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Mini Review

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The Bioactive Compounds in Medicinal Mushrooms have Potential Protective Effects against Neurodegenerative Diseases

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ABSTRACT

The Comprehensive and Alternative Medicine (CAM) to treat Neurodegenerative Diseases (NDs) has attracted attention from healthcare professionals and scientific researchers recently. Although in its early research stage, a good number of studies have been performed to investigate the potential preventive or even therapeutic effects of some medicinal mushrooms on NDs. We reviewed recent scientific publications reporting the extraction and identification of the bioactive compounds in medicinal mushrooms commonly used in Asian countries for their potential protective effects against NDs. Five medicinal mushrooms - *Hericium erinaceus, Termitomyces albuminosus, Ganoderma lucidum, Dictyophora indusiata, Mycoleptodonoides aitchisonii*- have been covered in this review. *In vitro*, *in vivo*, and clinical studies have been conducted to confirm the potential protective effects of these compounds against neurodegenerative diseases. Because of the limited research, no clear mechanisms of the preventive actions can be proposed. More animal and human studies are needed in the future to confirm the anti-neurodegenerative effects and understand the mechanism of the protective action of these bioactive compounds.

KEYWORDS: Neurodegenerative Diseases; Mushrooms; Neurite; Bioactive Compounds; Anti-oxidative effects.

ABBREVIATIONS: ND: Neurodegenerative Diseases; AD: Alzheimer's disease; PD: Parkinson's Disease; HD: Huntington's Disease; NGF: Nerve Growth Factor; BDNF: Brainderived neurotrophic factor; ER: Endoplasmic Reticulum.

INTRODUCTION

Neurodegenerative Diseases (NDs) are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. This causes problems with movement (called ataxias), or mental functioning (called dementias), most commonly seen diseases including Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD). Currently, there is no effective treatment that can cure NDs, the treatments can only delay the progression of the diseases for a short term. Therefore, the prevention of the NDs occurrence also attracts researchers' interests. One hypothesis of the pathogenesis of these diseases is proposed as increased free radical generation, and the consequent elevated oxidative stress in neural system.[1] For other types of chronic diseases such as cancer, epidemiological, animal, and *in vitro* studies show that the consumption of plant source food can potentially reduce the risk of neurodegenerative diseases attributing to the high anti-oxidative capacity of bioactive compounds in these foods. Mushrooms have been recognized as a healthy functional food because of the high protein and low fat content as well as their phytochemical components like vitamin D and polyphenols.[2-4] Mushroom-derived phytochemical components have anti-oxidative

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effects and have been confirmed to have therapeutic effects on some chronic diseases like cancer. Researchers deduce that the bioactive compounds in medicinal mushrooms can potentially reduce the risk of NDs *via* similar action principles.

The potential anti-neurodegenerative actions of medicinal mushrooms have been intensively investigated in numerous animal and cell line studies. In addition to the well-studied polysaccharides such as β-glucan, many small molecules are under investigation for the potential health beneficial effects. The mechanistic studies show that bioactive compounds in various medicinal mushrooms can inhibit activities of neurotransmitter enzyme, stimulate neurite growth, or play a role on anti-inflammatory and anti-oxidative activities.[5] In this review, we summarize the small bioactive molecules in various medicinal mushrooms that potentially carry the function of reducing oxidative stress in neural systems.

BIOACTIVE COMPOUNDS IN MEDICINAL MUSHROOMS POTENTIALLY AGAINST NEURODEGENERATIVE DISEASES

Hericium Eerinaceus

Hericium erinaceus has the common names as Lion's mane mushrooms or Pom Pom mushrooms, which is also a culinary mushroom in Asian countries. A clinical trial of daily consumption of 2.88 g *H. erinaceus* fruiting body dry powder for 16 wks has been performed in 30 Japanese men and women at age 50-80 years old who were diagnosed with mild cognitive impairment. The treatment can significantly (p<0.001) improve the cognitive function scale score (mean=27) of the mushroom-treated patients compared to the controls (mean=24) with no adverse effect detected.[6] Similar clinical trials have been performed in senior patients (average age is 75 for treatment group and 77.2 for controls) diagnosed with Parkinson's disease, degenerative orthopedic disease, cerebrovascular disease, etc. Oral administration of 5 g/day *H. erinaceus* dry powder for 6 months improved 6 out of 7 dementia patients' perceptual capacities.[7]

