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Modulation of neuroinflammatory pathways by medicinal mushrooms, with particular relevance to Alzheimer's disease

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ABSTRACT

Background: Alzheimer's disease (AD) is a significant cause of dementia demonstrated by severe and progressive cognitive impairment. While the deposition of amyloid beta (Aβ) plaques and the formation of neurofibrillary tangles (NFTs) are known to be the main pathological hallmarks of AD, accumulating evidence has demonstrated neuroinflammation as a driving force in the disease progression. Studies utilizing nonsteroidal anti-inflammatory drugs (NSAID) in AD patients have produced mixed results, in which safety reasons and adverse outcomes remain the major issues. However, targeting neuroinflammation in the management of AD is relevant, especially considering the use of natural products with potent anti-inflammatory activities and low toxicity being demonstrated to be beneficial in *in vitro* and *in vivo* studies.

Scope and approach: Medicinal mushrooms are gaining considerable interest in overall health maintenance and disease prevention due to their high nutritional content and diverse pharmacological properties. This review presents the anti-neuroinflammatory activities of bioactive components from medicinal mushrooms in various *in vitro* and *in vivo* models. The review focuses on the pathological effects on AD, with insights into other neurodegenerative diseases.

Key findings and conclusion: Extracts and compounds from medicinal mushrooms including *Hericium erinaceus*, *Antrodia camphorata*, *Ganoderma* spp., *Cordyceps* spp. and *Armillaria mellea* demonstrated anti-neuroinflammatory activities by suppressing the release of neuroinflammatory mediators via the involvement of toll-like receptor 4 (TLR4)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. Concerning the effectiveness, safety, and long history in traditional medicine, medicinal mushrooms could be explored as an alternative for AD therapy.

1. Neuroinflammation: a double-edged sword

Neuroinflammation is a defence mechanism responsible for protecting the CNS against infection, toxic metabolites, and injury (Lucas, Rothwell, & Gibson, 2006). It is helped by the presence and abundance of supporting glial cells such as microglia and astrocytes surrounding the neurons, participating in the inflammatory response (Kreutzberg, 1996). As the resident macrophage that accounts for approximately 10% of the CNS population, microglial cells mainly constitute the first line of defence with an innate capability to phagocytize foreign and toxic materials, release inflammatory mediators and cytokines, besides acting as antigen-presenting cells (van Rossum & Hanisch, 2004; Wyss-Coray & Mucke, 2002). The plasticity of microglial cells enables them to undergo structural changes, forming a specific phenotype depending on the signaling chemicals and regional conditions. In the absence of an external stimulus, microglial cells are in a "resting" state, with ramified morphology composed of long branching processes and a small cellular body. In the presence of a stimulus, activated microglial cells transform into the phagocytic and amoeboid-like structures to perform their immune-related functions (Fig. 1). These events, known as reactive gliosis, are accompanied by the release of inflammatory mediators including nitric oxide (NO) and prostaglandin E2 (PGE2), and

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pro-inflammatory cytokines such as interferon-gamma (IFN-γ), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumour necrosis factor-alpha (TNF-α) (van Rossum & Hanisch, 2004; Wyss-Coray & Mucke, 2002).

However, neuroinflammation is regarded as a double-edged sword as it may be beneficial and detrimental depending on the chronicity and severity of the process (Wyss-Coray & Mucke, 2002). In most cases, neuroinflammation is favourable for the activation of microglia, and it ceases once the threat has been eliminated and homeostasis restored. However, chronic and prolonged microglial activation may lead to overproduction of cytokines and neurotoxins, which may trigger the cascade of events culminating in progressive neuronal death, as observed in many neurodegenerative disorders including AD and Parkinson's disease (PD) (McGeer et al., 1988).

2. Neuroinflammation in Alzheimer's disease

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders which causes dementia, demonstrated by a progressive decline in cognitive and other intellectual functions. The most classical pathological hallmark of AD is characterized by deposition of amyloid plaques containing amyloid-β (Aβ) peptide, and formation of neurofibrillary tangles (NFTs) constituted by hyperphosphorylated tau protein, which further causes synaptic degeneration and neuronal death (Ittner & Götz, 2011). Although neuronal death primarily causes atrophy and reduction in brain volume, which manifests in cognitive impairment, there exists a close link between the neuron-glia system. Increasing evidence has clearly demonstrated microglia-mediated neuroinflammation as a major driver in AD progression (Heneka et al., 2015).

In the AD brain, deposits of Aβ and NFTs are potential sites of high inflammation. As illustrated in Fig. 2, reactive gliosis is beneficial in the early stage of the disease progression to aid in the clearance of the neurotoxic peptides and induction of the inflammatory signal to maintain homeostasis (Burda & Sofroniew, 2014). However, the adverse effects are seen after excessive and prolonged activation demonstrated by the spike in the level of pro-inflammatory mediators and ROS, which are potentially neurotoxic to the surrounding neurons. Numbers of studies have also suggested the vicious cycle theory in which inflammation could initiate AD by affecting the processing of amyloid precursor protein (APP) into Aβ peptides with the help of β- and γ-secretases (De Strooper & König, 2001; Sastre, Walter, & Gentleman, 2008). The levels of inflammatory substances above threshold value were reported to exacerbate the deposition of Aβ and NFTs and worsen disease progression (Rogers et al., 1996). Therefore, inflammation is closely related to AD, reinforcing the need to focus on targeting the inflammatory pathway for the disease management.

