bioactive compounds

Contents

1. Introduction

Inflammation is a physiological response to injury, characterised by loss of function and pain, heat, redness and swelling. It is usually associated with the pathogenesis of diseases such as diabetes, arthritis, obesity, metabolic syndrome, cancer and several cardiovascular diseases (Bellik et al., 2012; Moro et al., 2012; Ma, Chen, Dong, & Lu, 2013).

An immune stimulant causes the pro-inflammatory cells, such as macrophages and monocytes, to start to secrete a number of inflammatory mediators such as interleukins (IL 1β, IL-6, IL-8), tumor necrosis factor (TNF-α), nuclear factor-κB (NF-κB), intercellular adhesion molecule-1 (ICAM- 1), inducible type cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), 5-lipoxygenase (5-LOX), and inducible nitric oxide synthase (iNOS) (Moro et al., 2012; Choi et al., 2014a; Taofiq et al., 2015). Uncontrolled production of these inflammatory mediators has been known to cause several cell damage and also initiate the inflammation process (Kanwar, Kanwar, Burrow, & Baratchi, 2009).

Natural products are good resources for development of therapeutic compounds with anti-inflammatory potential and without or lower toxic effects (Yuan, Wahlqvist, He, & Yang, 2006). Several bioactive compounds from plants (Wang et al., 2013c), rhizomes (Debnath et al., 2013) and marine algae (Kim et al., 2014) have been isolated and their anti-inflammatory effect studied by various mechanisms.

Mushrooms are nutritionally functional foods that have been an integral part of our diet for years. They have not just been consumed for their culinary importance because of their unique taste and flavour (Kalač, 2013), but also because of their potential therapeutic properties which dates back to over 2000 years ago and are recognized as effective to treat and prevent varieties of disorders (Lim et al., 2007; Moro et al., 2012; Silveira et al., 2014). Presently they are significantly consumed in western countries (Lindequist, Niedermeyer, & Julich, 2005). The main commercial mushrooms are *Agaricus bisporus* L., *Lentinus edodes*

(Berk.) Pegler and *Pleurotus ostreatus* (Jacq. ex Fr.) P. Kumm, known to be a vital source of proteins, carbohydrates, minerals and vitamins (Dore et al., 2007). Mushrooms (fruiting bodies, mycelia or their submerged fermentation broth) are rich in several bioactive compounds, either if wild, edible or cultivated species (Alves et al., 2013b). These bioactive metabolites include phenolic compounds, terpenoids, polysaccharides, lectins, steroids, glycoproteins and several lipid components ((Reis, Barros, Martins, & Ferreira, 2012)). Several studies have been conducted to evidence the bioactive properties of mushroom extracts as well as of their secondary metabolites such as antioxidant (Ferreira, Barros, & Abreu, 2009; Heleno, Martins, Queiroz, & Ferreira, 2015; Puttaraju, Venkateshaiah, Dharmesh, Urs, &Somasundaram, 2006), antitumor (Carocho & Ferreira, 2013; Ferreira, Vaz, Vasconcelos, & Martins, 2010; Moradali, Mostafavi, Ghods, & Hedjaroude, 2007), antimicrobial (Alves et al., 2012, 2013a), immunomodulator (Borchers, Krishnamurthy, Keen, Meyers, & Gershwin, 2008), antiatherogenic (Mori, Kobayashi, Tomita, Inatomi, & Ikeda, 2008) hypoglycemic (Hu, Wang, Lien, Liaw, & Lee, 2006) and anti-inflammatory (Moro et al., 2012; Tung et al., 2013; Han et al., 2013; Xu et al., 2013; Choi et al., 2014a; Taofiq et al., 2015) activities.

Most research studies conducted on the pharmacological potential of mushrooms are mainly focused on crude extracts. Nevertheless, it is also important to identify the bioactive compounds responsible for each one of the ascribed bioactivities. In this context, the anti-inflammatory activity of several mushroom species has been reported as well as of their bioactive metabolites. It has been related with a reduction in the production of nitric oxide (NO) and other inflammatory mediators such as interleukins (IL 1β, IL-6, IL-8), tumor necrosis factor (TNF-α) and prostaglandin E2 (PGE2), causing reduction of inflammation (Jedinak, Dudhgaonkar, Wu, Simon, & Sliva, 2011; Moro et al., 2012; Fangkrathok, Junlatat,

& Sripanidkulchai, 2013; Choi et al., 2014a; Lee et al., 2014; Gunawardena et al., 2014; Taofiq et al., 2015).

2. Inflammatory mediators and cell signalling

Inflammation is one of most important biological responses to remove harmful toxins or pathogens from the body (Jung et al., 2013). During inflammation, macrophages, monocytes and other inflammatory cells secrete excess inflammatory mediators, among them NO. Macrophages are the first line of defence against invading pathogens. They are large specialized cells that engulf and digest cellular debris, microbes, and cancer cells in a process called phagocytosis. They play important roles in non-specific host defence mechanism and help to initiate other defence mechanisms. Beyond stimulating the immune system, macrophages play a crucial role in the inflammatory response through the release of a variety of factors. Production of these mediators in inflammatory cells increases following exposure to immune stimulants including bacterial endotoxin lipopolysaccharide (LPS) or viral proteins (Hseu et al., 2005). This bacteria component initiates several signal transduction pathways that are central to the pathogenesis of inflammation (Jeong et al., 2010).

NO is a short-lived free radical and a signalling molecule produced from L-arginine by the inducible nitric oxide synthase (iNOS) enzyme (Hämäläinen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007; Castro et al., 2014). NO, known to induce vasodilation in the cardiovascular system through a Ca^{2+}-dependent pathway, play an important function in the immune and nervous systems as well as in cell death (Hseu et al., 2005; Sharma, Al-Omran, & Parvathy, 2007). It gives an anti-inflammatory effect under normal physiological conditions, being also involved in many pathological diseases in the body (Cirino, Distrutti, & Wallace, 2006; Joo et al., 2014).

Reactive oxygen species (ROS) production play an important role in the modulation of inflammation. Major ROS produced within the cell are superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), peroxide anion (O_2^{2-}), hydroxyl ion (OH^-) and hydroxyl radical ($OH\cdot$). Nitric oxide is less reactive but has the ability to attack superoxide ion (O_2^-) to form peroxynitrite $ONOO^-$ (Castro et al., 2014). This peroxynitrite and several oxidative products can accumulate in the cells causing several oxidative damages and increased cytotoxicity leading to tumor development, DNA damage and cell proliferation (Quang, Harinantenaina, Nishizawa, Hashimoto, Kohchi, Soma, & Asakawa, 2006a; Fangkrathok, Junlatat, & Sripanidkulchai, 2013). The inhibition of NO and other inflammatory mediators overproduction in cells may prevent the occurrence of inflammatory diseases and cancer (Cirino et al., 2006; Sharma, Al-Omran, & Parvathy, 2007).

Another class of important pro-inflammatory mediator is the tumor necrosis factor-α (TNF-α) secreted by activated macrophages, T-lymphocytes, mast cells, natural killer cells, monocytes and other defence cells (Habtemariam, 2013). Tumor necrosis factor-α (TNF-α) is one of the important pro-inflammatory mediators involved in the inflammatory process. When there is an immune stimulant, TNF-α attaches to some specific transmembrane receptors that tend to activate several signal transduction pathways responsible for production of more and more TNF-α to the site of infection (Bradley, 2008). As TNF-α continues to accumulate, it causes a wide range of human diseases, apoptosis, excess pain and cell damage. Regulation of the transcription factor NF-κB is the key component of TNF-α regulation (Habtemariam, 2013). The inhibition of TNF-α in LPS activated THP-1 monocytic cells, or RAW 264.7 macrophage cells, is generally used as *in vitro* model for evaluating the anti- inflammatory effects of various materials including mushroom extracts (Wu, Lu, Lai, & Ng, 2013a). Some of the studied mushrooms whose mechanism of action is the inhibition of TNF-α release are shown in **Table 1**.

NF-κB is a transcription factor that regulates the expression of several pro-inflammatory cytokines and enzymes such as IL-1β, TNF-α, iNOS, and COX-2 that play vital roles in apoptosis, in the immune system, as well as in the inflammation (Hseu, Huang, & Hsiang, 2010). When there is an immune stimulant such as lipopolysaccharide, viral proteins or cytokines, the NF-κB becomes activated (Kim et al., 2003). Toll like receptors (TLRs) and tumor necrosis factor receptor (TNFr) localised in the macrophages membrane have the ability to detect these pathogen-associated microbial patterns (PAMPs) necessary for activation of several signalling cascade (**Figure 1**). After ligand binding, these receptors activate the myeloid differentiation protein 88 (MyD88) responsible for activation of mitogen activated protein kinase (MAPKs). This MAPKs further activate the IKK kinases (IKKα, IKKβ, IKKγ) leading to phosphorylation of IkB proteins complex (Hasnat, Pervin, Cha, Kim, & Lim, 2015). Cytosolic IKB forms a complex with NF-κB and the IkB proteins becomes degraded allowing NF-κB to translocate to the nucleus where it triggers the transcription of several chemokine and cytokine genes involved in the innate and adaptive immune response (Kim et al., 2003). Some polyphenols have been known to inhibit specific steps in the pathway leading to NF-κB release (Ruiz & Haller, 2006). These authors investigated the anti-inflammatory mechanisms of flavonoids that were able to inhibit the phosphorylation of IkB preventing translocation of NF-kB to the nucleus. Hence, finding natural inhibitors of NF-kB for treatment and prevention of various inflammatory diseases have been the target of several scientists (Kim et al., 2003).

3. NSAIDs and their mechanism of action

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of medications commonly administered to manage pain and inflammation (Moro et al., 2012). Most of them are available over the counter in the United States while the rest needs prescription (Meek, van

de Laar, & Vonkeman, 2010). Several side effects have been associated with frequent administration of NSAIDs particularly in the gastrointestinal (GI) tract where they cause bleeding, intestinal perforation and peptic ulcer (Dugowson & Gnanashanmugam, 2006). Other less pronounce side effects include renal dysfunction, high blood pressure and cardiovascular toxicity (Elsayed, Hesham, Mohammad, & Aziz, 2014). NSAIDs act by inhibiting the intracellular cyclo-oxygenase enzymes which has two isoforms (COX-1 and COX-2). Cyclooxygenase are enzymes involved in the process of inflammation (Noreen, Ringbom, Perera, Danielson, & Bohlin, 1998). They catalyse the rate-limiting step in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes from arachidonic acid (Zhang, Mills, & Nair, 2003; Diyabalanage, Mulabagal, Mills, DeWitt, & Nair, 2008; Stanikunaite, Khan, Trappe, & Ross, 2009; Han, Oh, & Park, 2011; Fangkrathok, Junlatat, & Sripanidkulchai, 2013).