Hericenones (A-H) and Erinacines (A-K & P-Q), originating from fruiting bodies and mycelia respectively, are identified as the bioactive compounds that induce Nerve Growth Factor (NGF) synthesis both *in vitro* and *in vivo*.[5,7] Dilinoleoylphosphatidylethanolamine (DLPE) from fruiting bodies of *H. erinaceum* reduces oxidative stress in Endoplasmic Reticulum (ER) of Neuro-2a cells. 100 ng/ml DLPE significantly (p<0.005) reduced cell viability of Neuro-2a cells treated with tunicamycin, demonstrating the protective effects against oxidative stress.[8]

Termitomyces Albuminosus

Termitomyces albuminosus is consumed as edible mushrooms in many Asian countries such as China, Japan, Singapore as well as South American countries like Chile. This mushroom is also called Termite mushrooms or "Ji Zong" mushrooms in Chinese. Cerebrosides named termitomycesphins A, B, C, D, G, and H have been extracted and identified from dried fruiting bodies of *T.albuminosus*. The treatment of 10 μg/ml termitomycesphins A-D for 6 d and 1 μM G and H for 48 hrs increase rat pheochromocytoma PC12 cell neurite outgrowth by 20% and 20-50%, respectively.[9-10] Five fatty acid amides termitomycamide A, B, C, D, and E have been isolated from the same mushrooms. The treatment of 0.1 μg/ml termitomycamide B and E can significantly (p<0.01) reduced ER stress-induced Neuro-2a cell death by 20%.[11] The animal and human studies of this mushroom against neurodegenerative diseases are lacking.

Ganoderma Lucidum

Ganoderma lucidum is a widely used medicinal mushroom in Asian countries with the common name "Ling Zhi" in Chinese. It has been traditionally used to treat many chronic diseases such as cancer, diabetes, hypotension, insomnia, etc. There are numerous bioactive compounds that have been found in *G. lucidum*, including triterpinoids, nucleotides, sterols, steroids, fatty acids, etc. Many *in vitro* and *in vivo* studies demonstrate the neuroprotective effects of the bioactive compounds, however, the clinical trial to examine the neuroprotection of *G. lucidum* is lacking. The mechanistic studies show that the bioactive compounds can regulate aging-related gene to elongate yeast lifespan, and increase neurotrophin such as Nerve Growth Factor (NGF) and Brainderived neurotrophic factor (BDNF) to protect the neuronal cells death induced by serum deprivation.[12-14]

Dictyophora Indusiata

Dictyophora indusiata is an edible as well as medicinal mushroom in Asian countries. This mushroom has the common names as Veiled lady mushrooms or Bamboo mushrooms. Although it has a long history of being consumed in Asian countries, the investigation of the bioactive compounds associated with neurodegenerative diseases is very limited. Until now, dictyophorine A and B have been isolated from the mushroom and can significantly improve the amount of Nerve Growth Factor (NGF) in astroglial cells.[15] A more recent study identified dictyoquinazol A, B, and C in *D. indusiata*, and found that 5 μM dictyoquinazol A, B, and C treatment can reduce excitotoxin-induced cortical cell death. The protective effect is in a dose-dependent manner with ~20% for 0.5 μM and >60% for 5 μM.[16]

Mycoleptodonoides Aitchisonii

Mycoleptodonoides aitchisonii is an edible mushroom that is called "Bunaharitake" in Japanese. This mushroom is a rare type that has been consumed, which may be the reason that it has not been well investigated for the potential preventive effect against human diseases. Some bioactive compounds have been isolated and identified in this mushroom (Table 1). The treatment of 0.1 μg/ml 3-(hydroxymethyl)-4-methylfuran-2(5H)-one and (3R,4S,1'R)-3-(1'-hydroxy-ethyl)-4-methyldihydrofuran-2(3H)-one for 24 hrs significantly (p<0.01) reduced tunimycin-induced Neuro-2a cell death, indicating the protective

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effect against Endoplasmic Reticulum (ER) stress-induced cell death.[17] The treatment of 0.6 μM 5-hydroxy-4-(1-hydroxyethyl)-3-methylfuran-2(5H)-one and 5-phenylpentane-1,3,4-triol for 24 hrs has the same protective effect to the aforementioned bioactive compounds on ER stressed Neuro-2a cells.[18] The investigation on this mushroom is currently performed only *in vitro*.

The bioactive small molecules from the aforementioned medicinal mushrooms are summarized in Table 1.

