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

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References
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,
2. Inflammatory mediators and cell signalling

Inflammation is one of the 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$_2$O$_2$), peroxide anion (O$_2^{2-}$), hydroxyl ion (OH$^-$) and hydroxyl radical (OH$•$).

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, & Sripandikulchaisri, 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 IκB proteins complex (Hasnat, Pervin, Cha, Kim, & Lim, 2015). Cytosolic IκB forms a complex with NF-κB and the IκB 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 IκB preventing translocation of NF-κB 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
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 PGH₂, which is converted to other prostanoid species including PGD₂, PGE₂, prostacyclin (PGI₂), and thromboxane (TXA₂) 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 sulphanilamide 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™ 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-κB 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 susceptibility to heating.

*Ganoderma lucidum* (Curtis) P. Karst., is a medicinal 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 activity 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*, *Craterellus 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 opposition, ethanolic extracts of *Agaricus bisporus* Portobello, *Boletus edulis* 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 application 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 (C₅H₈)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 compounds 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 (IC₅₀ 15.1 µg/mL), reduced IL-6 production (IC₅₀ 14.4 µg/mL) and decreased the secretion of PGE₂ and NO in a dose-dependent manner with IC₅₀ 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 IC₅₀ values of 2.57, 1.45, 12.06, 10.73, and 9.45 µM, compared to hydrocortisone used as the control with IC₅₀ 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 *vitro* in carrageenan induced hind mouse paw edema model as well as in *vivo* 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 precursor 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 mushrooms 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 fermentation 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 (IC₅₀ 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 IC₅₀ 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 IκB-α complex leading to dissociation of the complex, and its proteasomal degradation, allowing NF-κB 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.
| 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                 |
| Species                          | Country     | Extractant           | Concentration | Effect                                                                 | Reference               |
|---------------------------------|-------------|----------------------|---------------|------------------------------------------------------------------------|-------------------------|
| Daedalea gibbosa (Pers.)        | Korea       | Water, 70% ethanol   | 2             | Reduced expression of TNF-α, IL-1β and IL-6.                           | Lim, 2011               |
|                                 | Israel      | Ethyl acetate, 1, 2   |               | Reduced level of NO via decreased iNOS promoter activity, reduced TNF-α | Ruimi et al., 2010b     |
| Flammulina velutipes (Curtis)   | Australia   | Ethanol, 1, 2         |               | Reduced level of NO, TNF-α                                            | Gunawardena et al., 2014|
| Singer                          | Taiwan      | Water, 80% methanol   | 1             | Reduced level of NO                                                    | Chu et al., 2015        |
| Ganoderma lucidum (Curtis) P.   | Korea       | Ethanol, 25% ethanol, 1, 2 |               | Inhibited NO, PGE2, IL-1β and TNF-α                                   | Yoon et al., 2013       |
| Karst.                          | Wales       | Hot methanol, 1       |               | Inhibited NO production                                               | Park et al., 2005       |
| Lactarius deliciosus (L. ex Fr.) | Canada     | Ethanol, 1, 2         |               | Inhibited NO production, level of TNF-α released                      | Van et al., 2009         |
| 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    | Ethanol, 1, 2         |               | Inhibited NO & TNF-α levels, suppressed iNOS activity                 | Fangkrathok et al., 2013|
| Lignosus rhinocerotis (Cooke)   | Malaysia    | Water and methanol, 2, 4 |               | Reduced paw swelling, reduced level of TNF-α                          | Lee et al., 2014        |
| Ryvarden                        | Portugal    | Ethanol, 1            |               | Inhibited NO production                                               | Taofiq et al., 2015     |
| Macrolepiota procera, (Scop.)   | Israel      | Ethyl acetate, 1      |               | Reduced level of NO                                                   | Ruimi et al., 2010a     |
| Singer                          | Korea       | Ethanol, 2            |               | Reduced TFN-α release, inhibited NF-κB activation                      | Lee et al., 2012        |
| Marasmius oreades (Bolton) Fr   | Korea       | Methanol, 1, 2        |               | Reduced level of NO, inhibited PGE2, IL-1β, IL-6 expression            | Yayeh et al., 2012      |
| P. Karst                        | Korea       | Methanol, 70%         | 1             | Decreased iNOS promoter activity and NO production                   | Kim et al., 2006        |
| Phellinus baumii Pilát          | Korea       | Ethanol, 70%          | 3             | Inhibited inflammation                                                | Kim et al., 2004        |
| Phellinus linteus (Berk. & M. A. Curtis) Teng | Korea  | Ethanol, 70%          | 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

Pleurotus floridus Singer  Iran  Water  1  Reduced level of NO  Ghazanfari et al., 2009

Pleurotus floridus Singer  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

Pleurotus sajor-caju (Fr.) Singer  Australia  Ethanol  1, 2  Reduced level of NO, TNF-α  Gunawardena et al., 2014