Prostaglandins (PG) are hormone-like chemicals in the body that perform ‘‘housekeeping’’ functions required for normal physiological activities. They are structurally related and have regulatory roles as well as pathological implication (Silveira et al., 2014). Cyclooxygenase enzymes catalyzes the conversion of arachidonic acid to PGH_2, which is converted to other prostanoid species including PGD_2, PGE_2, prostacyclin (PGI_2), and thromboxane (TXA_2) by the action of specific synthases (**Figure 2**) (Joo & Sadikot, 2012). COX-1 is primarily involved in the regulation of homeostatic functions and is constitutively expressed in a wide variety of cells, promoting physiological functions, such as gastric mucosal protection, control of renal blood flow, hemostasis, autoimmune responses, lungs, central nervous system, cardiovascular system and reproductive functions (Grosser, Fries, & Fitzgerald, 2006).

On the other hand, COX-2 is an inducible isoform of prostaglandin synthase in activated macrophages, fibroblasts, and endothelial cells that are responsible for inflammation. They

are expressed significantly due to stimuli such as cytokines, endotoxins, viral proteins and growth factors. COX-2 originates inducing prostaglandins, which contributes to the development of the four cardinal signs of inflammation: pain, heat, redness and swelling, thus being considered as the main target for the anti-inflammatory action (Fitzgerald, 2004).

The search for selective inhibitors of COX-2 is considered important, on the basis of the theory that the side effects, such as gastric lesions, that occurred from inhibition of COX-1 activity, were observed with some non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) (**Supplementary material S1**) such as dexamethasone, diclofenac and indomethacin (Lu et al., 2013). Until now, very few compounds of natural origin have been reported to possess COX-2 inhibitory effects. Yoshikawa et al. (2005) were the first to report the potential of lanostane triterpenoids and their glycosides as selective inhibitors of COX-2 enzyme.

Usually, NSAIDs inhibit both isoforms of the cyclooxygenase enzyme but the recently discovered selective COX-2 inhibitors (**Supplementary material S2**) are specific for the COX-2 isoform, thus exerting the anti-inflammatory property of COX-2 inhibition while theoretically evading the adverse effect associated with COX-1 isoform inhibition (Nowak, 2012). Considerable resources have thus been invested in the pharmaceutical industries for development and design of drugs that act through selective inhibition of COX-2 to control inflammation with improved tolerability, less adverse effects, and without affecting normal metabolic processes (Shukla, Bafna, Sundar, & Thorat, 2014).

4. Methodologies for anti-inflammatory activity screening

4.1. *In vitro* assays

4.1.1. Nitric oxide assay. The Griess reaction is a simple technique that is widely used for quantification/detection of NO. It was discovered by Johann Peter Griess (1829–1888), a

German organic chemist. The basic reaction involves reacting sulphaniliamide and N-(1-naphthyl) ethylenediamine (NED) to form a stable azo compound. The absorbance of this compound at 540 nm is directly proportional to the nitrite concentration in the sample. Several *in vitro* measurement of NO production in LPS stimulated RAW 264.7 cells have been reported by several authors in the past, and this is one of the possible ways to screen various extracts and bioactive compounds with potential anti-inflammatory properties. RAW 264.7 cells are seeded in 96-well plates, they are then treated with different concentrations of the sample to be studied followed by stimulation with LPS. The cell culture supernatant is then transferred to a new plate followed by addition of sulphanilamide and NED solutions. The NO produced is determined by measuring the absorbance at 540 nm. This assay is one of the most common and widely used for evaluation of anti-inflammatory activity as reported by different authors (Moro et al., 2012; Taofiq et al., 2015).

4.1.2. Cytokine enzyme linked immunosorbent assay (ELISA). The enzyme linked immunosorbent assay (ELISA) is used for the detection and quantification of proteins typically secreted or released from cells. This method is usually used for quantification of cytokines and other inflammatory mediators such as interleukin (IL-1β, IL-6, IL-8) and tumour necrosis factor (TNF-α), as reported in a number of publications (Jedinak, Dudhgaonkar, Wu, Simon, & Sliva, 2011; Fangkrathok, Junlatat, & Sripanidkulchai, 2013; Lee et al., 2014; Gunawardena et al., 2014). RAW 264.7 cells are usually plated in a 24-well plate in the culture medium, and then incubated with the sample to be screened at different concentrations. Cell culture supernatants are finally collected and assayed according to the instructions of the ELISA kit manufacturer (e.g., BD Pharmingen, San Diego CA, USA; DuoSet, R&D Systems, UK; MAX ^{TM} Set (Deluxe); BioLegend, San Diego, CA, USA) to determine the amount of TNF-α and IL-6 released from the cells.

4.1.3. COX-1 and COX-2 catalyzed prostaglandin biosynthesis assay

The cyclooxygenase enzymes have been extensively used to study the anti-inflammatory potential of natural agents. This is not a very common method for anti-inflammatory activity assessment, but it has been reported in some publications (Noreen, Ringbom, Perera, Danielson, & Bohlin, 1998; Zhang et al., 2003; Yoshikawa et al., 2005; Stanikunaite, Khan, Trappe, & Ross, 2009). COX activity is usually determined based on the conversion of arachidonic acid to PGE_2 and is expressed as a percentage of the control. RAW 264.7 cells are seeded in 96-well plates and incubated, being then stimulated with LPS to induce the production of COX-2 and other inflammatory mediators. Induced cells are treated with different concentrations of the samples. Arachidonic acid is added and the cells are further incubated. The amount of PGE_2 released in the medium can be determined with PGE_2 enzyme immunoassay kit (Cayman Chem. Co. Michigan, USA).

4.2. *In vivo* assays

A lot of studies have reported *in vivo* anti-inflammatory activity of natural products achieved by inducing inflammation in mouse and measuring the degree of swelling relative to a positive control. In these animal models there is capillary dilation, increase blood vessel permeability, and edema similar to the ones associated with human acute inflammation (Wang et al., 2013a). The carrageenan-induced hind paw edema model has been used in a lot of research studies (Jose, Ajith, & Jananrdhanan, 2004; Deng et al., 2013; Lee et al., 2014). The methodology involves treating animals with extract at different concentration and also a control group with indomethacin, dexamethasone or any other non-steroidal anti-inflammatory drug. This is followed by injection of hind paw with carrageenan in saline solution and by measuring the paw volume increment immediately and at different time

intervals (Lu et al., 2008). The degree of swelling induced by the injection is evaluated and the result compared with the control. Inflammation can also be induced by topical application of xylene in the ear of the mouse. After few minutes, the difference in swelling (Lu et al., 2008) is estimated. Other *in vivo* anti-inflammatory assay induce inflammation, either by the croton oil-induced ear edema test (Kim et al., 2004; Won & Park, 2005; Dore et al., 2007) or by TPA, 12-*O*-tetradecanoylphorbol-13-acetate induced inflammation in mice, and sacrificed by cervical dislocation, to take punch biopsies to weight (Kamo, Asanoma, Shibata, & Hirota, 2003; Dore et al., 2007; Liu et al., 2007).

5. Mushroom metabolites with reported anti-inflammatory activity

5.1. The anti-inflammatory potential of mushroom extracts

Numerous investigations have suggested that several mushroom species can exhibit anti-inflammatory potential based on their ability to reduce the production of inflammatory mediators (Kim et al., 2003; Padilha et al., 2009; Wen et al., 2011; Elsayed, Hesham, Mohammad, & Aziz, 2014 Taofiq et al., 2015). Their crude extracts (**Table 1**) have been described to display activity, and attention is now being focused on efforts to discover bioactive compounds capable to suppress the production of inflammatory mediators through gene expression downregulation of different types of inflammatory mediators (Kim et al., 2006, Fangkrathok, Junlatat, & Sripanidkulchai, 2013). Previous research studies have been carried out on several mushroom species, mainly in methanolic (Kim et al., 2003; Wen et al., 2011; Moro et al., 2012) and ethanolic (Won & Park, 2005; Kim et al., 2006; Ruthes et al., 2013b; Taofiq et al., 2015) extracts. Most studies have shown that these extracts display anti-inflammatory activity, but it is also crucial to identify the metabolites responsible for this bioactivity.

Different compounds have been isolated from mushrooms and implicated as responsible for the anti-inflammatory activity, e.g. polysaccharides (Dore, et al., 2007; Lu, et al., 2008; Lavi, Levinson, Peri, Hadar, & Schwartz, 2010; Adebayo, Oloke, Majolagbe, Ajani, & Bora, 2012; Ruthes, et al., 2013a, 2013b, 2013c; Chang, Lur, Lu, & Cheng, 2013; Castro et al., 2014; Silveira et al., 2014; Silveira et al., 2015), terpenes (Kamo, Asanoma, Shibata, & Hirota, 2003; Yoshikawa et al., 2005; Dudhgaonkar, Thyagarajan, & Sliva, 2009; Han et al., 2013; Ma, Chen, Dong, & Lu, 2013; Tung et al., 2013; Xu, Yan, Bi, Han, Chen, & Wu, 2013; Choi, et al., 2014a), phenolic compounds (Quang, Harinantenaina, Nishizawa, Hashimoto, Kohchi, Soma, & Asakawa, 2006a; Quang et al., 2006b Kohno et al., 2008; Stanikunaite, Khan, Trappe, & Ross, 2009; Hsieh et al., 2010; Lee, & Huang et al., 2011b; Chen et al., 2013; Taofiq et al., 2015), sterols (Huang, et al., 2010; Ma, Chen, Dong, & Lu, 2013; Li, Zhou, Lee, Shim, Kim, & Kim, 2014b), fatty acids (Zhang, Mills, & Nair, 2003; Han & Cui, 2012), polysaccharide – protein complexes (Chen, Gonzalez de Mejia, & Wu, 2011; Zhou, Chen, Ding, Yao, & Gao, 2014) and other bioactive metabolites (Chien, Chen, Kuo, Tsai, Lin, & Kuo, 2008; Jeong et al., 2010). The anti-inflammatory properties of mushrooms have interested many scientists and motivated the study of several species (**Table 1**).

Antrodia camphorata (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang also known as "*Taiwanofungus camphoratus*" is a well-known medicinal mushroom with a lot of pharmacological potential. It has been reported to have antioxidant, hepatoprotective, anti-inflammatory and immunomodulatory properties (Geethangili & Tzeng, 2011). Hseu, Huang, & Hsiang (2010) reported the anti-inflammatory effect of fermented culture broth of *A. camphorata* by measuring the level of pro-inflammatory cytokine IL-1β and TNF-α expression in different organs using ELISA kits. The extract was found to inhibit the LPS-induced production of cytokines and also to suppress LPS-induced NF-kB activation in transgenic mice. The same researchers also studied fermentation culture of *A. camphorata*

and examined its effect in LPS stimulated RAW 264.7 cells for NO, PGE2, iNOS and COX-2 protein expression. The results indicate that *A. camphorata* inhibit the production of TNF-α and IL-1β, NO and PGE2, as well as iNOS and COX-2 expression by blocking activation of NF-κB transcription factor.