3. Involvement of TLR4/NF-κB pathways

Toll-like receptors (TLRs) are transmembrane proteins that act as pattern-recognition receptors (PRRs) to specific pathogen-associated

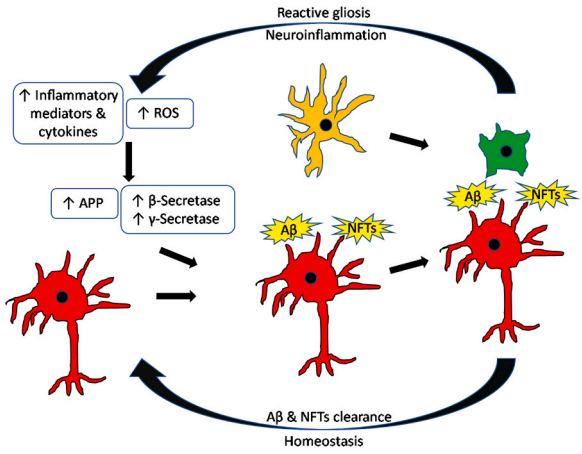

Fig. 2. Neuroinflammation as a double edged-sword in (Alzheimer's disease) AD: beneficial for the clearance of interfering protein aggregates to maintain neuronal survival, but detrimental if the inflammatory processes are prolonged and excessive. The neurons, resting microglia and activated microglia are in red, orange and green color respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs), which are responsible for initiating innate immune responses (Medzhitov, 2001). Theoretically, the binding of PRRs to the corresponding PAMPs/DAMPs will mediate the generation of inflammatory molecules essential for the advancement of effective immunity. First identified in *Drosophila*, the importance of TLRs as PRRs in innate immunity response was later found in microbial infection (Wright, 1999). There are currently more than ten identified mammalian homolog of TLRs, with each having distinct expression patterns and binding specifically to their PAMPs (reviewed in (Beutler, 2004)). Toll-like receptor 4 (TLR4), the first identified mammalian homolog of its family, is well-known to be expressed mostly in microglia, hence, is crucial for the mediation of neuroinflammation (Lehnardt et al., 2003). The activation of TLR4 is achieved by the binding of its classically known PAMPs, mainly bacterial lipopolysaccharides, and to some extent, certain viral proteins, endogenous proteins, and polysaccharide (Brubaker et al., 2015). Then, the bound TLR4 signals the activation cascades of various transcription factors, namely activator protein 1 (AP-1), signal transducer and activator of transcription 3 (STAT3), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).

NF-κB, one of the most crucial and versatile family of transcriptional factors, commands the expression of a vast array of genes associated with the immune and inflammatory responses (Li & Verma, 2002). The NF-κB family comprises five structurally-related proteins: NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB and c-Rel (May & Ghosh, 1997). In the absence of stimuli, NF-κB complexes (usually in the forms of homo- or

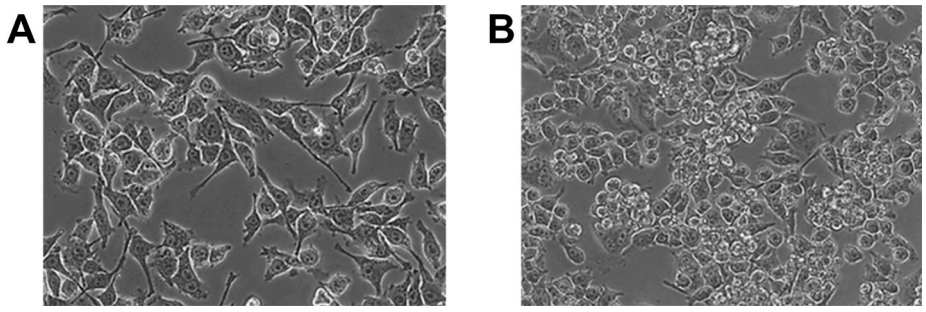

Fig. 1. Changes in morphology of the immortalized BV2 murine microglia from A) untreated to B) treated for 24 h with 1 μM lipopolysaccharides (LPS) from *Escherichia coli* O55:B5, a stimulus known to cause inflammatory response in microglial cells.

heterodimers of p60 and p65 subunits), are confined in the cytoplasm and attached to inhibitory proteins, including from the IκB family. To date, the IκB family consists of seven members: IκBα, IκBβ, IκBγ, IκBε, Bcl-3, IκBζ, and IκBNS in which IκBα is the best described and most crucial one (Hayden & Ghosh, 2008). Once the TLR ligands are stimulated, IκB proteins are rapidly phosphorylated, deactivated by ubiquitination, and later broken down by the proteasomes. This frees the NF-κB complex (mainly p65 and p50) to translocate into the nucleus to activate transcription and instantaneously provoke the release of pro-inflammatory mediators, including inducible nitric oxide synthase (iNOS) and NO (Davis et al., 2005), cyclooxygenase-2 (COX-2) and PGE2 (Minghetti, 2004; Oh et al., 2009) and cytokines like IFN-γ, IL-1β, IL-6, and TNF-α (Nakajima et al., 2006) from the glial cells (Fig. 3).

4. Current therapy of AD

In AD, the amyloid cascade hypothesis suggests the accelerated proteolytic cleavages of APP by β and γ secretase, which generates 40–42-residue Aβ. The minor residue, Aβ-42, is more amyloidogenic and tends to self-aggregate into fibrils and form deposits as ageing continues (Hardy & Higgins, 1992). Despite directly causing neuronal damage, the Aβ deposits, together with the NFTs, can also disrupt cholinergic transmission, particularly within the cholinergic neurons in the cerebral cortex and hippocampus. Deterioration of the cholinergic neurons may lead to the reduction of acetylcholine, an important neurotransmitter involved in cognitive processing (Coyle, Price, & Delong, 1983). Hence, the current treatment paradigm is focused on improving cholinergic neurotransmission mainly by the restoration of acetylcholine levels by inhibiting the activity of acetylcholine esterase (Francis et al., 1999).

Drugs designed to exert those actions, which include donepezil, rivastigmine, and galantamine, have shown efficacy in various animal and human models. Despite alleviating some AD symptoms, they do not halt the disease progression (Loveman et al., 2006; Rodda, Morgan, & Walker, 2009). Besides, there may be mild to severe side effects caused by these single-targeted drugs, reducing their application (Hansen et al., 2008; Takeda et al., 2006). The approach of targeting these extracellular processes may also not be substantial, as various intracellular events related to neuroinflammation are also disrupted throughout the progression of AD.

Hence, several studies have been made incorporating nonsteroidal anti-inflammatory drugs (NSAIDs) in AD patients which turned out to be promising, especially in the early stage of the disease progression. Although many attempts were reported to be negative, especially at the stage when clinical symptoms start to become evident (Imbimbo, Solfrizzi, & Panza, 2010; McGeer & McGeer, 2007), targeting neuroinflammation is still a relevant research interest.