Pleurotus sajor-caju (Fr.) Singer  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
| Species                     | Country | Extractant   | Solvent | Reduced Activity | Ref.         |
|----------------------------|---------|--------------|---------|------------------|--------------|
| *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.*
| Mushroom | Origin | Bioactive compound | Extraction solvent | Assay | Mechanism of action | Reference |
|----------|--------|--------------------|--------------------|-------|---------------------|-----------|
| Agaricus bisporus | Brazil | Fucogalactan | Water, ethanol | 5 | Decreased iNOS and COX-2 expression | Ruthes et al., 2013b |
| Agaricus bisporus | 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 chamingu 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 |
| Collybia dryophila (Bull.) P. Kumm. | Canada | (1→3),(1→4)β-Glucans | 85% ethanol | 1 | Inhibited NO production | Queiroz et al., 2010 |
| 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 |
| Species                        | Country | Type       | Solvent          | Method             | Effects                                                                 | Reference                  |
|--------------------------------|---------|------------|------------------|--------------------|-------------------------------------------------------------------------|----------------------------|
| *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          |
| *Pleurotus sajor-caju* (Fr.) Singer | 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     |
|                               | Brazil  | β-D-Glucan | chloroform-methanol (2:1, v/v), water and ethanol | 2                  | Inhibited production of pro-inflammatory genes                          | Silveira et al., 2014     |
| *Scleroderma nitidum* Berk. | Brazil  | Exopolysaccharide | Ethanol       | 3                  | Reduced edema                                                           | Silveira et al., 2015      |
| *Termitomyces albuminosus* (Berk.) R.Heim | Brazil  | β-Glucan   | 80% acetone     | 1, 2, 3             | Reduced level of NO, IFN-γ, IL-2, IL-10, suppressed paw edema           | Nascimento et al., 2012    |
|                               | China   | Crude polysaccharide | 80% Ethanol, water | 3, 4, 5             | Inhibition of edema formation                                            | Lu et al., 2008            |

n.m.- not mentioned. 1- Nitric oxide assay; 2- Cytokine enzyme linked immunosorbent assay (ELISA); 3- Carrageenan-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, Description                          | Bioactive compound                      | Extraction solvent | Assay | Mechanism of action                                                                 | Reference             |
|-----------------------------------|----------------------------------------------|------------------------------------------|--------------------|-------|-------------------------------------------------------------------------------------|-----------------------|
| *Antrodia camphorata*             | Taiwan (M.Zang & C.H.Su) Sheng H.Wu, Ryvarden & T.T.Chang | 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, Fomitellanol, cryptoporic acids | Ethanol, Isopropanol | 1, 2, 5 | Inhibited NO production                                                              | Xu 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, 95% ethanol | 1, 2 | Inhibited NO production; suppressed iNOS and COX-2 expression                        | Choi et al., 2014a Lee|
| *Inonotus obliquus* (Ach. ex Pers.) Pilát | Japan                                      | Triterpenes, Triterpenes butyl esters    | Methanol, Methanol | 4     | Suppressed TPA-induced edema                                                         | Akihisa et al., 2007  |
| *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   |
| *Poria cocos* F.A.Wolf            | China                                        | Lanostane-Type, Triterpenes              | Methanol           | 4     | Suppressed TPA-induced edema                                                         | Cai & Cai, 2011       |
| Species                          | Origin    | Compound Type     | Solvent   | Assay                                      |
|---------------------------------|-----------|-------------------|-----------|--------------------------------------------|
| *Sarcodon scabrosus* (Fr.), P.  | Japan     | Cyathane diterpenoid | Methanol  | Suppressed TPA-induced inflammation        |
| Karst.                          |           |                   |           | Hirota et al., 2002                        |
|                                 | Japan     | Diterpenoid       | Methanol  | 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.
| 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 derivatives | 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 | 1 | 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 gargar* 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 |
| Country | Compound | n.m. | Assay(s) | Effect | Reference |
|---------|----------|------|----------|--------|-----------|
| 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)
| 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     | Zhanxuic acid C                                         | n.m                       | 2     | Decreased TNF-α, IL-6, IL-12                                                         | Lin et al., 2015  |
|                                  | Taiwan     | Zhanxuic 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  |
|                                   | Taiwan     | Ergosterol peroxide, trametenolic acid                  | 95% Ethanol                | 1, 2  | Inhibited NO production and reduced NF-kB activity                                  | Liu et al., 2014  |
| *Ganoderma lucidum* (Curtis) P. Karst | India      | Ergosta-7,22-diene-3β-yl pentadecanoate                | Petroleum ether, chloroform n-hexane | 1, 2  | Inhibited NO production and release of TNF-α                                        | Joseph et al., 2011 |
| *Grifola frondosa* (Dicks.) Gray | Taiwan     | Ergosterol peroxide, Hericirine (ergosterol)           | 95% Ethanol                | 1, 2  | Inhibited NO and TNF-α, iNOS,COX2 expression was inhibited                          | Wu et al., 2013   |
| *Hericium erinaceum* (Bull.) Persoon | 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 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 | Methanol | 2 | Inhibited NO production | Wu et al., 2013b |
| | Taiwan | Antrodan (glycoprotein) | 95% Ethanol | 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 | N6-(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 | **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                                                                 | References                  |
|---------------------------------------------------------------------------|-----------------|-------|--------------------------------------------------------------------------------------|-----------------------------|
| 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-\(\alpha\) and IL-1\(\beta\), 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-1\(\beta\), IL-6, TNF-\(\alpha\) release          | Shin et al., 2009           |
| Ethynylbenzenoid                                                           | Synthesised     | 2     | Down-regulated TNF-\(\alpha\) expression                                            | Buccini et al., 2014        |
| Ergosterol                                                                | Commercial      |       | Inhibited NO production and cytokine release                                         | Kuo et al., 2011            |
| Hispidin                                                                  | Commercial      | 2     | Suppressed NF-\(\kappa\)B activity, induced \(\kappa\)B degradation                 | Shao et al., 2015           |
| Hispolon                                                                  | Synthesised     | 1, 2, 3| Inhibited NO production, TNF-\(\alpha\) release; reduced edema                      | Chang et al., 2011a         |
|                                                                            | Commercial      | 1     | Inhibition of NO production and iNOS expression                                      | Yang et al 2014             |
| Inotilone and methylinotilone                                              | Synthesised     | 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.