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Artikel Review

Moringa oleifera as the potential herb medicine for neurodegenerative diseases: a narrative review

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ABSTRACT

Neurodegenerative diseases, such as Alzheimer's and Parkinson's, significantly burden the global older adult population. These diseases are characterized by the degeneration of nerve cells and subsequent damage, leading to the gradual loss of neurological function and subsequently affecting the quality of life of older adult people. This study explores the potential role of Moringa oleifera (MO) on neurological diseases. MO, a plant rich in bioactive compounds such as flavonoids, polyphenols, saponins, and tannins, has been proven to possess potent antioxidant effects. Oxidative stress is a primary contributor to the pathogenesis of neurodegenerative diseases, and MO can protect nerve cell damage by enhancing antioxidant activity. In the context of Parkinson's disease, MO has demonstrated the ability to reduce cataleptic symptoms and protect dopaminergic neurons, which are crucial in preventing a decline in dopamine production in the brain. In Alzheimer's disease, MO can improve memory function, reduce oxidative stress, and inhibit the activity of Acetylcholinesterase (AChE) enzymes involved in neurotransmitter dysfunction. While further research is needed to gain a deeper understanding of MO's mechanisms and more specific therapeutic potential, the existing evidence suggests that its constituents and effects hold significant promise as a natural solution for combating the effects of neurodegenerative diseases. As the number of individuals affected by these diseases continues to rise worldwide, further investigation into MO as a neuroprotective agent could pave the way for developing more effective therapies for these conditions.

Keywords: *anti-oxidant, medicinal plants, Moringa oleifera, neurodegenerative disease, neuroprotective*

INTRODUCTION

Neurodegenerative diseases affect both the central nervous system and the peripheral nervous system. These diseases experience a gradual increase with age. Neurodegenerative diseases are characterized by the degeneration or death of nerve cells over time, resulting in the loss of neuron function (1). According to the Global Burden of Disease, the estimated number of people suffering from dementia globally is projected to increase from approximately 57.4 million cases in 2019 to around 152.8 million cases in 2050 (2). Other neurodegenerative diseases, such as Parkinson's and Alzheimer's, also have significant prevalence worldwide. Additionally, Alzheimer's is the leading cause of dementia in the elderly population, affecting about 70% of the total global

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dementia cases. The prevalence of Alzheimer's disease is particularly high in populations aged over 75 years, where almost all are at risk of developing this condition. According to estimates from the World Health Organization (WHO), more than 55 million people suffer from Alzheimer's worldwide. Meanwhile, Parkinson's disease typically occurs in adults aged over 66 years and tends to occur more frequently in men than women. WHO reports that over 10 million people worldwide have been diagnosed with Parkinson's disease (1). Based on the 2019 Global Burden of Disease, it is recorded that in the Asian region, the prevalence of neurological diseases in the same year reached 227 million cases, with a total of 64.4 million disability-adjusted life years in the Southeast Asian region (3). The number of individuals experiencing neurodegenerative conditions such as dementia in Indonesia reached approximately 1.2 million people in 2015. It is estimated that this figure will increase to around 2.8 million people by the year 2050 (4).

So far, therapy for neurodegenerative diseases has been purely supportive, aiming to slow down disease progression and alleviate symptoms, but it is unable to provide a comprehensive cure (5). Although the causes are not fully understood, several neurological components have been identified as contributors to neuronal pathology. For example, increased protein aggregation, glial activation or inflammation, mitochondrial dysfunction, neurotransmitter imbalance, autophagy, or oxidative stress, all may play a role in triggering these diseases (6). Neurodegenerative diseases have a multifactorial basis, and one of the main contributing factors is increased oxidative stress. This oxidative stress arises due to an imbalance between the production and accumulation of free radicals such as reactive oxygen species (ROS) and antioxidants in the body, particularly in the brain area. This factor plays a crucial role in the development of neurodegenerative diseases (7). Oxidative stress can be mitigated through the administration of antioxidants. Natural substances containing compounds such as flavonoids, polyphenols, saponins, steroids, and tannins can act as antioxidant agents. One example of a natural substance rich in antioxidants is Moringa oleifera (MO), or moringa, due to its high content of flavonoids like quercetin. MO contains a variety of bioactive compounds, such as vitamins, carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins, and saponins. MO contains bioactive compounds like flavonoids and phenols, which have the potential as antioxidant and anti-inflammatory agents. Based on this background, this review article aims to elucidate MO as a neuroprotective agent through antioxidant mechanisms in addressing several neurodegenerative diseases in in vivo testing (8).