The emergence of natural food products with multiple actions in the CNS has become promising. The fact that they are natural, which offers safety and tolerability with low risk of adverse effects in humans is also tempting. For instance, various pharmacological benefits of natural products, especially dietary polyphenols, have been illustrated, including curcumin, resveratrol, and epigallocatechin gallate (EGCG) that could be potentially explored as an AD therapeutic (Dhakal et al., 2019). Besides, flavonoids and polyphenols from dietary sources were demonstrated to be beneficial in ameliorating AD through suppression of neuroinflammatory pathways (Jaeger, Parylak, & Gage, 2018; Rahimifard et al., 2017).

5. Mushrooms as neuro-health promoters

Mushrooms contain a wide array of bioactive ingredients that encourage their application in human health maintenance and disease prevention (Cheung, 2010). Edible mushrooms, for example, *Lentinus edodes*, *Pleurotus ostreatus*, *Pleurotus pulmonarius*, *Schizophyllum commune*, *Flammunila velutipes*, and *Hericium erinaceus* are highly valued worldwide due to their nutritional content, ease of cultivation and exotic taste (Chang, 1999, 2006; Sánchez, 2010). On the other hand, renowned non-edible medicinal mushrooms such as *Antrodia camphorata*, *Ganoderma lucidum*, *Cordyceps militaris*., and *Lignosus rhinocerotis*, have been made available as extracts, decoctions, or supplements to facilitate the consumption of their bioactive components (Wasser, 2010). These culinary and medicinal mushrooms are valuable sources of bioactive compounds with multiple health benefits, including antioxidative, anti-inflammatory, immune-modulatory, anti-cancer, anti-asthmatic,

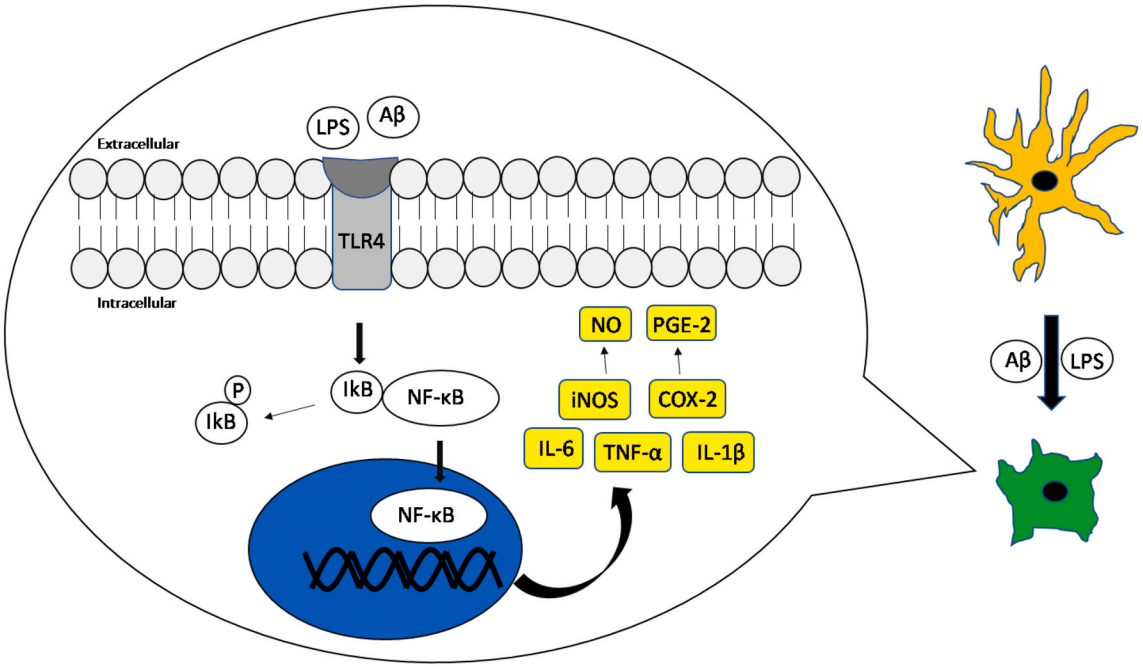

Fig. 3. Involvement of the toll-like receptor 4/nuclear factor kappa-light-chain-enhancer of activated B cells (TLR4/NF-κB) pathway in neuroinflammation. The resting microglia and activated microglia are in orange and green color respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

antibacterial and antiviral activities (reviewed in (Ma et al., 2018; Rathore, Prasad, & Sharma, 2017)). Multiple neuro health-promoting activities including improved synaptic plasticity, neuro-regenerative, neurite-outgrowth, anti-apoptotic, Aβ reduction, AChE and BACE1 inhibition have been documented in several mushroom species, most notably by *H. erinaceus*, *G. lucidum*, *C. militaris*, *A. camphorata*, *L. rhinocerotis* and *Armillaria mellea* (Phan, David, & Sabaratnam, 2017; Rahman, Abdullah, & Aminudin, 2016), which are crucially involved in the pathophysiology of AD. Besides, their anti-inflammatory activities were reported in various mammalian cells and tissues (Muszyńska, Grzywacz-Kisielewska, Kała, & Gdula-Argasińska, 2018; Taofiq, Martins, Barreiro, & Ferreira, 2016) with a recent focus on the nervous system. Increasing numbers of species have been shown to demonstrate anti-neuroinflammatory activities in the CNS, which has become a growing area for the therapeutic intervention of AD.

As discussed in previous sections, regarding the absolute importance of targeting neuroinflammation to tackle the basis of the disease progression, herein, we reviewed the neuroinflammatory activities of bioactive components from mushrooms in *in vitro* and *in vivo* studies with evidence of the mechanistic pathways involved. Comparisons were also made, if any, between the source of the bioactive compounds, either from the fruiting bodies, mycelia, or others, as well as the methods of extraction and isolation. The focus was on AD subjects, but with insights on other neurodegenerative diseases. To the best of our knowledge, this is the first review describing this aspect of the subject.

Table 1
Anti-neuroinflammatory activities of active compounds or extracts of mushrooms in AD models.

