IJNLS
INTERNATIONAL JOURNAL OF NATURE AND LIFE SCIENCES
Review article

International Journal of Nature and Life Sciences (IJNLS)
https://www.journalnatureandlifesci.com
e-ISSN: 2602-2397
Vol. 2(1), June 2018, pp. 1-9

Effects of *Ganoderma lucidum* in some neurological diseases

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Received: 08 December 2017, Revised: 14 December 2017, Published Online: 30 June 2018

Abstract

Ganoderma lucidum has been widely used in Asian countries for hundreds of years to promote health and longevity. The pharmacological functions of which had been reported, are the activation of innate immune responses, suppression of tumour and modulation of cell proliferations. Effective fractions of *Ganoderma lucidum* polysaccharides had already been reported to regulate the immune system. In recent years, studies on the neuroprotective effects of *G. lucidum* have begun to intensify. *G. lucidum* is believed to have a neuro-protective effect and this notion is supported by work carried out by scientists. Spesifically wherein a mixture of triterpenoid compounds in *G. lucidum* promoted neuronal survival and reduced fatigue. In addition, the potential use of this fungus for the treatment of neurological diseases has also been examined. It was shown that long-term consumption of *G. lucidum* can decrease the progression of Alzheimer's disease. This observed neuroprotective effect is achieved by promotion of neuritogenesis and reduction of senescence of the neurons. To summarize the studies on the neuroprotective effects of the intended *G. lucidum*, we want to shed some light on those who wish to study in this regard.

Key words: Alzheimer, Epilepsy, *Ganoderma lucidum*, Parkinson.

1. Introduction

Mushrooms have an established history of use in traditional oriental medicine. *G. lucidum* is a mushroom from the Polyporaceae family of Basidiomycota (Ji et al., 2007). Worldwide, the species name *G. lucidum* has been applied to Chinese Lingzhi which is well

known as a Basidiomycete and has been referred to as the “Mushroom of Immortality” (Li et al., 2013). Higher Basidiomycetes mushrooms contain biologically active compounds in fruit bodies, cultured mycelium and cultured broth. Medicinal mushrooms possess medicinal properties such as anti-tumor, immunomodulating, antioxidant, cardiovascular, anti-hypercholesterolemic, anti-viral, anti-bacterial, anti-parasitic, anti-fungal, detoxification, hepatoprotective, and anti-diabetic effects (Sharma et al., 2017). In modern clinical trials, the preparations of *G. lucidum* show therapeutic efficacy in treating cancer, hyperlipidemia, neurasthenia, insomnia, and so forth. In addition, its use has become increasingly widespread to prevent obesity; reduce cholesterol; for the maintenance of gut health; reduction of hypertension; control of diabetes and the stimulation of probiotics, amongst others (Jin et al., 2012; Paterson, 2006; Sanodiya et al., 2009). A variety of bioactive compounds, such as polysaccharides, triterpenoids and proteins, can be extracted from the fruiting bodies, cultured mycelia and spores of *G. lucidum* (Mizushina et al., 1999). It has been shown that *G. lucidum* polysaccharides (GLP) have antitumor and immunomodulatory activities. It is well known that *G. lucidum* has rich content of polysaccharides and triterpenoids as secondary metabolites and it is possible that both the polysaccharide and triterpenoid profiles could be used to differentiate between various *Ganoderma* species providing clarity with respect to classification. Sun et al recently established a high performance liquid chromatography (HPLC) based methodology to characterise species within the genus *Ganoderma* using polysaccharide fingerprint profiling (Sun et al., 2014). The effect of polysaccharide extract isolated from GLP on rat cortical neuronal cultures exposed to hypoxia/reoxygenation (H/R) was studied in vitro by firstime in Zhao in 2004. He has reported that adding GLP (1, 10, 100 microg/ml) has increased neuron viability. Besides the same quantity of GLP (1, 10, 100 microg/ml) significantly reduced malondialdehyde content and reactive oxygen species production and increased the manganese superoxide dismutase (Mn-SOD) activity; also, the translocation of nuclear factor-kappa B induced by H/R was blocked. These findings suggest that GLP might be useful in treating H/R-induced oxidative stress and Mn-SOD might play a critical role in the neuroprotective effect of GLP against H/R injury (Zhao et al., 2004).

