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Review

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.

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; Ma, Chen, Dong, & Lu, 2013; Moro et al., 2012).

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) (Choi, Nguyen, et al., 2014; Moro et al., 2012; 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, Kuang, et al., 2013), rhizomes (Debnath, Park, Kim, Jo, & Lim, 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

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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, Ferreira, Dias, et al., 2013). 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), antitumour (Carocho & Ferreira, 2013; Ferreira, Vaz, Vasconcelos, & Martins, 2010; Moradali, Mostafavi, Ghods, & Hedjaroude, 2007), antimicrobial (Alves et al., 2012; Alves, Ferreira, Froufe, et al., 2013), immunomodulator (Borchers, Krishnamurthy, Keen, Meyers, & Gershwin, 2008), antiatherogenic (Mori, Kobayashi, Tomita, Inatomi, & Ikeda, 2008) hypoglycemic (Hu, Wang, Lien, Liaw, & Lee, 2006) and anti-inflammatory (Choi, Nguyen, et al., 2014; Han et al., 2013; Moro et al., 2012; Taofiq et al., 2015; Tung et al., 2013; Xu et al., 2013) 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 (Choi, Nguyen, et al., 2014; Fangkrathok, Junlatat, & Sripanidkulchai, 2013; Gunawardena et al., 2014; Jedinak, Dudhgaonkar, Wu, Simon, & Sliva, 2011; Lee et al., 2014; Moro et al., 2012; 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 (Castro et al., 2014; Hämäläinen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007). 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 ($OH^\bullet$). 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 tumour development, DNA damage and cell proliferation (Fangkrathok et al., 2013; Quang, Harinantenaina, et al., 2006). 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 et al., 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, 2013). 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 molecular patterns (PAMPs) necessary for activation of several signalling cascade (Fig. 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