Species	Active form	Activity	Model	Ref.
Antrodia camphorata	Methanol extract of fruiting body	↓ iNOS mRNA and protein ↓ TNF-α mRNA ↓ STAT, ERK, and JNK phosphorylation ↓ NF-κB activation ↓ iNOS and COX-2 protein	LPS and IFN-γ-treated EOC13.31 microglia Aβ-treated EOC13.31 microglia	Liu et al. (2007)
	Antroquinonol from mycelia	↓ astrocyte activation in hippocampus	APP transgenic (J20) mouse model	Chang et al., (2015)
Ganoderma lucidum	Ethanol extract of fruiting body	↓ NO and PGE2 ↓ iNOS, COX-2, IL-1β and TNF-α mRNA and protein ↓ NF-κB translocation and activation ↓ IκB degradation ↓ TLR4 and MyD88 protein	LPS-treated BV2 microglia	Yoon et al. (2013)
	Polysaccharides from conidial powder	↓ IL-1β, IL-6, and iNOS ↑ TGFβ ↓ microglial migration, morphological alterations, and phagocytosis.	LPS-treated BV2 microglia and $A\beta_{42}$-treated primary mouse microglia	Cai, Li, and Pei (2017)
Cordyceps militaris	Cordycepin	↓ NO, PGE2 ↓ iNOS, COX-2, IL-1β and TNF-α mRNA and protein ↓ NF-κB translocation and activation ↓ IκB degradation ↓ Akt, p38, ERK-1/2, and JNK phosphorylation	LPS-treated BV2 microglia	Jeong et al. (2010)
	Cordycepin	↓ TNF-α and IL-1β ↓ iNOS and COX-2 mRNA ↓ NF-κB translocation and activation ↓ IκB degradation	LPS-treated BV2 microglia	Peng et al., (2015)
Hericium erinaceus	Ethanol extract of fruiting bodies	↓ NO	LPS-treated BV2 microglia	Kushairi et al., (2019)
	Mycelia and isolated erinacine A	↓ TNF-α and IL-1β mRNA in hippocampus ↑ NGF and NeuN mRNA in hippocampus ↓ escape latency in Morris water maze ↑ exploratory time and frequency in the novel arm in Y-maze test	Ageing mice (15-months old) fed with high-fat and high-sucrose diet	Tsai et al., (2019)
	Erinacine C	↓ NO, IL-6, TNF-α, and iNOS ↓ NF-κB expression ↓ IκBα phosphorylation ↓ Keap1 ↑ Nrf2 and HO-1	LPS-treated BV2 microglia	Wang et al., (2019)
	Erinacine A-enriched mycelia and ethanol extract	↓ cerebral Aβ plaque ↑ insulin-degrading enzyme (IDE) level in cerebral cortex ↓ plaque-activated microglia and astrocytes in cerebral cortex and hippocampus ↑ NGF to proNGF ratio	APPswe/PS1dE9 transgenic Alzheimer's mouse model	Tsai-Teng et al. (2016)
	Erinacine A and erinacine S	↓ Aβ plaque accumulation and production ↓ Iba-1 and GFAP level ↑ IDE level ↑ DCX-positive newly born granular neurons and BrdU-positive proliferating type 2 progenitors	APPswe/PS1dE9 transgenic Alzheimer's mouse model	Tzeng et al. (2018)
Agaricus bisporus	Vitamin D-rich mushroom powder	↑ IL-10 immunoreactive cells ↓ GFAP-stained astrocytes in the temporal cortex and hippocampus ↑ total neuron count	APPswe/PS1dE9 transgenic Alzheimer's mouse model	Bennett et al. (2013)
Armillaria mellea	Fraction 2 of ethyl acetate extract (daidzein, genistein)	↓ NO, TNF-α, IL-6, and IL-1β ↓ NF-κB p65, IκB-α, and JNKs phosphorylation	LPS-treated BV2 microglia	Geng et al. (2017)
Lignosus rhinocerotis	Linoleic acid	↓ NO ↓ iNOS and COX-2 mRNA	LPS-treated BV2 microglia	Nallathamby et al. (2016)
Cyathus africanus	Allocyathin B2 (polyoxygenated cyathane diterpenoid)	↓ NO	LPS-treated BV2 microglia	Wei et al. (2018)

6. Anti-neuroinflammatory activities of mushrooms in AD

Table 1 summarizes the anti-neuroinflammatory activities of bioactive components of mushrooms in AD. Most of the *in vitro* and *in vivo* studies to assess their beneficial effects were based in the LPS and Aβ model of neuroinflammation. LPS, as mentioned before, is a major PAMP to TLR4 and therefore represents an appropriate agent in models of neurodegeneration (Nava Catorce & Gevorkian, 2016). The fact that LPS induces cognitive deficits accompanied by the release of inflammatory molecules via TLR4/NF-κB as proposed in AD has made it the first-choice antagonist in neurodegeneration studies.

Meanwhile, although not a typical PAMPs, Aβ as explained above (in sections 1 and 2), has a special connection with microglia, and their interaction may cause neuroinflammatory cascades that might involve similar pathways as LPS does. For example, several members of TLRs were able to recognize Aβ (Frank et al., 2009; Okun et al., 2009), and the expression of TLR4 particularly was found to be upregulated in AD patients (Walter et al., 2007). Besides, the NF-κB activity in degenerating brain and Aβ-affected cells was elevated (Boissière et al., 1997; Carrero et al., 2012) while a study in TLR4-deficient microglia demonstrated the failure of Aβ to induce NF-κB activation (Reed-Geaghan et al., 2009). These data indicate that Aβ is actively involved in TLR4/NF-κB-mediated neuroinflammation in AD pathology. Altogether, this supports the rationale for abundant conceptual studies in developing new treatments based on the suppression of LPS and Aβ-mediated neuroinflammation via the TLR4/NF-κB pathway.

6.1. *Antrodia camphorata*

Antrodia camphorata, a mushroom unique to Taiwan, grows as a parasite on the inner cavity of the endemic tree *Cinnamomum kanehirae* Hayata (Lauraceae) (Chang and Chou, 1995). Regarded as "a gift from heaven" for the Taiwanese, this mushroom has been consumed as a traditional medicine for a wide range of health-related conditions (Wu & Ryvarden, 1997). Various pharmacological benefits of *A. camphorata* include its anti-oxidant, anti-inflammatory, anti-microbial, anti-diabetic, hepatoprotective, and neuroprotective activities (Geethangili & Tzeng, 2011; Yue et al., 2012). This mushroom is a source of a variety of bioactive compounds that include terpenoids, benzenoids, lignans, benzoquinone derivatives, polysaccharides, sterols, nucleotides, and fatty acids (Geethangili & Tzeng, 2011; Yue et al., 2012).