Gunawardena et al. (2014) studied the anti-inflammatory potential of five commercial mushroom species (*Agaricus bisporus*, *Agaricus bisporus* Portobello J.E.Lange*, Flammulina velutipes* (Curtis) Singer*, Lentinus edodes*, and *Pleurotus ostreatus* in LPS activated RAW 264.7 macrophages cells for NO production and also detected TNF-α level using ELISA kit. Three mushroom species showed the highest activity with the result expressed in terms of IC_{50} for NO production and TNF-α release respectively: *Pleurotus ostreatus* (0.077 mg/mL and 0.035 mg/mL), *Lentinus edodes* 0.027 mg/mL and 0.047 mg/mL) and *Flammulina velutipes* 0.024 mg/mL and 0.099 mg/mL). Gunawardena et al. (2014) also demonstrated the anti-inflammatory activity of extracts prepared from mushrooms after undergoing some food processing procedures. The results showed reduced activity compared to fresh samples, which implies that anti-inflammatory compounds present in these mushrooms were degraded, e.g due to suseptibility to heating.

*Ganoderma lucidum (*Curtis) P. Karst., is a medicianal mushroom that has been used to reduce allergies, inflammation, has anti-tumor and anti-aging potential, as well as health promoting effects. Ethanolic extract of *Ganoderma lucidum* was studied for its anti-inflammatory potential by stimulating murine BV2 cell line with LPS, and the amount of NO, PGE2 and Cytokine(IL-1β and TNF-α) in culture supernatants quantified as reported by Yoon et al. (2013). Treatment of cell line with extract up to 1 μg/ml significantly repressed the production of NO due to the inhibition of iNOS mRNA protein expression. The amount of cytokine release was measured by ELISA and a significant reduction in the level of cytokines after treatment with extract was observed. The anti-inflammatory ativity was

further associated to the inhibition of the NF-κB signaling pathway by the ethanolic extract. Methanolic extract of *Ganoderma lucidum* was also evaluated by Chu et al. (2015). RAW264.7 monocytic cells were stimulated with LPS and treated with extract at different concentrations. From the result, 100 µg/ml of extract significantly inhibited NO production in the culture medium up to 85%.

Moro et al. (2012) analysed six mushroom species from Spain (*Boletus edulis* Bull., *Cantharellus cibarius* Fr., *Craterellus cornucopioides* (L.) Pers., *Lactarius deliciosus,* (L. ex Fr.) S.F.Gray *Agaricus bisporus* and *Pleurotus ostreatus*) in what concerns the anti-inflammatory activity of their methanolic extracts through NO production in LPS stimulated RAW 264.7 cells. At a concentration of 0.5 mg/mL, *Agaricus bisporus, Cratarellus cornucopioides, Cantharellus cibarius* and *Lactarius deliciosus* showed 35%, 65%, 80% and 40% of NO production inhibition, respectively. The release of TNF-α production was estimated by ELISA kits, but methanolic extracts showed no reduction of TNF-α production in the macrophages.

Taofiq et al. (2015) studied the anti-inflammatory activity of ethanolic extracts of ten wild and four cultivated mushroom species from the Northeast of Portugal. RAW 264.7 macrophage cells were stimulated with LPS and then the amount of NO production was quantified using the griess reagent assay. The IC_{50} value responsible for 50% inhibition of NO production estimated and among the studied species was as follows: *Pleurotus ostreatus* presented the best results (96 µg/mL), followed by *Macrolepiota procera* (Scop.) Singer (162 µg/mL), *Boletus impolitus* Fr. (166 µg/mL) and *Agaricus bisporus* (190 µg/mL). In oposition, ethanolic extracts of *Agaricus bisporus* Portobello, *Boletus ed*ulis and *Boletus flagrans* Vittad., did not display activity.

Kim et al. (2004) studied the *Phellinus linteus* (Berk. & M. A. Curtis) Teng, an orange colour mushroom used in China, Japan and other oriental countries for health maintenance. The

ethanolic extracts obtained from the fresh fruiting bodies of *P. linteus* were investigated *in vivo* for anti-inflammatory potential based on their ability to inhibit inflammation (edema) induced by croton oil in mice. Topical aplication of extract at 1.0 mg per ear gave 41.5% edema inhibition, when compared with indomethacin, which gave rise to a quite higher inhibition (71.7%). Kim et al. (2006) also demonstrated the anti-inflammatory activity of the ethanolic extracts of *P. linteus* in LPS-stimulated RAW264.7 macrophages. The extracts at different concentrations dependently reduced iNOS promoter activity and NO production; at 0.5 mg/mL, the extract had 60% of NO production inhibition.

Cordyceps, a genus of mushroom known to grow on insects and have been reported to strengthen the immune system (Won & Park, 2005). Rao, Fang, Wu, & Tzeng (2007), studied anti-inflammatory activity using methanolic extracts from the fruiting body of *Cordyceps sinensis* (Berk.) Sacc., and by stimulating macrophages cells with LPS and NO production later quantified. The amount of TNF-α level and IL-12 were quantified by the ELISA test. From the results, 100 µg/mL of *C. sinensis* extract inhibited NO production by 70%. Han, Oh, & Park (2011) also studied the anti-inflammatory effect of hot water extract of *Cordyceps militaris* (L.) Fr. *in vivo* by inducing inflammation in mice. The extracts were known to inhibit inflammation as well as iNOS and TNF-mRNA expression in colon tissue of DSS-induced colitis and in LPS-stimulated RAW264.7 cells. Kim et al. (2003) also described the anti-inflammatory activity of another *Cordyceps* specie. Methanolic extracts of *C. pruinosa* (L.) Fr. were tested *in vitro* for inhibition of pro-inflammatory cytokines production by using ELISA kit as well as NO production in LPS stimulated RAW264.7 macrophages. The extracts were known to suppress gene expression of IL-1β, TNF-α, inducible nitric oxide synthase, and cyclooxygenase-2 enzyme. This is due to the inhibition of nuclear transcription factor NF-κB activation.

5.2. Polysaccharides

Mushrooms have been known as valuable sources of bioactive carbohydrates, namely polysaccharides which represent the main group with various health promoting properties (Villares, 2013). They include several different β-glucans (**Supplementary material S3**), fucomannogalactans, xylomannans and mannogalactans, known to play different biological roles such as the ones of antioxidation, anti-inflammatory, antitumour, antimicrobial, anti-aging, neuroprotective and immunomodulatory (Li et al., 2013).

Studies on the anti-inflammatory properties of carbohydrates have led to positive results as shown in **Table 2**. Several types of polysaccharides have been obtained from mushroom dry fruiting bodies or mycelia and tested for anti-inflammatory activity either *in vivo* (Lu et al., 2008; Ruthes et al., 2013c; Silveira et al., 2015), following a typical model similar to human acute inflammation, or *in vitro* for inhibition of cytokine or NO production (Dore et al., 2007; Chang et al., 2013; Castro et al., 2014).

Several pharmacological properties have been reported on the extracts and bioactive compounds isolated from *Cordyceps militaris*, namely the anti-inflammatory activity (Rao, et al., 2010). D-Glucose, D-mannitol and 3,4-*O*-isopropylidene-D-mannitol were isolated from its fruiting body and the anti-inflammatory potential evaluated in mouse peritoneal macrophages regarding the inhibition of NO production and cytokine release. Among the three cited compounds, D-Glucose showed the highest NO inhibition potential with an IC_{50} value of 11.3 µg/mL, followed by D-mannitol (14.2 µg/mL) and 3, 4-*O*-isopropylidene-D-mannitol (17.2 µg/mL). They also inhibit significantly cytokines (TNF-α and IL-12) production, indicating that they may be useful compounds for the design of anti-inflammatory agents.

Mushroom polysaccharides vary in structure and sometimes they exhibit different biological effects. Silveira et al. (2014) isolated a (1→3)-β-D-glucan from the fruiting body of

Pleurotus sajor-caju (Fr.) Singer and tested its anti-inflammatory effect in a monocytic cell line THP-1 after LPS induction, for inhibition of pro-inflammatory genes production. Monocyte cells showed a significant decrease in TNF-α expression (61.8% inhibition) while IL-1β and COX-2 mRNAs were also significantly inhibited (37.0% and 63.6%, respectively). Silveira et al. (2015) isolated a mannogalactan from *P. sajor-caju* by submerged fermentation. The purified polysaccharide was chemically characterized and its anti-inflammatory potential evaluated *in vivo* for reduction of carrageenan-induced paw edema in mice. The group treated with purified mannogalactan was able to reduce edema after 5-6h of exposure to 1% carrageenan, with 69-71% edema reduction observed, and was quite as effective as dexamethasone used as control. Therefore, mushroom polysaccharides have shown to be lead compounds for development of anti-inflammatory agents.

Agaricus bisporus is one of the most commonly consumed mushrooms in the world. Ruthes et al. (2013b) isolated and purified a fucogalactan from its dried fruiting bodies, and its anti-inflammatory effect was evaluated *in vivo* by formalin-induced pain in mice and detection of iNOS and COX-2 protein expression. Fucogalactan significantly decreased both iNOS and COX-2 expression by 53% and 54%, respectively, in relation to dexametasone used as control, which also affected both iNOS and COX-2 expression by 74.5% and 71.4%, respectively. The results reported showed significant inhibition of inflammatory pain and strongly confirm the anti-inflammatory potential of fucogalactan.

Xu, Yasuda, Nakamura-Tsuruta, Mizuno, & Ashida (2012) isolated a β-glucan (lentinan) from the fruiting bodies of *Lentinus edodes* and investigated this effects on NO and TNF-α production in LPS stimulated murine RAW 264.7 macrophages. Lentinan, at a concentration of 200 µg/mL, was found to significantly inhibit NO production (70%) and was dose-dependent. Also the amount of TNF-α released from RAW 264.7 cells was quantified and found to be suppressed by 75% at 200 µg/mL. Furthermore, the protein expression of iNOS

and the gene expression of iNOS mRNA and TNF-α mRNA were suppressed by lentinan suggesting its usefulness as an anti-inflammatory agent. Mizuno, Nishitani, Hashimoto, & Kanazawa (2009) also reported the anti-inflammatory effect of this compound, which was analysed for inhibition of TNF-α production as well as IL-8 expression. At 500µg/mL, it was able to down regulate IL-8 mRNA expression in RAW 264.7 stimulated with LPS.

5.3. Terpeneoids

Terpenoids are organic compounds found in plants, animals and macrofungi. They are empirically regarded as built up from isoprene, a hydrocarbon consisting of five carbon atoms with molecular formula $(C_5H_6)n$ as repeating unit (El Enshasy & Hatti-Kau, 2013). The terpene compounds are named based on the number of isoprene units, for example, monoterpenes (10 carbons), sesquiterpenes (15 carbons), diterpenes (20 carbons), sesterterpenes (25 carbons), triterpenes (30 carbons), and tetraterpenes (40 carbons). Among the large number of terpenes, triterpenoids are exclusively found in certain macrofungi, mainly Basidiomycetes, and are recognized for their biological activity and medicinal purposes. Several researchers have isolated some of these terpenoid coumpounds from mushrooms and, among them; the titerpenoids are the most reported (**Table 3**). Their ability to induce significant decrease in NO production as well as other cytokines was evaluated. Common examples include ganoderol, ianostane, lucidadiol and lucidone (**Supplementary material S4)** isolated, from the fruiting body of *Ganoderma lucidum* (Akihisa et al., 2007; Dudhgaonkar, Thyagarajan, & Sliva, 2009; Choi et al., 2014a).