In the following years, the number of *G. lucidum* in neurological studies increased with intense interest. This review will look at some neurological diseases (Alzheimer, Parkinson, Spinal cord injury and epilepsia) in which *G. lucidum* can provide beneficial results.

A. Traumatic spinal cord ınjury

Zhang et al. has studied on detecting proteins which is responsible from *G. lucidum* spores (GLS) effects injured spinal motor neurons in rats. Experiments were evaluated in three groups: control, unthreated and GLS-threated for 14 days. Six different proteins were detected from three groups. Collapsin response mediator protein 2 (CRMP-2), F-actin capping protein beta subunit (FCP-β), isocitrate dehydrogenase [NAD] subunit beta (IDH-β), ATPase, glutamate oxaloacetate transaminase-1 (GOT1) and M2 pyruvate kinase (M2-PK). CRMP-2, IDH-β, ATPase and GOT1 levels were higher in GLS threated group. Although FCP-βand M2-PK expressions were lower. As a coclusion GLS may promote the survival and axon regeneration of injured spinal motor neurons in rats (Zhang et al., 2006)

In an another reserch done by Gokce et al was to investigate if GLP can protect the spinal cord after experimental spinal cord injury. After the administration of GLP, decreases were observed in tissue caspase-3 activity, tumour necrosis factor-alpha levels, myeloperoxidase activity, malondialdehyde levels, and nitric oxide levels. Furthermore, he has reported that GLP treatment showed improved results in histopathological scores, ultrastructural scores, and functional tests (Gokce et al., 2015).

B. Alzheimer's disease

Promoting neurogenesis is a promising strategy for the treatment of cognition impairment associated with Alzheimer's disease (AD). They have been found that oral administration of the polysaccharides and water extract from *G. lucidum* promoted neural progenitor cell (NPC) proliferation to enhance neurogenesis and alleviated cognitive deficits in transgenic AD mice. GLP also promoted self-renewal of NPC in cell culture. Their findings have been suggested that GLP could serve as a regenerative therapeutic agent for the treatment of cognitive decline associated with neurodegenerative diseases (Lai et al., 2008).

Recent studies have shown the loss of synaptic density proteins in each individual neuron during the progression of AD. It was recently reported that beta-amyloid (Abeta) could cause synaptic dysfunction and contribute to AD pathology. Lai et al. have been reported that aqueous extract of *G. lucidum* significantly attenuated Abeta-induced synaptotoxicity by preserving the synaptic density protein, synaptophysin. In addition, *G. lucidum* aqueous extract antagonized Abeta-triggered DEVD cleavage activities in a dose-dependent manner. Further studies elucidated that phosphorylation of c-Jun N-terminal kinase, c-Jun, and p38

MAP kinase was attenuated by *G. lucidum* in Abeta-stressed neurons. The results prove a hypothesis that anti-aging *G. lucidum* can prevent harmful effects of the exterminating toxin Abeta in AD (Huang et al., 2017).