Antrodia camphorata was the first mushroom described to possess anti-neuroinflammatory activities (Liu et al., 2007). Cold water, methanol, and hot water extracts were prepared from wild fruiting bodies, and artificially cultivated fruiting bodies (solid-state culture) and mycelia (liquid-state fermentation). The methanol extract of the wild fruiting bodies (MW) was shown to reduce both mRNA and protein expression of iNOS in LPS/IFN γ-activated EOC13.31 mouse microglial cells by dose-dependent manner, apparently better than the cold water and hot water extracts. MW also caused a dose-dependent decrease in TNF-α gene expression. MW demonstrated the best activity followed by ethanol extract from solid-state (MS) and then liquid-state culture (ML). ML showed mild activity, only visible at the highest concentration. This demonstrated that fruiting bodies of *A. camphorata*, either wild collected or artificially cultivated, provided beneficial anti-neuroinflammatory agents. In the same study, MW of *A. camphorata* successfully inhibited the phosphorylation of STAT, ERK, JNK, and the activation of NF-κB in the LPS/IFN γ-activated EOC13.31 microglial cells. The effectiveness of MW was further shown in β-amyloid-activated microglia in which iNOS and COX-2 protein expression were remarkably reduced (Liu et al., 2007).

This was in accordance with a previous study that demonstrated better neuroprotective activities by fruiting bodies of the mushroom compared to the mycelia (Wang et al., 2012). The fruiting body possessed stronger anti-oxidative and anti-inflammatory abilities, reflected by a reduction in TBARS, MDA, and ROS in Aβ40-treated PC-12 cells and Aβ40-infused brain. The fruiting bodies also showed a better reduction in the Aβ40 accumulation and *p*-tau protein expression accompanied by an improvement in working memory ability. The chemical analysis revealed that the fruiting body contained higher contents of triterpenoids and total phenol as opposed to the mycelium (Wang et al., 2012). In other studies, the bioactivities of the fruiting bodies of *A. camphorata* were also attributed to the presence and abundance of terpenoids (Huang et al., 2012; Huang et al., 2014). Additionally, these compounds were shown to protect immortalized PC12 neurons and primary rat neonatal cortical neurons from amyloid-β-induced toxicity (Chang et al., 2012; Chen et al., 2006). However, large-scale production of terpenoids from *A. camphorata* is laborious due to the slow growth rate and specific host preference of the fruiting bodies. Hence, there is a growing interest in large-scale production of the mycelium by artificial cultivation (Joshi, 2017). This is indeed beneficial as the mycelium is the part where antroquinonols (ubiquinone derivatives) with increasingly proven pharmacological activities are predominantly found in *A. camphorata* (Lee et al., 2015; Tsai et al., 2011; Zhang et al., 2017). A wide range of potential health benefits by antroquinolols was recently documented, especially their anti-cancer properties in breast, lung, pancreas, colon, brain, liver, and ovary (Angamuthu et al., 2019). Interestingly, antroquinonol consumption for two months was demonstrated to reduce the degree of astrogliosis accompanied by improvement in the learning and memory of transgenic AD mice. The compound was also able to cross the blood-brain barrier with no detectable adverse effects (Chang et al., 2015). In the case of *A. camphorata*, we conclude that terpenoids from the fruiting bodies, and more recently, antroquinolols from the mycelia could be potentially explored for AD therapeutics.

6.2. *Ganoderma lucidum*

Ganoderma lucidum or known as "Lingzhi" in China and "Reishi" in Japan, is one of the most famous medicinal mushrooms with a long history of application since ancient times, especially in Asia (Lin, 2005; Sliva, 2003). The pharmacological activities of *G. lucidum* in disease prevention/treatment as well as improvement of overall wellness and longevity, are linked with a broad class of bioactive compounds found in the spores, fruiting body, and mycelium, including polysaccharides, triterpenes, sterols, amino acids, and nucleotides (Boh et al., 2007; Sanodiya et al., 2009).

The ethanol extract of the fruiting bodies (EGL) attenuated LPS-stimulated PGE2, NO, TNF-α and IL-1β production along with transcriptional suppression of COX-2, iNOS, TNF-α and IL-1β in BV2 microglia in a dose-dependent manner (Yoon et al., 2013). EGL also prevented IκB-α degradation, nuclear translocation of the NF-κB p65 subunit and NF-κB transcription in LPS-stimulated BV2 microglia. Also, protein expression of TLR4 and MyD88 were markedly inhibited by EGL, which suggests the involvement of TLR4 and MyD88 and the downstream NF-κB pathway in the anti-neuroinflammatory activities (Yoon et al., 2013). Recently, polysaccharides extracted from *G. lucidum* conidial powder (GLP) stimulated anti-neuroinflammation in LPS-treated BV2 microglia and Aβ42-treated primary mouse microglia demonstrated by reduction of IL-1β, IL-6, and iNOS while the expression of an anti-inflammatory cytokine, transforming growth factor beta (TGFB) was up-regulated. Further, GLP suppressed inflammatory-related microglial migration, morphological alterations, and phagocytosis probabilities, which were found to be associated with monocyte chemoattractant protein 1 (MCP-1) and complement component 1q (C1q) expression (Cai et al., 2017).

6.3. *Cordyceps militaris*

Cordyceps militaris, also known as caterpillar fungus (Ascomycota), is a mythical medicinal mushroom, famous for its bioactive compound cordycepin (3′-deoxyadenosine) (Cunningham et al., 1950). The

adenosine analogue offers various pharmacological benefits (Tuli et al., 2013) with a recent focus on the CNS. The anti-neuroinflammatory effects of cordycepin were demonstrated in LPS-activated BV2 microglia (Jeong et al., 2010; Peng et al., 2015). In one of the studies, increasing concentrations of cordycepin suppressed the over-production of NO, PGE2, and inflammatory cytokines as well as down-regulating the mRNA expression of iNOS and COX-2 without exerting toxic effects. Cordycepin was also found to prevent IκB-α degradation and NF-κB translocation. In addition, cordycepin notably suppressed the phosphorylation of ERK-1/2, JNK, p38 kinase, and Akt survival pathways (Jeong et al., 2010).