Ganoderma lucidum has been used in the past to promote health and longevity in Asia. Choi et al. (2014a) isolated 12 triterpenes from its fruiting body and the anti-inflammatory activity evaluated in LPS induced RAW 264.7 cells. Seven triterpenes; butyl lucidenate E2 (GT-1), butyl lucidenate D2 (GT-2), butyl lucidenate P (GT-3), butyl lucidenate Q (GT-4),

Ganoderiol F (GT-5), methyl ganodenate J (GT-7) and butyl lucidenate N (GT-12), out of the studied twelve triterpenes, showed significant decrease in NO production. 20 μM of GT-2 showed up to 70% inhibition of NO production relative to the control. Dudhgaonkar, Thyagarajan, & Sliva (2009) also studied triterpene rich ethanolic extracts from *G. lucidum* in LPS stimulated RAW 264.7 macrophage cells. The extract at 10–50 μg/mL suppressed TNF-α production in RAW 264.7 cells (IC_{50} 15.1 μg/mL), reduced IL-6 production (IC_{50} 14.4 μg/mL) and decreased the secretion of PGE_2 and NO in a dose-dependent manner with IC_{50} values of 28.2 μg/ml and 11.4 μg/mL, respectively.

Cyathus africanus H. J. Brodie, also known as "bird nest fungi", usually grows on animal dungs, woody debris and soil rich in humus. Han et al. (2013) isolated diterpenes from its fruiting body and the anti-inflammatory activity was evaluated regarding NO production in LPS induced macrophages. Five diterpenes showed potent NO inhibition with IC_{50} values of 2.57, 1.45, 12.06, 10.73, and 9.45 μM, compared to hydrocortisone used as the control with IC_{50} value of 53.78 μM.

Piptoporus betulinus (Bull. ex Fr.) P. Karst., also known as "bracket fungi" is an edible mushroom that is geographically restricted to the cold climates. Kamo, Asanoma, Shibata, & Hirota, (2003) isolated six lanostane-type triterpene acids from its fruiting bodies collected in Japan. The anti-inflammatory activity was tested *in vivo* by inducing inflammation (edema) in mouse ear using TPA (12-*O*-tetradecanoylphorbol-13-acetate). The isolated compounds suppressed the TPA-induced edema up to 49-86% at 400 nmol/ear application. Some of the isolated compounds (polyporenic acids A, three derivatives of polyporenic acid A and a novel compound (+)-12α, 28-dihydroxy-3α-(3′-hydroxy-3′-methylglutaryloxy)-24-methyllanosta-8, 24(31)-dien-26-oic acid) have displayed higher activity than indomethacin used as positive control.

5.4. Polyphenols

Phenolic compounds are characterized by at least one aromatic ring (C6) and one or more hydroxyl groups (Michalak, 2006). These molecules, including phenolic acids, are a group of secondary metabolites from fungi and plants, secreted for protection against UV light, insects, viruses and bacteria (Heleno, Martins, Queiroz, & Ferreira, 2015). Mushrooms are known to produce an amazing diversity of secondary metabolites. Phenolic compounds are one of the most important groups of these metabolites, being attractive because of their multifunctional properties. These compounds provide protection against several chronic diseases such as cancer, brain malfunction and several cardiovascular illnesses. Different research studies have reported the bioactive potential of phenolic acids, but only few studied the bioactive properties of their synthesised metabolites (Heleno, Martins, Queiroz, & Ferreira, 2015).

Several classes of phenolic compounds (**Supplementary material S5**) and some of their derivatives, present in mushroom extracts, have been evaluated and known to have anti-inflammatory activity (**Table 4**).

Antrodia camphorata, very common in Taiwan, has enormous amount of bioactive compounds with reported pharmacological potential (Geethangili & Tzeng, 2011). Several benzenoids and benzene derivatives have been isolated from *A. camphorata* and tested for anti-inflammatory activity. Chen et al. (2013) isolated three new benzenoids from *A. camphorata* and evaluated their anti-inflammatory activity in LPS induced RAW 264.7 cells regarding the inhibition of NO production. The IC_{50} values of the three compounds (3-isopropenyl-2-methoxy-6-methyl-4,5-methylenedioxyphenol (1), 4,4'-dihydroxy-3,3'-dimethoxy-2,2'- dimethyl-5,6,5',6'-bimethylenedioxybiphenyl (2), 2,3-methylenedioxy-4-methoxy-5-methylphenol (3)) were 1.8, 18.8 and 0.8 μg/mL. Other phenolic derivatives from *A. camphorata* are antrocamphin and benzocamphorin that have attracted considerable

attention recently because of their significant anti-inflammatory activity. Liao, Kuo, Liang, Shen, & Wu (2012) isolated benzocamphorin F from the fruiting body of *Taiwanofungus camphoratus* and evaluated its anti-inflammatory activity in murine microglial cells (BV2). Inhibition of NO production was expressed in terms of IC_{50} and the compound reached a value of 8.6 µM compared to L-NAME, a non-specific NOS inhibitor, with an IC_{50} of 12.0 µM.

Albatrellus caeruleoporus (Peck) Pouzar is an edible mushroom that grows on woody debris as well as on the ground, common in North America. Quang et al., (2006b) chemically characterized its methanolic extracts in terms of phenolic acids and evaluated their anti-inflammatory potential in LPS induced RAW 264.7 cells regarding NO production. All four identified grifolin derivatives showed a significant reduction in NO production with IC_{50} values of 23.4, 22.9, 29.0, and 23.3 µM compared to 88.4 µM of NG-methyl-L-arginine (L-NMMA), a potent inhibitor of NO production used as control.

Elaphomyces granulatus Fr. is an inedible mushroom known as "false truffle" in the United Kingdom and widely distributed in Europe and North America. Stanikunaite, Khan, Trappe, & Ross (2009) studied the ethanolic extracts of *E. granulatus* and isolated syringaldehyde and syringic acid from its fruiting body. Extracts and phenolic acids were evaluated for their anti-inflammatory activity in RAW 264.7 macrophages cells by the COX-1- and COX-2-catalyzed prostaglandin biosynthesis assay. The extracts caused a 68% inhibition of COX-2 activity at 50 µg/mL. Syringaldehyde and syringic acid moderately inhibited COX-2 activity with IC_{50} values of 3.5 µg/mL and 0.4 µg/mL, respectively. NS-398, a specific inhibitor of COX-2, was used as a positive control and had IC_{50} 0.2 µg/mL.

Phellinus linteus is a medicinal mushroom used for centuries in oriental countries to prevent several diseases (Kim, Song, Kim, Kim, Lim, & Park, 2004). Several phenolic compounds have been isolated from the fruiting body and mycelia of *P. linteus;* among them are caffeic

acid, hispolon, hispidin, hydroxybenzaldehyde and inotilone (Huang, Huang, & Deng, 2012a). Lin et al. (2014b) isolated hispolon from fermentation broth of *P. linteus* and its anti-inflammatory activity was evaluated in LPS induced RAW 264.7 cells regarding inhibition of NO production. Hispolon at 10 mg/mL inhibited NO production by 72.1% and suppressed the expression levels of iNOS. Hence this compound has useful therapeutic potential, additional research studies need to be conducted in order to understand its mechanism of action. Huang, Huang, & Deng (2012a) isolated inotilone, another important phenolic compound with reported anti-inflammatory potential, from the fruiting body of *P. linteus* and tested the anti-inflammatory effects *in vivo* in carrageenan induced hind mouse paw edema model as well as *in vitro* for inhibition of NO production and iNOS expression. Carr-induced mouse paw edema volume was significantly decreased to 56.2%, NO production was inhibited up to 26.2–59.7%, TNF-α release was inhibited up to 10.6–40.3% while iNOS expression was significantly inhibited in a dose-dependent manner. Inhibition of NF-kB and MAPK activation were also observed and are the major mechanisms responsible for cytokine and other inflammatory mediator release.

5.5. Steroids

Steroids are organic compounds with three hexagonal and one pentagonal carbon rings arranged in specific configuration with several functional groups found in plants, animals and fungi (Streck, 2009). Ergosterol is a precussor of vitamin D found in mushrooms membrane and known to vary among species depending on the physiological state of the mushroom (Chiocchio & Matković, 2011). Steroids in general have been reported to play several biological functions such as anti-tumor, anti-oxidant, immune function as well as prevention of common diseases (Phillips et al., 2011).

Steroids (**Table 5**) such as trametenolic acid, ergosterol peroxide, and ergosterol (**Supplementary material S6**) have been isolated from mushrooms and were reported to present anti-inflammatory activity.

Inonotus obliquus (Ach. ex Pers.) Pilát, also known as "chaga mushroom" is a medicinal mushroom used in Russia and other North-European countries. Among others, anti-tumour and immunomodulatory properties were reported (Fan, Ding, Ai, & Deng, 2012). Ma, Chen, Dong, & Lu (2013) isolated six main constituents from its fruiting body and their anti-inflammatory activity was evaluated for NO production in RAW 264.7 cell lines. Among the isolated compounds, ergosterol peroxide and trametenolic acid had the highest anti-inflammatory potential and significantly inhibited NO production by 36.88% and 50.04%, respectively. Other steroidal compounds isolated from mushrooms (e.g. lanosterol, 3β-hydroxy-8, 24-dien-21-al, ergosterol and inotodiol) had relatively low percentages of NO production inhibition.

Antrodia camphorata is a medicinal mushroom with reported anti-inflammatory activity (Hseu et al., 2005; Liu et al., 2007; Hsieh et al., 2010; Hseu, Huang, & Hsiang, 2010; Lee et al., 2011b; Liao, Kuo, Liang, Shen, & Wu, 2012; Deng et al., 2013; Chen et al., 2013). Ergostatrien-3β-ol was isolated from the fruiting body of *A. camphorata* by submerged fermentation (Huang et al., 2010). The anti-inflammatory activity was evaluated *in vivo* for reduction of NO production as well as for serum levels of TNF-α using a commercial ELISA kit. This compound significantly inhibited NO and TNF-α levels after Carrageenan injection and inhibited iNOS and COX-2 protein expression in the animal model. These results suggest that the compound may be useful to develop new anti-inflammatory agents, and the mechanism of action may be related to inhibition of iNOS expression.