METHOD

Literature review or article reviews were conducted utilizing databases such as Google Scholar, GARUDA, PubMed, and Mendeley, encompassing publications within the last 10 years. The purpose of using this method is to present, expand understanding, and enhance knowledge by summarizing published content and providing factual information or new analysis from relevant literature reviews. A total of 27 articles were identified,

consisting of 22 indexed international journals, 3 non-indexed international journals, and 2 accredited national journals (Figure 1). Keywords used in the journal publication search were Moringa Oleifera, neurodegenerative, in vivo, Pharmacological potential, Memory, Dementia, Parkinson's, Alzheimer's, and Oxidative Stress.

Here are the inclusion and exclusion criteria:

a. Inclusion Criteria

1) The independent variable of the research is MO extract. The dependent variable is neurodegenerative diseases.
2) Published articles are in journals indexed in Sinta or Scopus or have an ISSN (International Standard Serial Number).
3) Research articles use experimental methods.
4) Research articles from 2010 to 2023.

b. Exclusion Criteria

1) Research in the form of theses or dissertations.
2) Articles that are not accessible in full text.
1) Articles published before 2010.

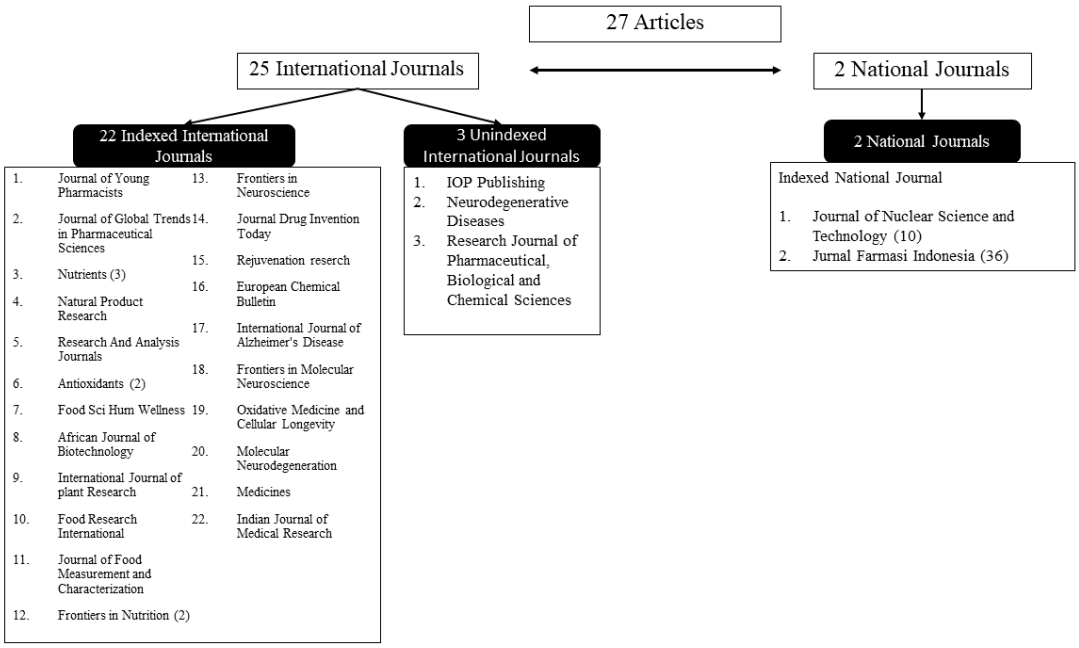

Figure 1. Chart of Journals Used in the Research Methodology

DISCUSSION

1. Moringa Oleifera

Moringa oleifera, or MO, is a plant commonly known as the drumstick tree or moringa. This plant originates from the Western Himalayas, India, Africa, and the Arabian Peninsula. MO is extensively cultivated in tropical and subtropical regions, including Indonesia, where it is known as "kelor." Additionally, this plant is grown in countries such as Central and South America, Sri Lanka, India, Mexico, Malaysia, and the Philippines (9,10). MO can grow up to 10-15 meters in height with