FUTURE RESEARCH

Neurodegenerative disease is difficult to be cured by using the current available therapies. The prevention or delay this disease progress becomes an important therapy. The investigations of isolating and identifying the effective bioactive compounds in medicinal mushrooms that potentially prevent the neurodegenerative disease occurrence provide promising scientific data to demonstrate the potential of medicinal mushrooms as a prevention or treatment to the disease. The studies of the bioactive compounds in these mushrooms are still in early investigation stage. In addition to the aforementioned bioactive compounds in the medicinal mushrooms, various anti-oxidants have been reported in different mushrooms for their potential therapeutic effects on neurodegenerative diseases. For example, mushroom-derived ergothioneine has been confirmed to have anti-oxidative effects *in vitro* and *in vivo*.[19,20] One recent animal study showed oral administration of ergothioneine improved memory and learning abilities of Alzheimer's disease (AD) model mice.[21] Until now, most studies have been only performed in cell lines or animal models. Medicinal mushrooms are traditionally consumed in Asian countries. Very limited data come from human studies. Meanwhile, the investigations of certain bioactive compound are not well established. For many potential bioactive compounds, only one or two publications reported the data from very limited experiments.

Mushroom	Compound	Protection	References
Hericium erinaceum	Hericenones (A-H)	Induce NGF synthesis	5,7
	Erinacines (A-K & P-Q)		
	Dilinoleoyl-phosphatidylethanolamine (DLPE)	Reduce oxidative stress in ER	8
Termitomyces albuminosus	Termitomycesphins A, B, C, D,	Increase neuron cell growth	9
	Termitomycesphins G and H	Promote neurite growth	10
	Termitomycamide B and E	Reduce oxidative stress in ER	11
Ganoderma lucidum	Ganodermaside C and D	Regulate aging-related gene UTH1 in yeast and prolong the lifespan	12
	Ganodermaside A and B	Regulate aging-related gene UTH1 in yeast and prolong the lifespan	13
	Ganolucidic acid A	Have BDNF-like neurotrophic activities	14
	Ganoderic acid S1	Have BDNF-like neurotrophic activities	14
	Ganodermic acid TQ	Have BDNF-like neurotrophic activities	14
	Methyl ganoderic acid A and B	Have BDNF- and NGF-like neurotrophic activities	14
	Ganodermatriol	Have BDNF-like neurotrophic activities	14
	7-oxo-ganoderic acid Z	Have BDNF-like neurotrophic activities	14
	4,4,14-trimethyl-5-chol-7,9(11)-dien-3--oxo-24-oic aci	Have BDNF-like neurotrophic activities	14
Dictyophora indusiata	Dictyophorine A	Promote NGF synthesis	15
	Dictyophorine B	Increase NGF secretion level	15
	Dictyoquinazol A	Protect cortical neurons from excito-toxicity	16
	Dictyoquinazol B	Protect cortical neurons from excito-toxicity	16
	Dictyoquinazol C	Protect cortical neurons from excito-toxicity	16
Mycoleptodonoides aitchi-sonii	3-(hydroxymethyl)-4-methylfuran-2-(5H)-one	Protect Neuro-2a cells from ER stress	17
	(3R,4S,1'R)-3-(1'-hydroxy-ethyl)-4-methyldihydrofuran-2(3H)-one	Protect Neuro-2a cells from ER stress	17
	5-hydroxy-4-(1-hydroxyethyl)-3-meth-ylfuran-2(5H)-one	Protect Neuro-2a cells from ER stress	18
	5-phenylpentane-1,3,4-triol	Protect Neuro-2a cells from ER stress	18

Table 1: Bioactive compound in medicinal mushrooms that potentially have anti-neurogenerative effects.

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It is worth to notice that mushrooms have been traditionally used as medicinal foods in some countries for the therapeutic effects. Meanwhile, the scientific research confirmed multiple potential therapeutic bioactive compounds in mushrooms, which indicates the whole food consumption is an effective approach for the health improvement purpose. However, more investigations on the bioavailability, efficacy, and interactions of bioactive compounds of the whole food are needed to confirm the concept.

Based on the current literature review, both *in vitro* and *in vivo* studies are needed for further investigation on the anti-neurodegenerative effects of the bioactive compounds; further mechanistic studies are needed to provide evidence for these compounds to be potential therapies against neurodegenerative diseases.

CONFLICTS OF INTEREST

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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