Pleurotus species are among the most cultivated edible muhrooms in the world with high nutritional value and reported medicinal properties. Several *Pleurotus* species have been

studied for the anti-inflammatory effect of their extracts as well as their bioactive metabolites; examples are *Pleurotus citrinopileatus* Singer; *Pleurotus eryngii* (DC.) Quél; *Pleurotus florida* Singer; *Pleurotus ostreatoroseus* Singer; *Pleurotus ostreatus* (Jacq. ex Fr.) P. Kumm.; *Pleurotus pulmonarius* (Fr.) Quél; *Pleurotus sajor-caju* (Fr.) Singer and *Pleurotus tuber-regium* (Rumph. ex Fr.) Singer. Liu et al. (2014) reported the anti-inflammatory activity of ethanolic mycelia extract of *Pleurotus tuber-regium* produced by submerged fermetation broth in LPS induced murine macrophage cell line RAW 264.7. Two compounds, cerevisterol (CE) and ergosta-4, 6, 8(14), 22-tetraen-3-one, were isolated, characterised and their anti-inflammatory activity evaluated. From the result, both compounds at 10μM inhibited NO production in a dose dependent manner, very similar to control. They also significantly inhibited TNF-α, IL-6, and PGE2 release from the cell culture supernatant. The anti-inflammatory activity was reported to be due to down regulation of iNOS and COX-2 mRNA protein expression.

5.6. Other metabolites

Beside the major compounds with reported anti-inflammatory activity, other bioactive metabolites (**Supplementary material S7**) such as fatty acids, succinic and maleic derivatives, adenosine, cordycepin and glycopeptides have been studied (**Table 6**) and known to inhibit the production of inflammatory mediators as well as to suppress the induced inflammation *in vivo*.

Fomes fomentarius is an inedible mushroom specie common in Europe, Asia and North America, known for its large fruiting body and decomposing property. Its fruiting body was extracted with methanol and methyl 9-oxo-(10E, 12E)-octadecadienoate isolated (Choe, Yi, Lee, Seo, Yun, & Lee, 2015). The anti-inflammatory activity was evaluated in peritoneal macrophages for NO, PGE2 production, TNF-α and IL-6 release. At 20 μg/mL, the

compound significantly inhibited NO and PGE2 by 65% and 50%, respectively, while TNF-α and IL-6 levels were inhibited up to 35% and 13%, respectively. Finally, the mechanism of action of the compound was found to be due to inhibition of iNOS and COX-2 protein expression and also due to a slight inhibition of phosphorylation of ERK1/2 kinase.

Polysaccharide protein complexes obtained from mushroom have been known to play several biological functions such as immunomodulatory, antitumour and antioxidant (Wu, Chen, & Siu, 2014). The anti-inflammatory activity of several glycoproteins have been reported by some authors (Chen, De Mejia, & Wu, 2011; Lau, Abdullah, Aminudin, Lee, & Tan, 2015). The anti-inflammatory activity of a glycopeptide from *Ganoderma capense* (Lloyd) Teng was evaluated in RAW264.7 cells for NO production and for iNOS enzyme activity (Zhou, Chen, Ding, Yao, & Gao, 2014). It was found that LPS-induced NO production and iNOS expression were significantly inhibited in a dose-dependent manner.

Many studies have reported the fatty acids composition of commercial and wild mushroom species (Barros, Baptista, Correia, Casal, Oliveira, & Ferreira, 2007). Agaricoglycerides is a fungal secondary metabolite made up of esters of chlorinated 4-hydroxy benzoic acid and glycerol. Han & Cui (2012) isolated this compound from fermented broth of *Grifola frondosa* (Dicks.) Gray and evaluated its anti-inflammatory activity by measuring *in vivo* levels of COX-2, ICAM-1, and iNOS. TNF-α and IL-1β levels were also quantified using an ELISA kit. Exposure to the compound at 500 mg/kg significantly decreased the level of IL-1β and TNF-α, and suppressed iNOS expression in LPS induced cells.

5.7 Commercial and synthesised compounds

Researchers have attempted to synthesize compounds with improved properties as drug candidates with the potential to inhibit production of NO and other inflammatory mediators

such as interleukins (IL 1β, IL-6, IL-8), TNF-α and PGE2. Some synthesised and commercial compounds with positive anti-inflammatory potential have been reported (**Table 7**).

Taofiq et al. (2015) studied the anti-inflammatory activity of commercial phenolic acids (*p*-hydroxybenzoic and *p*-coumaric acids) and cinnamic acid, and of their synthesised metabolites (glucuronated *p*-coumaric acid, methylated *p*-coumaric acid, glucuronated cinnamic acid, methylated cinnamic acid, methylated *p*-hydroxybenzoic acid, glucuronated *p*-hydroxybenzoic acid) from parental phenolic acids (Heleno, Ferreira, Calhelha, Esteves, & Queiroz, 2014). All compounds were then tested for their potential to inhibit NO production in LPS stimulated RAW 264.7 cells. Cinnamic acid had the highest activity (IC_{50} value 182 µM), followed by *p*-hydroxybenzoic (239 µM) and *p*-coumaric (442 µM) acids, in comparison with dexamethasone (40 µM) used as control. Among the synthesized metabolites, CoA-GP (glucuronated derivative of *p*-coumaric acid) and CoA-M1 (methylated derivative with the methoxy group at the *para* position) presented strong anti-inflammatory activity with IC_{50} values of 58 µM and 35 µM, respectively.

Several publications have reported the medicinal properties of *Cordyceps* mushroom, including the anti-inflammatory activity (Kim et al., 2003; Won & Park, 2005; Rao, Fang, & Tzeng, 2007; Rao, Fang, Wu, & Tzeng, 2010; Han, Oh, & Park, 2011). This mushroom contains a lot of bioactive compounds and "Cordycepin" an adenosine analogue is the most important one. Jeong et al. (2010) studied the anti-inflammatory activity of commercial cordycepin in LPS stimulated murine BV2 microglia cells for inhibition of NO production as well as PGE2, and pro-inflammatory cytokine release. Cordycepin at 7.5 µg/mL, decreased levels of NO production up to 65% while the PGE2 concentration measured using ELISA kit was also repressed up to 60%. This anti-inflammatory mechanism was found to be due the inhibition of iNOS and COX-2 protein expression. Choi et al. (2014b) also studied the anti-inflammatory potential of cordycepin in LPS stimulated RAW 264.7 macrophage cell line for

NO production, cytokine (TNF-α and IL-1β) levels and PGE2 production. At 30 μg/mL exposure of induced cells to cordycepin, there was significant decrease in NO, TNF-α, IL-1β and PGE2 levels. The mechanism of inhibition was further confirmed by decreased levels of LPS-induced NF-κB/p65 levels in the nucleus and inhibition of phosphorylation of IkB-α complex.

6. Concluding remarks

The present review focuses on the anti-inflammatory activity of some important worldwide edible, wild and medicinal mushrooms as well as on the bioactive metabolites they contain, which are responsible for the imparted anti-inflammatory activity. Research studies available in literature, on both edible and inedible mushroom species, highlight their anti-inflammatory activity, conclusion drawn mainly based on the extracts evidences and not on the bioactive compounds themselves. Among the existing mushroom species, *Agaricus bisporus, Phellinus linteus*, *Cordyceps* species, *Antrodia camphorate, Pleurotus species* and *Ganoderma lucidum* have been the most extensively studied.

Nevertheless the intensive research done in field, it is difficult to compare results reported by different researchers, partly due to the diverse methodologies used to evaluate the anti-inflammatory activity of both mushroom extracts and isolated compounds. Among them, nitric oxide assay is the most widely used assay for *in vitro* measurement of NO production in LPS stimulated RAW 264.7 cells. Other methods include *in vitro* evaluation of TNF-α inhibition in LPS activated THP-1 monocytic cell, measurement of inhibition of expression of iNOS, COX-2 and other pro-inflammatory mediators using cytokine enzyme linked immunosorbent assay (ELISA) kit and COX-1- and COX-2-catalyzed prostaglandin biosynthesis assay. In what concerns *in vivo* anti-inflammatory studies, many have been carried out by inducing inflammation in mice either by croton oil-induced ear edema test, the

carrageenin-induced paw edema model, TPA (12-*O*-tetradecanoylphorbol-13-acetate) induced ear edema or xylene induced edema and the activity of the extracts or compounds evaluated by observed reduction of edema.

Also the IC_{50} values, concentration responsible for 50% inhibition of inflammatory mediators production, even for the same mushroom species using the same anti-inflammatory assay, might be different as the bioactive compounds are released depending upon the type of cultivation environment, solvent and extraction procedure, extraction time and mushroom maturation..

Among the several bioactive compounds isolated from mushrooms and studied for anti-inflammatory activity, polysaccharides, terpenes and phenolic derivatives are the most implicated and known to show positive bioactivity. Only few research studies reported the bioactivity of ergosterol, fatty acids, glycopeptides, and nucleic acid analogues as well as of other metabolites.

Hence, mushrooms have valuable therapeutic compounds whose mechanism of action need to be fully elucidated and corroborated by conducting clinical trials in order to confirm the effectiveness of some of these mushroom-based inhibitors of NF-κB pathway as well as inhibition of the cyclooxygenase enzyme responsible for expression of many inflammatory mediators. This will consolidate the basis for the development of mushroom-based nutraceuticals or drugs effective against inflammation.

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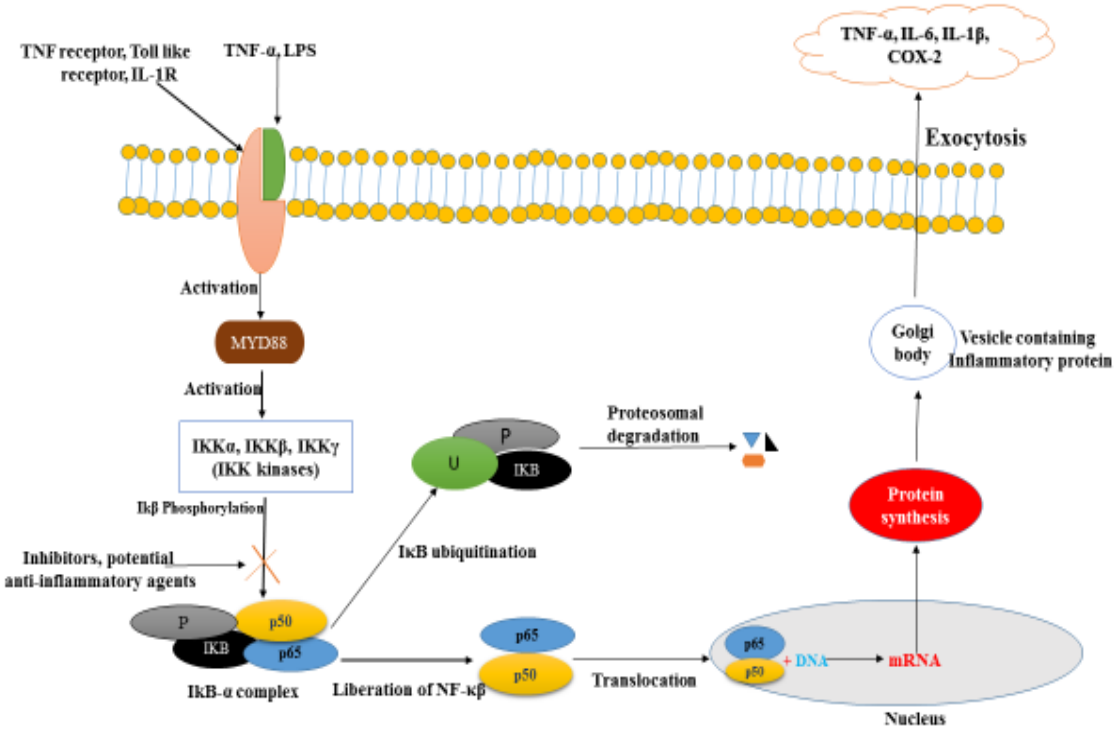

Figure 1. Schematic diagram of nuclear factor-κB (NF-κB) pathway. Macrophage cells express membrane receptors such as toll-like receptors (TLRs) and tumor necrosis factor receptors (TNFR). These receptors recognize pro-inflammatory stimuli such as lipopolysaccharides and viral proteins. Attachment of these pathogen-associated molecular patterns (PAMPs) to membrane receptors activates the myeloid differentiation protein 88 (MyD88). MyD88 activates specific protein kinases that are responsible for activation of IKK kinase (IKKα, IKKβ, IKKγ). This kinase further phosphorylates IkB-α complex leading to dissociation of the complex, and its proteasomal degradation, allowing NF-kB to translocate to the nucleus, where it binds to specific DNA sequences encoding the pro inflammatory cytokines (e.g., IL-1, IL-2, IL-6, TNF-α as well as Cyclooxygenase-2 (Cox-2) and inducible nitric oxide synthase (iNOS).