a diameter of 20-40 cm and has a taproot. Its leaves are egg-shaped, measuring 1-3 cm in length and 4 mm to 1 cm in width, with smooth edges and rounded bases. The flower buds are whitish-yellow and emit a distinct aroma. MO has been used for thousands of years as traditional medicine in Africa and has been proven to have numerous benefits. All parts of this plant are utilized for food, industrial, and medicinal purposes. Research also indicates that all parts of the plant, such as leaves, seeds, flowers, and roots, possess various significant pharmacological activities. Therefore, MO is considered a herbal plant with great potential as a source of natural medicine (11). Moringa oleifera (MO) plant is reported to have various beneficial pharmacological activities such as antioxidant, neuroprotective, anti-inflammatory, and anti-apoptotic properties. MO contains tannins, sterols, terpenoids, flavonoids, saponins, and anthraquinones that can help enhance antioxidant enzyme activity in the brain, mitochondrial function, and neurogenesis (9). Several of these bioactive compounds have also been reported to have potential as anticancer, anti-diabetic, antimicrobial, hypoglycemic, hepatoprotective, and lipid-lowering agents (12). Several studies mention that MO contains more vitamin C than oranges, 10 times the vitamin A of carrots, 9 times the protein of yogurt, 15 times the potassium of bananas, 17 times the calcium of milk, and 25 times the iron of spinach (11).

The study by Nair et al. demonstrates that Moringa oleifera (MO) water extract has the potential to prevent oxidative damage in the brains of 18-month-old rats by reducing lipid peroxidation and lipofuscin pigments. Additionally, the MO water extract enhances the activity of antioxidant enzymes in the brains of 18-month-old rats. In the group aged 6 months after administration of the MO water extract, there was a significant increase in the activity of the superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) enzymes, as well as an increase in the expression of the sod-1, sod2, and CAT genes. The group aged 12 months experienced a significant increase in the activity of the SOD, CAT, and GPx enzymes, as well as an increase in the expression of the sod-2 and CAT genes. In the group aged 18 months, there was a significant increase in the activity of the antioxidant enzymes CAT and GPx, as well as an increase in the expression of the sod-1, sod-2, and CAT genes, accompanied by a significant decrease in lipid peroxidation (13).

Here is the taxonomic classification of the MO plant (14):

Kingdom : Plantae
Class : *Eudicotyledoneae*
Subclass : *Magnoliidae*
Clado : *Malvidae*
Ordo : Brassocales
Famili : Moringaceae
Genus : Moringa
Species : *Moringa oleifera L.*

Table 1. Components of Bioactive Compounds in Moringa Oleifera (10,15–19)

Compounds	Rate	Pharmacological Activities
Flavonoid		Antidiabetic, **antioxidant**, anticancer, and antibiotic
Quercetin (%)	35-43,75	
Kaempferol (%)	35	
Isorhamnetin (%)	24	
Apigenin (%)	6	
Miristin (mg)	0.207	
Vitamin		**Antioxidant**
Vitamin B1 (mg)	2.02	
Vitamin B2 (mg)	21.3	
Vitamin B3 (mg)	7.6	
Vitamin C (mg)	15.8	
Vitamin E (mg)	10.8	
Alkaloids (%)	22.93	Antihypertensive, anticancer and antibacterial
Fenol (%)	4.20	**Antioxidant, anti-inflammatory**, and anticancer
Saponin (%)	35.75	Anticancer
Tanin (%)	0.33	Anti-cancer, **anti-inflammatory**, anti-hepatotoxic, and **antioxidant**
Asam Amino		**Antioxidant**
Arginine (%)	1.78	
Histidine (%)	0.716	
Triptofan (%)	0.486	
Fenilalanin (%)	1.64	
Treonin (%)	1.375	
Leusin (%)	1.96	
Isoleusin (%)	1.177	
Valin (%)	1.413	
Mineral		Antidepressant, antihypertensive
Kalsium (%)	3.64	
Potassium (%)	0.30	
Magnesium (%)	0.50	
Fosfor (%)	1.50	
Sodium (%)	0.164	
Sulfur (%)	0.63	
Iron mg/kg	31.03	