Similar results were seen in LPS-treated BV2 microglia in which cordycepin managed to turn around an increase in inflammatory cytokines and NF-κB activation (Peng et al., 2015). On the other hand, the LPS-conditioned BV2 medium significantly caused impairment in the growth and development of primary hippocampal neurons. However, treatment with cordycepin was able to reverse the adverse effects of LPS demonstrated by enhancement of the hippocampal neuronal cell viability, growth cone morphology, neurite extension, and development of the dendritic spine (Peng et al., 2015).

6.4. *Hericium erinaceus*

Hericium erinaceus, also known as lion's mane or monkey's head mushroom, is the best characterized culinary and medicinal mushroom in the field of neuro health promotion. The bioactive components from the mycelia and fruiting bodies, including unique terpenoids (hericenones and erinacines), phenolic acids, and polysaccharides, are primarily attributed to the beneficial effects on the nervous system (Friedman, 2015; Thongbai et al., 2015). In the past decade, increasing numbers of anti-neuroinflammatory activities of this fungus were reported. The mycelium and isolated erinacine A (cyathane diterpenoid) were found to improve spatial learning abilities in 15-months old-aged mice fed with high-fat and high-sucrose diet, demonstrated by a decrease in escape latency in the Morris water maze and increased exploratory time and frequency in the novel arm in the Y-maze test. At the molecular level, both the mycelia powder and erinacine A decreased TNF-α and IL-1β mRNA expression in the hippocampus, suggesting their anti-neuroinflammatory activities (Tsai et al., 2019). Further, one month of oral treatment of the mycelia and its erinacine A-enriched ethanol extract was found to reduce the activation of astrocytes and microglia in the cerebral cortex and hippocampus of APPswe/PS1dE9 transgenic AD mice. The anti-neuroinflammatory activities together with the reduction of Aβ deposits and the spike in the level of insulin-degrading enzyme (IDE) in the cerebral cortex, as well as improvement of NGF expression and hippocampal neurogenesis, were likely associated with the improvement of nesting test behaviour in the AD mouse model (Tsai-Teng et al., 2016).

A further study of isolated erinacine A and erinacine S (sesterterpene) from the mycelia was made in terms of their capability to prevent AD-related pathology, also in APPswe/PS1dE9 mice. A 30-day administration of erinacine A and S successfully diminished cerebral Aβ plaque and glial cell activation and enhanced the level of IDE and hippocampal neurogenesis. However, only erinacine A was found to reduce the level of insoluble Aβ and C-terminal fragment of APP, besides improving AD-related behaviour in burrowing, nesting, and Morris water maze tests (Tzeng et al., 2018). In another study, erinacine C isolated from the mycelium also showed promising activities in LPS-activated BV2 microglia by suppressing the overproduction of NO, IL-6, TNF-α, and iNOS. The anti-neuroinflammatory mechanism was further confirmed as erinacine C displayed marked inhibition of NF-κB expression and IκBα phosphorylation. In addition to its nuclear transcription factor erythroid 2-related factor (Nrf2)/heme oxygenase-1 (HO-1) antioxidative activities, erinacine C with its strong NF-κB-related anti-neuroinflammatory properties could be an excellent neuroprotectant (Wang et al., 2019).

Apart from the mycelium, the ethanol extract of the fruiting bodies contains hericenones (Phan et al., 2014), a group of neurotrophic meroterpenoids, demonstrated in a preliminary study to reduce the NO production in BV2 microglia without causing cytotoxicity (Kushairi et al., 2019). Altogether, it can be concluded that the mycelia of *H. erinaceus* is an attractive source of bioactive compounds including erinacine A, C, and probably S to target neuroinflammation in AD. However, the accumulating reports of neurotrophic and neuroprotective activities utilizing components from the fruiting bodies, especially hericenones (Kushairi et al., 2019; Mori et al., 2008; Zhang et al., 2015), could also be considered for future applications.

7. Anti-neuroinflammatory activities of mushrooms in other models of neurodegenerative diseases

Looking at a broader perspective, the theory of neuroinflammation causing large scale death to the neurons in AD is somewhat applicable to other CNS diseases. As microglia and other supporting cells are residing almost anywhere in the brain region, their roles in mediating neuroinflammation can also be depicted in other diseases like PD (Hirsch & Hunot, 2009), epilepsy (van Vliet et al., 2018), intracerebral haemorrhage (Chen et al., 2014) and psychiatric disorders including anxiety and depression (Furtado & Katzman, 2015a; 2015b). As summarized in Table 2, we review how anti-neuroinflammatory activities of mushrooms can help in other neurodegenerative diseases. Also, in Fig. 4, we compiled together a collection of unique compounds from mushrooms that demonstrated anti-neuroinflammatory activities in AD and other models of neurodegenerative diseases.

7.1. *Parkinson's disease*

A number of studies have indicated microglia-mediated neuroinflammation, particularly in the substantia nigra as one of the contributing factors towards Parkinson's disease (PD) pathophysiology, making it a good target for therapeutics (Hirsch & Hunot, 2009; Joshi & Singh, 2018). Adding to the long list of pharmacological activities of *G. lucidum*, the standardized methanol extract of fruiting bodies containing 0.6% polysaccharide and 0.35% ergosterol demonstrated remarkable neuroinflammatory suppression in primary rat microglia activated by LPS and 1-methyl-4-phenylpyridinium (MPP+)-treated MES 23.5 cell membranes (neuron-glia co-culture model) (Zhang et al., 2011). MPP+ is a metabolic product of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), an agent widely used to cause symptoms of PD in animal models by destroying dopaminergic neurons in the substantia nigra. In the experiments, the standardized extract of *G. lucidum* managed to notably reduce NO, TNF-α, IL-1β, and superoxide release accompanied by downregulation of TNF-α and IL-1β mRNA expression (Zhang et al., 2011).