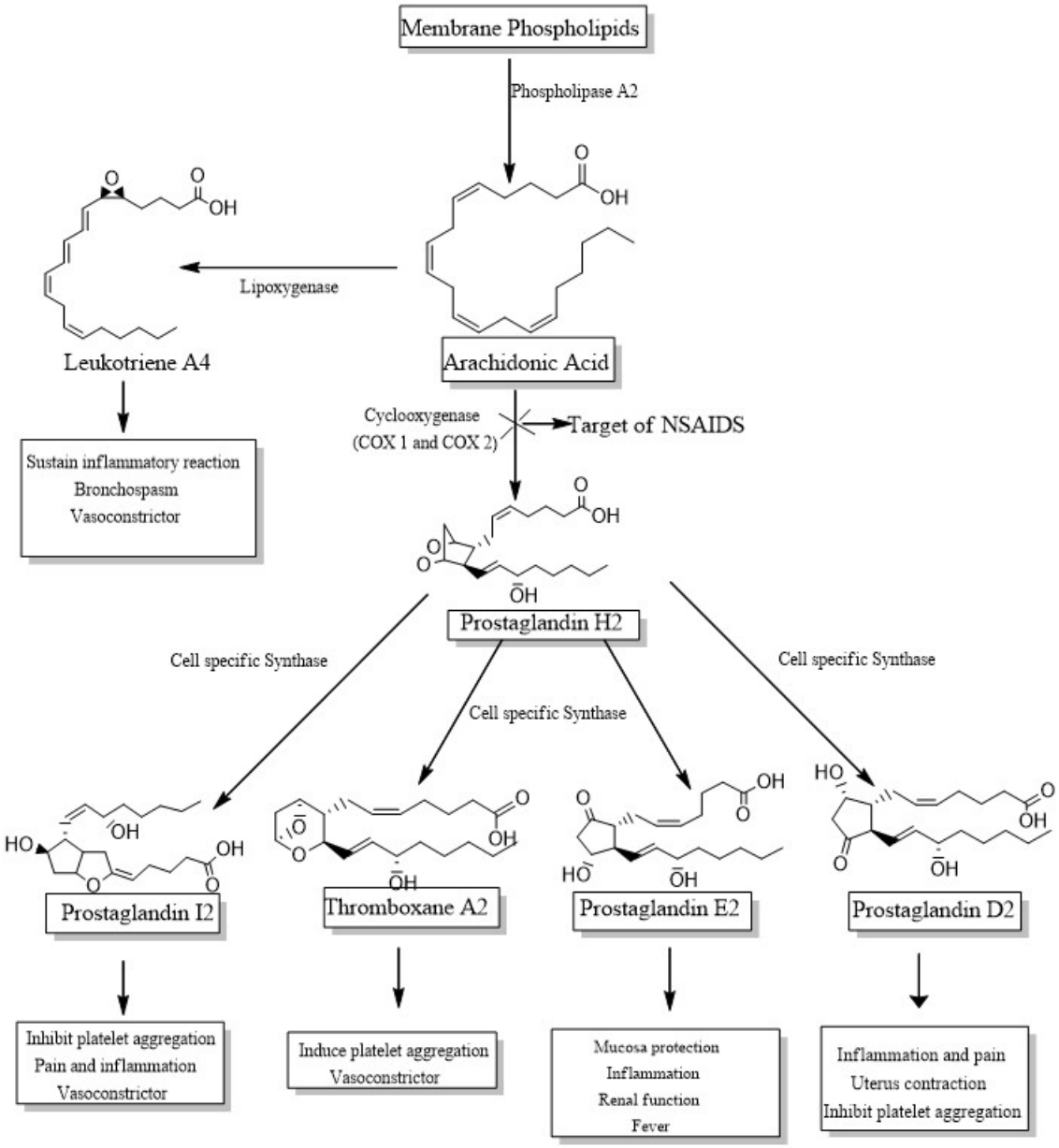

Figure 2. Schematic diagram of the biosynthetic pathway of common prostaglandins.

Table 1. Previous studies on anti-inflammatory activity of different mushroom species.

Mushroom	Origin	Extract	Assay	Mechanism of action	Reference
Agaricus bisporus J.E.Lange	Spain	Methanol	1, 2	Inhibited NO production, level of TNF-α released	Moro et al., 2012
	Australia	Ethanol	1,2	Reduced level of NO, TNF-α	Gunawardena et al., 2014
	Portugal	Ethanol	1	Inhibited NO production	Taofiq et al., 2015
A. bisporus Portobello J.E.Lange	Australia	Ethanol	1,2	Reduced level of NO, TNF-α	Gunawardena et al., 2014
Agaricus blazei Murill	Japan	n.m.	2	Decreased level of IL-6, IL-8 and IL-10	Bernardshaw et al., 2006
	Brazil	Water	4	Reduced edema	Mourão, et al., 2011
	Korea	Methanol	2	Inhibited IL-6, PGD2 release	Song et al., 2012
Amauroderma rugosum (Blume & T. Nees) Torrend	Malaysia	Ethanol	1	Inhibited NO production	Chan et al., 2013
	Malaysia	Ethanol	1, 2	Inhibited NO production, suppressed TNF-α release	Chan et al., 2015
Antrodia camphorata (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang	Taiwan	n.m.	2	Inhibited TNF-α, IL-1β and NF-κβ	Hseu et al., 2010
	Taiwan	Water and methanol	5	Inhibited edema	Liu et al., 2007
	Taiwan	n.m.	1, 2	Reduced NO, TNF-α & IL-1β production	Hseu et al., 2005
Antrodia cinnamomea Chang & Chou	Taiwan	Methanol	1	Inhibited NO, TNF-α, IL-6 production and COX-2 expression	Wen et al., 2011
Antrodia salmonea T.T. Chang & W.N. Chou	Taiwan	Ethanol	1, 2, 4	Reduced NO and Cytokine release, paw edema inhibition	Huang et al 2012b.
Boletus impolitus Fr.	Portugal	Ethanol	1	Inhibited NO production	Taofiq et al., 2015
Cantharellus cibarius Fr.	Spain	Methanol	1, 2	Inhibited NO & level of TNF-α released	Moro et al., 2012
Cordyceps militaris (L.) Fr.	Korea	70% Ethanol	3, 4	Inhibited Inflammation	Won et al., 2005
	Korea	Water	1, 2	Inhibited NO production, IL-6 and TNF-α inhibition	Joung, et al., 2014

		water			
	Korea	70% ethanol	2	Reduced expression of TNF-α, IL-1β and IL-6.	Lim, 2011
Daedalea gibbosa (Pers.)	Israel	Ethyl acetate	1, 2	Reduced level of NO via decreased iNOS promoter activity, reduced TNF-α	Ruimi et al., 2010b
Flammulina velutipes (Curtis) Singer	Australia	Ethanol	1,2	Reduced level of NO, TNF-α	Gunawardena et al., 2014
*Ganoderma lucidum (*Curtis) P. Karst.	Taiwan	Water, 80% methanol	1	Reduced level of NO	Chu et al., 2015
	Korea	25% ethanol	1, 2	Inhibited NO, PGE2, IL-1β and TNF-α	Yoon et al., 2013
Inonotus obliquus (Ach. ex Pers.) Pilát	Korea	Hot methanol	1	Inhibited NO production	Park et al., 2005
	Canada	Ethanol	1, 2	Inhibited NO production, level of TNF-α released	Van et al., 2009
Lactarius deliciosus (L. ex Fr.) S.F.Gray	Spain	Methanol	1, 2	Inhibited NO production, level of TNF-α released	Moro et al., 2012
Lentinus edodes (Berk.) Pegler	Australia	Ethanol	1,2	Reduced level of NO, TNF-α	Gunawardena et al., 2014
Lentinus polychrous (L.) Fr.	Thailand	80% Ethanol	1, 2	Inhibited NO & TNF-α levels, suppressed iNOS activity	Fangkrathok et al., 2013
Lignosus rhinocerotis (Cooke) Ryvarden	Malaysia	Water and methanol	2, 4	Reduced paw swelling, reduced level of TNF-α	Lee et al., 2014
Macrolepiota procera, (Scop.) Singer	Portugal	Ethanol	1	Inhibited NO production	Taofiq et al., 2015
Marasmius oreades (Bolton) Fr	Israel	Ethyl acetate	1	Reduced level of NO	Ruimi et al., 2010a
Naematoloma sublateritium (Fr.) P. Karst	Korea	Ethanol	2	Reduced TNF-α release, inhibited NF-κB activation	Lee et al., 2012
Phellinus baumii Pilát	Korea	Methanol	1, 2	Reduced level of NO, inhibited PGE2, IL-1β, IL-6 expression	Yayeh et al., 2012
Phellinus linteus (Berk. & M. A. Curtis) Teng	Korea	70% Ethanol	1	Decreased iNOS promoter activity and NO production	Kim et al., 2006
	Korea	70% Ethanol	3	Inhibited inflammation	Kim et al., 2004
	Korea	70% Ethanol	1	Inhibited NO production	Kim et al., 2007