2. Bioavailability of Moringa oleifera

Bioavailability (BA) refers to the amount of compounds digested, absorbed, and metabolized in a process that can reach systemic circulation. Studies on BA play a crucial role in investigating the potential benefits of herbal plants as alternative therapies. Recent studies on free phenolic compounds (such as gallic acid, caffeic acid, morin, kaempferol) and mono/oligosaccharides (such as mannose and stachyose) in moringa leaves indicate that these compounds have high levels of bioaccessibility (6–210%). Additionally, compounds such as gallic acid, chlorogenic acid, vanillin, and rutin show higher bioaccessibility levels in the stomach, while

p-coumaric acid and quercetin demonstrate higher values in the small intestine (20).

Swetha et al. revealed that research findings on the in vitro bioaccessibility of polyphenols in defatted Moringa oleifera seed flour (DMSF) indicate that bound phenols are more readily accessible than free phenols. Additionally, in vivo bioavailability studies indicate high concentrations of catechin in plasma (34 µg/100 µL) and liver (54 mg/100 mg tissue) compared to other polyphenols, followed by epicatechin and gallic acid. These results also show that the peak time (Tmax) and area under the curve (AUC) for catechin in plasma are 2 hours and 321.95 ± 11.2, respectively. These bioavailability studies are expected to serve as a basis for further investigation into the health-supporting properties of DMSF polyphenols in targeted tissues (21).

Recent studies conducted on iron-deficient rats detected very low iron bioavailability in air-dried powdered MO leaf. However, the chemical profile of all Moringa products varies significantly, not only among different parts of the plant used but also due to cultivation practices, processing, and storage conditions, which primarily determine the nutritional content and anti-nutrient constituents. Anti-nutrients, such as phytic acid or tannins, are present in significant amounts and can affect the bioavailability of micronutrients. Therefore, further research is needed to determine the bioavailability of Moringa oleifera and its various products (22).

3. Potential of Moringa oleifera in Parkinson's Disease

Parkinson's disease (PD) is a common neurodegenerative disorder primarily characterized by the gradual loss of dopaminergic neurons (DAergic) in the brain. This occurs due to the accumulation of α-synuclein in a brain region called the substantia nigra (SN) in the midbrain. These neurons are responsible for releasing the neurotransmitter dopamine (DA), which plays a crucial role in controlling movement smoothness and body balance. Several factors such as dopamine, iron, calcium, mitochondria, and nerve inflammation can contribute to the onset of oxidative stress and neuronal damage observed in PD (23). Parkinson's disease is one of the most common neurological disorders affecting the elderly. Common symptoms of Parkinson's disease include tremors, stooped posture, rigidity, and bradykinesia. Although these symptoms may not appear in the early stages of the disease, as the disease progresses, they become more frequent. Symptoms and signs of Parkinson's typically do not develop until the loss of dopaminergic neurons reaches 70-80%. Therefore, early identification of Parkinson's patients in the period between suspected loss of dopaminergic cells and clinically evident parkinsonism becomes crucial in the development of effective neuroprotective treatment strategies (24,25).

In vivo studies have shown that administration of haloperidol (1 mg/kg, i.p) significantly induces catalepsy in Swiss albino mice. Catalepsy is a symptom of extrapyramidal disorders resembling Parkinson's disease in animals. Haloperidol acts as an antagonist of D2 and D3 receptors, so when repeatedly administered in a certain environment, it causes a gradual increase in catalepsy from day to day (catalepsy sensitization). The exact cause of Parkinson's disease is still not fully understood, but disturbances in the central nervous system can be caused by oxidative stress, free radicals due to toxins, or drugs

that damage dopaminergic neurons in the Substantia nigra. However, administration of ethanol extract of MO (200 mg/kg, i.p) reduces catalepsy in mice. The anti-cataleptic activity of MO may be due to its antioxidant potency or its effects on monoamines in the brain. M. oleifera leaf extract is believed to have antioxidant activity and neurotrophic effects (26).