Qin and friends has explored the efficacy of *G. lucidum* preparation (Ling Zhi) in treating APP/PS-1 transgenic mouse models of Alzheimer's disease (AD). Methods APP/PS-1 transgenic mice of 4 months were randomly divided into model group, GLtreatment groups, including high [2250 mg/(kg·d)] and middle [750 mg/(kg·d)] dose groups, i.e.LZ-H and LZ-M groups and the positive control group (treated with donepezil hydrochloride [2 mg/(kg·d)]). In addition, C57BL/6J wild mice were selected as normal group. The animals were administered for 4 months. The senile plaques and neurofibrillar tangles in the cerebrum and cerebellum were dissolved or disappeared in LZ-H and LZ-M groups. Decrease of amyloid angiopathy was found in LZ-H and LZ-M groups. The immature neurons appeared more in hippocampus and dentate nucleus of LZ-H and LZ-M groups than those in AD model and donepezil hydrochloride groups. The LZ-H and LZ-M groups had more new neuron stem cells grown up incerebellum. Electromicroscopic examination showed the hippocampal neurons in LZ-H and LZ-M group were integrated, the nuclear membrane was intact and the mitochondria in the cytoplasm, endoplasmic reticulum, golgi bodies, microtubules and synapses were also complete. The microglial cell showed no abnormality. No toxicity appeared in the pathological specimens of mice treated with *G. lucidum* preparation. In conclusion the *G. lucidum* preparation can dissolve and decline or dismiss the senile plaques and neurofibrillar tangles in the brain of AD mice and also reduce the amyloid angiopathy (Qin et al., 2017).

C. Parkinson's disease

Parkinson's disease (PD) is a common and debilitating degenerative disease resulting from massive degenerative loss of dopamine neurons, particularly in the substantia nigra. The most classic therapy for PD is levodopa administration, but the efficacy of levodopa treatment declines as the disease progresses. The neuroprotective strategies to rescue nigral dopamine neurons from progressive death are currently being explored, and among them, the Chinese herbs and herbal extracts have shown potential clinical benefit in attenuating the progression of PD in human beings (Chen et al., 2007).

Abundant evidence has suggested that neuroinflammation participates in the pathogenesis of Parkinson's disease (PD). The emerging evidence has supported that microglia may play

key roles in the progressive neurodegeneration in PD and might be a promising therapeutic target.

Meanwhile, *G. lucidum* extracts significantly prevented the production of microglia-derived proinflammatory and cytotoxic factors, including nitric oxide, tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), in a dose-dependent manner and down-regulated the TNF-α and IL-1β expressions on mRNA level. In addition, *G. lucidum* extracts antagonized the reduction of [(3)H]DA uptake induced by MPP(+) and microglial activation. In conclusion, these results have been suggested that *G. lucidum* may be a promising agent for the treatment of PD through anti-inflammation (Ding et al., 2010).

In an other research, primary dopaminergic cell cultures prepared from embryonic mouse mesencephala were used to investigate the neuroprotective effects and the potential mechanisms of GLP on the degeneration of dopaminergic neurons induced by the neurotoxins methyl-4-phenylpyridine (MPP(+)) and rotenone (Ding, 2017). Results revealed that GLP can protect dopamine neurons against MPP(+) and rotenone at the concentrations of 100, 50 and 25 μg/ml in primary mesencephalic cultures in a dose-dependent manner. Interestingly, either with or without neurotoxin treatment, GLP treatment elevated the survival of neurons, and increased the length of neurites of dopaminergic neurons. The study has indicated that GLP possesses neuroprotective properties against MPP(+) and rotenone neurotoxicity through suppressing oxidative stress in primary mesencephalic dopaminergic cell culture owning to its antioxidant activities (Guo et al., 2016).

In addition, accumulating data have suggested that *G. lucidum* extracts may promote neuronal survival and neurite growth, and facilitate functional recovery of brain injures by invoking distinct mechanisms that are related to their neuroprotective roles as the antioxidants, dopamine transporter inhibitor, monoamine oxidase inhibitor, free radical scavengers, chelators of harmful metal ions, modulating cell survival genes and signaling, anti-apoptosis activity, and even improving brain blood circulation. New pharmaceutical strategies against PD will hopefully be discovered by understanding the various active entities and valuable combinations that contribute to the biological effects of *G. lucidum* and herbal extracts (Chen et al., 2007).