	Taiwan	n.m.	1, 2	Inhibited NO and TNF-α production	Lin et al., 2014b
	Korea	Ethanol, Ethyl acetate	1, 2	Inhibited NO and PGE2 production	Song et al., 2014
Pleurotus eryngii (DC.) Quél.	Taiwan	Ethanol	1, 2	Reduced level of NO, inhibition of PGE2 release	Lin et al., 2014a
Pleurotus florida Singer	India	Methanol	4	Reduced edema	Jose et al., 2004
	Iran	Water	1	Reduced level of NO	Ghazanfari et al., 2009
	Korea	60% acetone, 80% methanol	1, 4	Reduced level of NO, inhibited edema	Im et al., 2014
Pleurotus ostreatoroseus Singer	Brazil	ethanol	1	Inhibited NO production	Corrêa et al., 2015
Pleurotus ostreatus (Jacq. ex Fr.) P.Kumm.	Portugal	Ethanol	1	Inhibited NO production	Taofiq et al., 2015
	Australia	Ethanol	1,2	Reduced level of NO, TNF-α	Gunawardena et al., 2014
	USA	Water	2	Inhibited production of TNF-α, IL-6, and IL-12	Jedinak et al., 2011
Pleurotus sajor-caju (Fr.) Singer	Malaysia	95% ethanol	1	Reduced level of NO	Saad et al., 2014
Pleurotus tuber-regium (Rumph. ex Fr.) Singer	Belgium	95% ethanol	1, 2	Reduced level of NO, Inhibit TNF-α, and IL-6 release	Liu et al., 2014
Polyporus dermoporus Pers.	Brazil	Ethanol	1, 3, 4	Inhibited edema, reduced level of NO	Dore et al., 2014
Poria cocos F.A.Wolf	Korea	Ethanol	1, 2	Inhibited NO, PGE2, TNF-α, and IL-1β production, suppressed NF-kB activity	Jeong et al., 2014
Russula virescens (Schaeff.) Fr.	Korea	70% ethanol	1, 2	Reduced level of NO and inhibition of TNF-α mRNA expression	Hur et al., 2012
Termitomyces albuminosus (Berk.) R.Heim	China	80% Ethanol	4, 6	Reduced edema	Lu et al., 2008

Tremella fuciformis Berk.	Korea	80% methanol	1	Reduced iNOS expression and NO production	Li et al., 2014a
Tricholoma matsutake Sing	Korea	Dichloromethane	1	Inhibited NO production	Lim et al., 2007
Tuber aestivum Vittad.	Serbia	Methanol	7	Inhibited COX-1 activity	Beara et al., 2014
Tuber magnatum Pico	Serbia	Methanol	7	Inhibited COX-1 activity	Beara et al., 2014

n.m.- not mentioned; 1- Nitric oxide assay; 2- Cytokine enzyme linked immunosorbent assay (ELISA); 3- Croton induced ear edema test; 4- Carrageenin-induced paw edema test; 5- TPA (12-O-tetradecanoylphorbol-13-acetate) induced ear edema; 6- Xylene induced edema. 7- COX-1- and COX-2-Catalyzed prostaglandin biosynthesis assay *in vitro*.

Table 2. Polysaccharides isolated from mushrooms with reported anti-inflammatory activity.

Mushroom	Origin	Bioactive compound	Extraction solvent	Assay	Mechanism of action	Reference
Agaricus bisporus J.E.Lange	Brazil	Fucogalactan	Water, ethanol	5	Decreased iNOS and COX-2 expression	Ruthes et al., 2013b
	Brazil	Fucogalactan	Chloroform, methanol	7	Inhibited acetic acid induced inflammation	Komura et al., 2010
Agaricus blazei Murill	China	Soluble polysaccharide	Water	2	Inhibited TNF-α, IL-1β, COX-2, iNOS, and ICAM-1 Levels	Wang et al., 2013b
Agaricus brasiliensis Peck	Brazil	Fucogalactan	Chloroform, methanol	7	Inhibited acetic acid induced inflammation	Komura et al., 2010
Agrocybe chaxingu Huaag	Korea	β-Glucan	n.m.	1, 6	Inhibited NO production and edema formation	Lee et al., 2009
Amanita muscaria (L.) Lam.	Brazil	Fucomannogalactan	Hot, cold water and aq. KOH	5	Reduced formalin-induced inflammatory pain	Ruthes et al., 2013c
Armillariella mellea (Vahl) P.Kumm.	Taiwan	Polysaccharides and sulphated polysaccharides	Hot water, 95% ethanol	2	Inhibited TNF-α and IL-6 secretion	Chang et al., 2013
Caripia montagnei (Berk.) Kuntze	Brazil	β-Glucan	chloroform-methanol (1:1,v/v), 80% acetone	1, 3	Inhibited NO production, edema inhibition	Castro et al., 2014
	Brazil	β-Glucan	80% acetone	1, 2, 3	Inhibited NO production, decreased cytokine release, edema reduction	Queiroz et al., 2010
Collybia dryophila (Bull.) P. Kumm.	Canada	(1→3),(1→4) β-Glucans	85% ethanol	1	Inhibited NO production	Pacheco-Sanchez et al., 2006
Cordyceps militaris (L.) Fr.	Taiwan	Glucose, D-mannitol, 3,4-*O*-isopropylidene-D-mannitol	Methanol	1, 2	Inhibited NO production, decreased cytokine release	Rao et al., 2010
	Korea	(1–3)-β-D-Glucan	Chloroform-methanol	2	Inhibited IL-1β, TNF-α, COX-2 release.	Smiderle et al., 2014
Geastrum saccatum Fr.	Brazil	β-Glucan	Acetone, water, ethanol	1, 3, 6	Reduced nitrate/ nitrite and interleukin level	Dore et al., 2007
Lactarius rufus (Scop.) Fr.	Brazil	(1→3),(1→6)-β-D-Glucans	Water, ethanol	5	Inhibited pain	Ruthes et al., 2013a

Lentinus edodes (Berk.) Pegler	Japan	β-Glucan	n.m.	1, 2	Inhibited NO production, level of TNF-α released	Xu et al., 2012
	Japan	Lentinan	n.m.	2	Down regulated IL-8 mRNA expression	Mizuno et al., 2009
	Brazil	Heterogalactan	Water	7	Inhibited acetic acid-induced inflammation	Carbonero et al., 2008
Pleurotus pulmonarius (Fr.) Quél.	Israel	Glucan	Water, Ethanol	2	Inhibited TNF-α released from cells	Lavi et al., 2010
	Nigeria	β-D-Glucan	95% Acetone	3	Inhibited edema formation	Adebayo et al., 2012
	Brazil	(1→3),(1→6) β-glucan	chloroform-methanol	7	Inhibited induced inflammation	Smiderle et al., 2008
Pleurotus sajor-caju (Fr.) Singer	Brazil	β-D-Glucan	chloroform-methanol (2:1, v/v), water and ethanol	2	Inhibited production of pro-inflammatory genes	Silveira et al., 2014
	Brazil	Exopolysaccharide	Ethanol	3	Reduced edema	Silveira et al., 2015
Scleroderma nitidum Berk.	Brazil	β-Glucan	80% acetone	1, 2, 3	Reduced level of NO, IFN-γ, IL-2, IL-10, suppresed paw edema	Nascimento et al., 2012
Termitomyces albuminosus (Berk.) R.Heim	China	Crude polysaccharide	80% Ethanol, water	3, 4, 5	Inhibition of edema formation	Lu et al., 2008

n.m.- mot mentioned. 1- Nitric oxide assay; 2- Cytokine enzyme linked immunosorbent assay (ELISA); 3- Carrageenin-induced paw edema test; 4- Xylene induced edema; 5- Formalin test; 6- Croton induced ear edema test; 6- TPA (12-O-tetradecanoylphorbol-13-acetate) induced ear edema; 7- Acetic acid induced inflammation test

Table 3. Terpenes isolated from mushrooms with reported anti-inflammatory activity.

Mushroom	Origin	Bioactive compound	Extraction solvent	Assay	Mechanism of action	Reference
Antrodia camphorata (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang	Taiwan	Eburicoic acid Dehydroeburicoic acid	Methanol	1, 2, 5	Inhibited NO production and cytokine release; Suppressed Carrageenin -induced edema	Deng et al., 2013
Cyathus africanus H. J. Brodie	China	Diterpenoid	Ethyl acetate	1	Inhibited NO production	Han et al., 2013
Cyathus hookeri Berk.	China	Cyathane diterpenoid	Ethanol	1	Inhibited NO production	Xu et al., 2013
Fomitella fraxinea (Bull.) Imazeki	Japan	Fomitellanols,cryptopo ric acids,	Isopropanol	3	Inhibited COX-1 activit	Yoshikawa et al., 2013
Fomitopsis nigra (Berk.) Imaz.	Korea	Pachymic acid	Methanol	2	Inhibition of ICAM-1, Cox-2, and iNOS expression	Lee et al., 2013
Fomitopsis pinicola (Sw.:Fr.) P. Karst.	Japan	Lanostane triterpenoids, triterpene glycosides	70% Ethanol	3	Inhibited COX-2 activity	Yoshikawa et al., 2005
*Ganoderma lucidum (*Curtis) P. Karst.	Korea	Lanostane triterpenes	Water and ethyl acetate	1, 2	Inhibited NO production; suppressed iNOS and COX-2 expression	Choi et al., 2014a Lee
	USA	Triterpene	95% ethanol	1, 2	Inhibited TNF-α, PGE_2 and NO production; suppressed IL-6 production	Dudhgaonkar et al., 2009
	Japan	Triterpene acids	Methanol	4	Suppressed TPA-induced edema	Akihisa et al., 2007
	Japan	Triterpene butyl esters	Methanol		Inhibited NO production; suppressed iNOS and COX-2 activity	Tung et al., 2013
	China	Ganoderic acid C1	Methylene chloride	2	Inhibited TNF-α production	Liu et al., 2015
Inonotus obliquus (Ach. ex Pers.) Pilát	China	Triterpenes	Ethanol	1	Inhibited NO production	Ma et al., 2013
Laetiporus sulphureus (Bull.) Murrill	Korea	Acetyl Eburicoic Acid	Methanol	1	Inhibited NO production	Saba et al., 2015
Piptoporus betulinus (Bull. ex Fr.) P. Karst.	Germany	Lanostanoids	Ethyl acetate, chloroform, methanol	3	Inhibited COX-1 activity	Kemami et al., 2004
	Japan	Lanostane-Type Triterpene	Methanol	4	Suppressed TPA-induced edema	Kamo et al., 2003
Poria cocos F.A.Wolf	China	29-hydroxypolyporenic acid C, polyporenic	70% ethanol	1	Inhibited NO production	Cai & Cai, 2011

		acid C				
Sarcodon scabrosus (Fr.), P. Karst.	Japan	Cyathane diterpenoid	Methanol	4	Suppressed TPA-induced inflammation	Hirota et al., 2002
	Japan	Diterpenoid	Methanol	4	Suppressed TPA-induced inflammation	Kamo et al., 2004

1- Nitric oxide assay; 2- Cytokine enzyme linked immunosorbent assay (ELISA); 3- COX-1- and COX-2-Catalyzed Prostaglandin Biosynthesis Assay *in Vitro*; 4- TPA (12-*O*-tetradecanoylphorbol-13-acetate) induced ear edema; 5- Carrageenin-induced paw edema.