7.2. *Brain ischemia*

Reduction of glucose and oxygen transport to the brain during ischemia leads to a cascade of events such as oxidative stress, inflammation, and dysfunction of the blood-brain barrier that finally results in neuronal death. Accumulating evidence has demonstrated the crucial roles played by oxidative stress and inflammation in the pathophysiology of ischemia (Huang, Upadhyay, & Tamargo, 2006; Iadecola & Alexander, 2001). Studies utilizing extracts from different mushroom species have shown promising results for the treatment of ischemia. The ethyl acetate crude extract of *A. camphorata* (EtOAc-AC) and its active constituent ergostatrien-7,9 (11),22-trien-3β-ol (EK100) were found to reduce brain infarction accompanied by improvement in the behaviour of acute ischemic stroke mouse model (Wang et al., 2019). Both EtOAc-AC and EK-100 reduced the expression levels of NF-κB p65 and caspase 3 in the cerebral cortex, indicating anti-neuroinflammatory activities while promoting neurogenesis and neuroprotection, by

Table 2
Anti-neuroinflammatory activities of mushrooms' active compounds or extracts in other models of neurodegenerative diseases.

Species	Active form	Activity	Model	Ref.
Antrodia camphorata	Ergostatrien-7,9 (11),22-trien-3β-ol from ethyl acetate extract of fruiting body	↓ p65NF-κB expression in the cortex	Acute ischemic stroke mouse model	Wang et al., (2019)
Ganoderma lucidum	Spore powder	↓ NF-κB expression	Pentylenetetrazol-induced epilepsy in adult Wistar rats	Zhao et al., (2008)
	Standardized methanol extract of fruiting bodies containing polysaccharide and ergosterol	↓ NO, TNF-α, IL-1β, and superoxide ↓ TNF-α and IL-1β mRNA	Primary rat microglia activated by LPS and MPP + -treated MES 23.5 cell membranes	Zhang et al., (2011)
	Hot water extract of fruiting body	↓ IL-8 and TNF-α in the hippocampus	Focal cerebral ischemia/reperfusion Wistar rats	Zhang et al., (2014)
Cordyceps militaris	Cordycepin	↓ NLRP3 inflammasome components expression ↓ IL-1β and IL-18	Mouse model of intracerebral haemorrhage	Cheng et al. (2017)
	Cordycepin	↓ NF-κBp65, TNF-α, and IL-6	Mice model of chronic unpredictable mild stress	Tianzhu, Shihai, and Juan (2014)
	Cordycepin-enriched WIB-801C	↓ migration of cultured microglia/ macrophages ↓ infiltration of ED-1 and MPO positive inflammatory cells into ischemic lesions	Rat model of cerebral ischemic stroke (middle cerebral artery occlusion)	Hwang et al. (2016)
	Dried, hot-water extract & cordycepin	↓ GFAP immunoreactive astrocytes and Iba-1 immunoreactive microglia	Gerbils model of transient forebrain ischemia	In et al., (2008)
Hericium erinaceus	Ethanol extract of fruiting bodies	↓ hippocampal COX-2-expressing astrocyte and microglia	Mouse model of status epilepticus induced by pilocarpine	Jang et al. (2019)
	Standardized extract containing hericenones and amyloban	↓ serum TNF-α ↑ serum IL-10	LPS-induced inflammation mouse model	Yao et al. (2015)
Cordyceps sinensis	Ethanol extract	↓ IL-1β, TNF-α, iNOS, ICAM-1, and COX-2	Rat model of focal cerebral ischemia/ reperfusion	Kong et al. (2015)

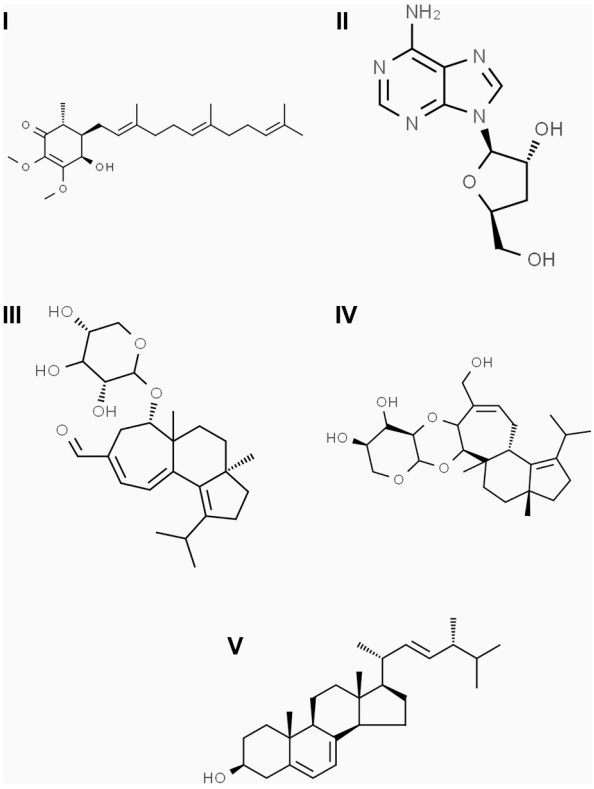

Fig. 4. Unique anti-neuroinflammatory compounds from mushrooms: I) Antroquinonol ($C_{24}H_{38}O_4$), II) Cordycepin ($C_{10}H_{13}N_5O_3$), III) Erinacine A ($C_{25}H_{36}O_6$), IV) Erinacine C ($C_{25}H_{38}O_6$) and V) Ergosterol ($C_{28}H_{44}O$).

activation of PI3k/Akt and inhibition of GSK-3 pathways (Wang et al., 2019). The hot water extract of *G. lucidum* fruiting bodies was shown to reduce IL-8 and TNF-α expression in the hippocampus of focal cerebral ischemia/reperfusion Wistar rats. Pre-treatment with the extract also reduced ischemia-induced neuronal loss in the hippocampus (Zhang et al., 2014).