D. Epilepsy

Epilepsy is a disease which is usually seen among childhood. This neurological disorder can cause behavioral or cognitive impairment (Tuchman et al., 2009). GLS are known as anti-

epileptic agents. However, there are slightly researchs on the anti-epileptic effects of its chemical constituents ganoderic acids (GAs). To better understant the mechanism of GLS activity there should be different researchs. This study by Wang et al. used in vitro model of epileptiform discharge hippocampal neurons allowed to investigate the anti-epileptic effects and mechanism of GLS activity. Neurotrophin-4's expression was substantially increased however the expression of N-Cadherin was decreased in the GLS treated group compared with the model group. Among the results of the research GLS may protect hippocampal neurons by promoting neurotrophin-4 expression and inhibiting N-Cadherin expression (Wang et al., 2013).

In an another research, GLP effects were examined by the changes of intracellular calcium and CaMK II α expression in an epileptic neuron model. Primary hippocampal neurons were divided into 5 groups: Control group, two model groups and two GLP groups. Control group, neurons were cultured with Neurobasal medium, for 3 hours; Model group I: neurons were incubated with Mg(2+) free medium for 3 hours; Model group II: neurons were incubated with Mg(2+) free medium for 3 hours then cultured with the normal medium for a further 3 hours; GLP group I: neurons were incubated with Mg(2+) free medium containing GLP (0.375 mg/ml) for 3 hours; GLP group II: neurons were incubated with Mg(2+) free medium for 3 hours then cultured with a normal culture medium containing GLP for a further 3 hours. As a result, The CaMK II α expression in the model groups was less than in the control groups. Although GLP groups was higher. Ca(2+) fluorescence intensity in GLP group I was significantly lower than that in model group I after 30 seconds, while in GLP group II, it was reduced significantly compared to model group II after 5 minutes (Wang et al., 2014).

E. Neuronal differentiation

There are very few studies of *G. lucidum* effect on neuronal differentiation. In the research by Cheung et al. an in vitro model was used to indicate the bioactive compounds in *G. lucidum*. Among the investigation *G. lucidum* extracts were affected PC12 cells neuronal differentiation and prevented these cells from apoptosis caused by nerve growth factor. This research present the first evidence of the presence of neuroactive compounds that mediate the neuronal differentiation and neuroprotection of the PC12 cells, but also reveal the potential signaling molecules involved in its action (Cheung et al. 2000). In an different study, 13 herbal medicines neuroprotective effect was examined. Neuroprotective activities were

studied using staurosporine-induced apoptosis of the cultured neurons. Extract of *G. lucidum* inhibited staurosporine-induced apoptosis by 30 - 50% in a dose-dependent manner. In conclusion of this study this herbal medicine might potentially offer a novel preemptive neuroprotective approach in neurodegenerative diseases and might be developed for use in persons at risk. Inhibition of N-methyl-N-nitrosourea-induced retinal photoreceptors in vivo apoptosis was examined in an another study. 30-50 day old female Sprague-Dawley rats were used to detect the dose-response effect of GSL by electroretinogram (ERG) analysis. Rats were divided in to 5 groups randomly. One group was a control group. Other four groups received different daily GSL doses (0.5, 1, 2 and 4 g/kg, respectively). Retina tissue samples were obtained sequentially 0 h before and 1, 3, 7 and 10 d after MNU injection. RT-PCR and immunofluorescence assays were used to detect Expressions of Bax, Bcl-xl and Caspase-3. Next stepi photoreceptor cell apoptosis was confirmed by terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-digoxigenin nick-end labeling (TUNEL) signals. In conclusion of the study GSL had a dose-response effect on retina ERG and reversed retinal photoreceptor damage induced by MNU. Therfore, GSL may regulate the expressions of Bax, Bcl-xl and Caspases-3, inhibiting MNU-induced rat photoreceptor cell apoptosis and protecting retinal function (Gao et al., 2010).

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