Table 4. Phenolic compounds and derivatives isolated from mushrooms with reported anti-inflammatory potential.

Mushroom	Origin	Bioactive compound	Extraction solvent	Assay	Mechanism of action	Reference
Agaricus bisporus J.E.Lange	Japan	2-Amino-3H-phenoxazin-3-one	Ethyl acetate	1,2 3	Inhibited NO, COX1 and COX 2 activity and cytokine release	Kohno et al., 2008
Albatrellus caeruleoporus (Peck) Pouzar	Japan	Grifolin dervatives	Methanol	1	Reduced NO production	Quang et al., 2006b
Antrodia camphorata (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang	Taiwan	Benzenoids	Ethylacetate, methanol	1	Inhibited NO production	Chen et al., 2013
	Taiwan	Antrocamphin A (Benzenoids)	95% Ethanol, ethyl acetate, water	1, 2	Inhibited NO production, Down-regulated iNOS and COX-2 expression	Hsieh et al., 2010
	Taiwan	Antrocamphin A and its analogue	n.m		Inhibited NO production	Lee et al., 2011
	Taiwan	Benzocamphorin	Ethanol	1	Inhibited NO production	Liao et al., 2012
*Daedalea quercina (*L.) Pers.	Germany	Quercinol	n.m	2	Inhibited COX 2 enzyme activity	Gebhardt et al., 2007
Daldinia childiae Ces. & De Not.	Japan	Benzophenone derivatives	n.m	1	Supressed NO production	Quang et al., 2006a
Elaphomyces granulatus Fr.	USA	Syringaldehyde and syringic acid	95% Ethanol	2	Inhibited COX-2 activity	Stanikunaite et al., 2009
Grifola gargal Singer	Japan	Ergothioneine	hot water	3	Inhibited TNF-α-induced IL-6 release	Ito et al., 2011
Inonotus xeranticus (Berk.) Imazeki & Aoshima	Korea	Davallialactone	n.m	1, 3	Inhibited NO production and cytokine release	Lee et al., 2008
	Korea	Davallialactone	n.m	3	Inhibition of ICAM-1, COX-2, and iNOS expression	Lee et al., 2011a
Neolentinus lepideus (Fr.) Redhead & Ginns	China	Benzoquinone, cinnamic acid derivatives	Ethyl acetate	1	Inhibited NO production	Li et al., 2013
Phellinus gilvus (Schwein.) Pat	Korea	protocatechualdehyde	Water	1	Inhibited NO production, inhibited iNOS, COX-2 expression	Chang et al., 2011b
Phellinus linteus (Berk. & M. A. Curtis) Teng	Taiwan	Inotilone	95% Ethanol	1,3 4	Inhibited NO, cytokines and MAPK Activation; suppressed edema.	Huang et al., 2012

	Taiwan	Hispolon	n.m	1, 2	Inhibited NO production and cytokine release	Lin et al., 2014

n.m – not mentioned; 1- Nitric oxide assay; 2- COX-1- and COX-2-Catalyzed Prostaglandin Biosynthesis Assay in Vitro 3- Cytokine enzyme linked immunosorbent assay (ELISA)

Table 5. Common steroids isolated from mushrooms with reported anti-inflammatory activity.

Mushroom	Origin	Bioactive compound	Extraction solvent	Assay	Mechanism of action	Reference
Antrodia camphorata (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang	Taiwan	Ergostatrien-3β-ol	Methanol, ethyl acetate	1, 2, 3	Decreased IL-1β and TNF-α release; inhibited NO and reduced edema	Huang et al., 2010
	Taiwan	Zhankuic acid C	n.m	2	Decreased TNF-α, IL-6, IL-12	Lin et al., 2015
	Taiwan	Zhankuic acid A	n.m	2	Inhibited TNF-α and IL-6 levels, inhibits iNOS, COX2 expression	Chen et al., 2014
Cordyceps militaris (L.) Fr.	Taiwan	Ergosterol	Methanol	1, 2	Inhibited NO production, decreased cytokine release	Rao et al., 2010
Ganoderma lucidum (Curtis) P. Karst	India	Ergosta-7,22-diene-3β-yl pentadecanoate	Petroleum ether, chloroform	3	Suppressed edema	Joseph et al., 2011
Grifola frondosa (Dicks.) Gray	Taiwan	Ergosterol peroxide	n-hexane	2	Inhibited IL-1β, IL-6 and TNF-α	Wu et al., 2013
Hericium erinaceum (Bull.) Persoon	Korea	Hericirine (ergosterol)	Methanol	1, 2	Inhibited NO production and cytokine release	Li et al., 2014
	Korea	Ergostane-type sterol	Methanol	1, 2	Inhibited NO production and release of TNF-α	Li et al., 2015
Inonotus obliquus (Ach. ex Pers.) Pilát	China	Ergosterol, ergosterol peroxide, trametenolic acid	Ethanol	1	Inhibited NO production	Ma et al., 2013
Pleurotus tuber-regium (Rumph. ex Fr.) Singer	Belgium	Cerevisterol, ergosta 4,6,8(14),22-tetraen-3-one	95% Ethanol	1, 2	Inhibited NO and TNF-α, iNOS,COX2 expression was inhibited	Liu et al., 2014
Sarcodon aspratus (Berk.)	Japan	Ergosterol, ergosterol peroxide, 9,11-dehydro ergosterol peroxide	Acetone	2	Decreased TNF-α level, reduced NF-kB activity	Kobori et al., 2007

n.m- not mentioned; 1- Nitric oxide assay; 2- Cytokine enzyme linked immunosorbent assay (ELISA); 3- Carrageenin-induced paw edema test.

Table 6. Other compounds isolated from mushrooms with reported anti-inflammatory activity.

Mushroom	Origin	Bioactive compound	Extraction solvent	Assay	Mechanism of action	Reference
Agrocybe aegerita (V. Brig.) Singer	USA	Fatty acids	Methanol	1	Inhibited COX-II enzyme activity	Zhang et al., 2003
Antrodia camphorata (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang	Taiwan	Succinic and maleic derivatives	Methanol	3	Decreased IL-1β and TNF-α release	Chien et al., 2008
Antrodia cinnamomea Chang & Chou	China	Maleimide and Maleic Anhydride	Methanol	2	Inhibited NO production	Wu et al., 2008
	Taiwan	Maleimide Derivatives	95% Ethanol	2	Inhibited NO production	Wu et al., 2013b
	Taiwan	Antrodan (glycoprotein)	Double-distilled water	2	Inhibited NO production	Chiu et al., 2014
Coprinus comatus (O.F.Müll.) Pers	China	Triglycerides	Acetone	3	TNF-α, IL-1β Inhibition	Ren et al., 2012
Cordyceps cicadae	Taiwan	N^6-(2-Hydroxyethyl)adenosine cordycepin, adenosine	Ethanol	3	Inhibited production of cytokines	Lu et al., 2015
Cordyceps militaris (L.) Fr.	Korea	Cordycepin	n.m	2, 3	Inhibited NO production and cytokine release	Jeong et al., 2010
	Taiwan	Cordycepin	Methanol	2, 3	Inhibited NO production; Decreased cytokine release	Rao et al., 2010
	Korea	Cordycepin, α-Dimorphecolic acid	70% ethanol	2, 3	Inhibited NO and PGE2 production	Yoon et al., 2015
Cordyceps sinensis (Berk.) Sacc.	China	cordymin	Water	3, 5	Decreased IL-1β and TNF-α level, inhibition of acetic acid-induced constriction	Qian et al., 2012
Fomes fomentarius (L.) Fr.	Korea	Methyl 9-Oxo-(10E,12E)-octadecadienoate	Methanol	2, 3	Decreased iNOS expression; Inhibited TNF- α production	Choe et al., 2015
Ganoderma capense (Lloyd) Teng	China	Glycopeptide	n.m	2	Inhibited NO production	Zhou et al., 2014

Grifola frondosa (Dicks.) Gray	China	Agaricoglycerides	Ethyl acetate, acetone	3	Decreased IL-1β and TNF-α; inhibited ICAM-1, iNOS, and COX-2 expression	Han et al., 2012
	USA	Fatty acid fraction	Hexane, ethyl acetate, methanol	1	Inhibited COX1 and COX 2 enzyme activity	Zhang et al., 2002
Lignosus rhinocerotis (Cooke) Ryvarden	Malaysia	Polysaccharide-Protein complexes	Hot, cold Methanol	3, 4	Inhibited TNF- α production; reduced carrageenin-induced edema	Lau et al., 2015
Pleurotus citrinopileatus Singer	Taiwan	Nonlectin glycoprotein	n.m	2,3	Inhibited NO and PGE2	Chen et al., 2011

n.m- not mentioned; 1- COX-1- and COX-2-catalyzed prostaglandin biosynthesis assay in vitro; 2- Nitric oxide assay; 3- Cytokine enzyme linked immunosorbent assay (ELISA); 4- Carrageenin-induced paw edema test; 5- Acetic acid induced inflammation test

Table 7. Synthesised and commercial compounds with reported anti-inflammatory activity.

Compounds	Type	Assay	Mechanism of action	Refrences
Cinnamic acid, *p*-hydroxybenzoic acid, *p*-coumaric acid	Commercial	1	Inhibited NO production	Taofiq et al., 2015
Glucuronated *p*-coumaric acid, methylated *p*-coumaric acid	Synthesised	1	Inhibited NO production	Taofiq et al., 2015
Glucuronated cinnamic acid, methylated cinnamic acid	Synthesised	1	Inhibited NO production	Taofiq et al., 2015
Methylated *p*-hydroxybenzoic acid, glucuronated *p*-hydroxybenzoic acid	Synthesised	1	Inhibited NO production	Taofiq et al., 2015
Cordycepin	Commercial	1, 2	Reduced NO, TNF-α and IL-1β, suppressed phosphorylation of MAPKs	Choi et al., 2014b
	Commercial	1	Reduced NO production	Imamura et al., 2015
	Commercial	1,2	Inhibited NO production and cytokine release	Jeong et al., 2010
	Commercial	1, 2	Inhibited NO production, decreased IL-1β, IL-6, TNF-α release	Shin et al., 2009
Ethynylbenzenoid	Synthesized	2	Down-regulated TNF-α expression	Buccini et al., 2014
Ergosterol	Commercial		Inhibited NO production and cytokine release	Kuo et al., 2011
Hispidin	Commercial	2	Suppressed NF-***κ***B activity, induced I*κ*B degradation	Shao et al., 2015
Hispolon	Synthesized	1, 2, 3	Inhibited NO production, TNF-α release; reduced edema	Chang et al., 2011a
	Commercial	1	Inhibition of NO production and iNOS expression	Yang et al 2014
Inotilone and methylinotilone	Synthesized	1, 2	Decreased nitrite and prostaglandin level	Kuo et al., 2009

1-Nitric oxide assay; 2- Cytokine enzyme linked immunosorbent assay (ELISA); 3- Carrageenin-induced paw edema test.