Cordycepin-enriched *C. militaris* extract, WIB801C, conferred anti-ischemic effects through its anti-inflammatory activities in rats with middle cerebral artery occlusion (MCAO). The extract was found to decrease monocyte chemoattractant protein-1 (MCP-1)-induced migration of cultured microglia as well as reducing the infiltration of ED-1 and myeloperoxidase (MPO)-positive inflammatory cells into the ischemic region. Post-ischemic treatment of WIB801C extract also decreased cerebral ischemic infarction, oedema, white matter, and blood-brain barrier injury (Hwang et al., 2016). In another study, cordycepin and the hot water extract of *C. militaris* were able to reduce hydroxynonenal (HNE) protein expression, which indicated decreased lipid peroxidation in the ischemic CA1 region in gerbils. Both treatments also significantly decreased glial activation demonstrated by the reduction of GFAP and Iba-1 immunoreactivity in the ischemic area (In et al., 2008). In addition, cordycepin was demonstrated to exert a neuroprotective effect in intracerebral haemorrhage (ICH) mice model by downregulating NLRP3 inflammasome components expression as well as reducing IL-1β and IL-18 level (Cheng et al., 2017). The ethanol extract from another cordyceps species, *C. sinensis* (EEOS), also demonstrated neuroprotective action via its anti-inflammatory activity against ischemia. In a study involving a rat model of focal cerebral ischemia/reperfusion, EEOS was able to inhibit the production of IL-1β, TNF-α, iNOS, ICAM-1, and COX-2 proteins (Kong et al., 2015).

7.3. Epilepsy

Epilepsy, characterized by recurrent seizures, is also associated with inflammation in the brain (van Vliet et al., 2018), and natural products were found to be useful (Ekstein & Schachter, 2010). In the rat model of pentylenetetrazol (PTZ)-induced epilepsy, the administration of the *G. lucidum* spore powder was found to reduce neuronal apoptosis in the hippocampus and cerebral cortex partly by suppression of NF-κB expression, and ultimately increased the seizure latency (Zhao et al., 2008). A recent study demonstrated the neuroprotective effects of *H. erinaceus* ethanol extract in pilocarpine-induced status epilepticus in the mouse hippocampus. The ethanol extract promoted neuronal survival by suppressing hippocampal COX-2-expressing astrocytes and microglia (Jang et al., 2019).

7.4. Depression

Evidence suggests that over-activation of the inflammatory response is one of the critical factors in psychiatric symptoms, including depression (Brites & Fernandes, 2015; Furtado & Katzman, 2015a). Cordycepin isolated from *C. militaris* was found to impose beneficial effects on chronic unpredictable mild stress (CUMS) induced behavioural deficits in mice. The treatment with cordycepin led to a decrease of NF-κB p65, TNF-α, IL-6, and 5-HT_{2A}R levels in mice hippocampus. In contrast, an increase of serotonin, dopamine, and BDNF levels were observed to reduce depressive-like behaviour (Tianzhu et al., 2014). In LPS-treated mice, amycenone, a commercialized standardized extract from *H. erinaceus* fruiting bodies containing 0.5% hericenones and 6% amyloban, managed to improve symptoms of depression. At the molecular level, amycenone was found to decrease the serum TNF-α levels, but the levels of anti-inflammatory cytokine IL-10 were increased (Yao et al., 2015).

8. Possible involvement of neurohormesis mechanisms

Recently, an emerging approach of targeting neurohormesis through the manipulation of cellular-stress pathways has been demonstrated to be useful against a wide range of neurological disorders including dementia (Calabrese and Calabrese et al., 2017, Calabrese and Giordano et al., 2017; Calabrese et al., 2016), autism (Calabrese et al., 2016) and schizophrenia . Brain cells are basically capable of adapting and surviving persistent redox perturbation and the mitochondrial damage owing to the integrated survival response system tightly regulated by the redox-dependent genes known as vitagenes. The vitagene network in turn produces corresponding proteins comprised of heat shock proteins (HSPs), sirtuins, thioredoxin, lipoxin A4 (LXA4), as well as Nrf2-dependent enzymes: heme oxygenase-1 (HO-1) and γ-glutamyl cysteine ligase which sense the redox imbalance, and functionally enhance cell survival under physiopathological conditions (Calabrese et al., 2011; Calabrese et al., 2010). LXA4 is an endogenous lipoxygenase-derived eicosanoid mediator produced from arachidonic acid that functions as a “signal stop” in the inflammatory reaction by suppressing the production of pro-inflammatory mediators including the ROS and RNS (Machado et al., 2006; Yang et al., 2014). Hence, there exists a significant relationship between the redox-modulated vitagene defence system and neuroinflammatory pathways in the modulation of a healthy cognitive state.

Recently, medicinal mushrooms including *Coriolus versicolor* and *H. erinaceus* have been shown to enhance the vitagene defence system including the cellular stress response and LXA4 expression in the brain regions relevant to AD pathophysiology (Salinaro et al., 2018). The biomass of *C. versicolor* containing mycelium and primordia (young fruiting body) was supplemented to adult male rats for 30 days and the results showed significant improvement of LXA4 expression in the brain, particularly in the cerebral cortex and hippocampus (Trovato et al., 2016). In addition, the protein expression of HO-1, heat shock protein 70 (Hsp70) and thioredoxin in the brains were also upregulated. The increase in HO-1 and Hsp70 expression was significant in the cerebral cortex, substantia nigra and hippocampus, most notably in the hippocampus (Trovato et al., 2016). In another study, 3-months supplementation of *H. erinaceus* biomass in the adult male rats resulted in the upregulated LXA4 expressions in the brains, with the highest levels in the cerebral cortex, followed by hippocampus, substantia nigra, striatum, and cerebellum. Similarly, the levels of HO-1, Hsp70 and thioredoxin in the brains were also increased (Trovato et al., 2016). Interestingly, there were no associated changes reported in the expression levels of IκB-α, NF-κB, p65, iNOS and COX-2 suggesting that the neuroprotective and anti-neuroinflammatory mechanisms depend hugely on the neurohormetic pathway. LXA4 signalling and stress-responsive vitagene proteins activation could potentially be explored as a new area in AD therapeutics.

9. Conclusion and future trends

Neuroinflammation plays a major role in Alzheimer’s Disease, as well as Parkinson’s Disease, brain ischemia, epilepsy and depression. Here we have comprehensively reviewed studies on the medicinal mushrooms in relation to their abilities to reduce destructive neuroinflammatory activities. The long history of medicinal mushrooms being used safely as beneficial foods and in traditional medicine, suggests that their bioactive components could be useful in future developments in prevention and/or treatment of inflammation associated with these diseases and in the expanded use of such mushrooms in the wider population. Future perspectives should be directed to understand and enhance their bio-availabilities, especially across the BBB, to perform their actions in the CNS. Emphasis should also be put on the pharmacokinetics and pharmacodynamics to effectively translate the application in humans.

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