Giapocco et al. conducted a study to evaluate the potential neuroprotective effects of isothiocyanates isolated from MO in treating and preventing Parkinson's disease. The researchers used C57BL/6 mice as research subjects and induced Parkinson's disease by administering 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) compound. For one week, the mice were given daily pre-treatment with moringin and glucomoringin (GMG), and then the behavior of MPTP-induced mice was evaluated to record motor deficits. The results showed that dendrites on neurons from the substantia nigra of MPTP-induced mice experienced a significant decrease. However, pretreatment with moringin was able to prevent damage to these neurons. Additionally, it was found that pretreatment with moringin also protected dopaminergic neurons by restoring tyrosine hydroxylase enzyme levels to normal levels (27).

Singh et al. reported that administration of MPTP to rats as a model for inducing Parkinson's disease shows behavioral and pathophysiological symptoms similar to Parkinson's disease. MPTP not only causes motor disturbances in rats but also results in degeneration of dopaminergic neurons. Administration of MPTP also produces behavioral, biochemical, and immunohistological symptoms similar to human PD patients. Oxidative stress is considered one of the main factors in the onset of neurodegenerative diseases, followed by chronic inflammation in selected brain regions. Several factors make the brain more vulnerable to oxidative stress, including mitochondrial dysfunction, neurotransmitter oxidation, decreased catalase levels, and increased redox-active transition metals. However, after administration of ethanol extract of MO leaves, there was a reduction in oxidative stress characterized by a significant decrease in oxidative stress markers (MDA and NO) and an increase in antioxidant enzyme activity (SOD, CAT, GSH). Ethanol extract of MO leaves also improved motor coordination and balance in rats after MPTP administration (28).

4. Potential of Moringa oleifera in Dementia

Dementia is a complex condition in older adults characterized by a decline in cognitive function and memory. The relationship between oxidative stress and dementia is closely related, especially in the context of Alzheimer's disease. Oxidative stress, involving the accumulation of ROS and cellular damage, has been associated with damage to cellular components such as DNA and proteins, disrupting the normal function of neurons and brain cells, and triggering chronic inflammation. Amyloid plaques and neurofibrillary tangles found in the brains of Alzheimer's patients are believed to be related to oxidative damage. Antioxidants, which can inhibit the effects of oxidative stress by suppressing ROS, have the potential to protect the brain from oxidative damage and may slow the progression of dementia. Cognitive impairment due to oxidative stress can impact the ability to perform daily activities such as dressing and eating. Understanding the role of oxidative stress in dementia is

important for the development of prevention and treatment strategies that protect the brain from oxidative damage, slow the progression of dementia, and improve the quality of life of affected individuals (29,30).

In vivo studies involving the administration of MO extract to AF64-induced dementia model rats for seven days have shown that MO extract can improve memory function and neuronal density. This is achieved by reducing oxidative stress, resulting in increased activity of antioxidant enzymes such as SOD, CAT, and GSH in the hippocampal tissue (31). Additional in vivo studies using Wistar albino rats induced with scopolamine as a dementia model also showed that administration of MO extract can improve the memory ability of rats by reducing oxidative stress. This leads to increased activity of antioxidant enzymes and decreased activity of acetylcholinesterase (AChE) enzyme (32).

The research conducted by Arozal et al. indicates that oral administration of Moringa oleifera seed oil (MOO) in scopolamine-induced rats can improve memory impairment and inhibit the increase in AchE enzyme activity in the hippocampal tissue. The mechanisms involved in this improvement include increased expression of tropomyosin-related kinase B (TrkB) neurotrophic factor receptor and nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB) protein in the hippocampus. However, administration of Moringa oleifera leaf extract in water (MOEs) did not show similar effects. Therefore, oral administration of MOO can inhibit the increase in AchE enzyme activity and improve scopolamine-induced memory impairment, while MOEs does not have the same effect (33).

Other research findings have demonstrated that Moringa oleifera exhibits neuroprotective and anti-neuroinflammatory activities due to its rich phytochemical content with antioxidant and anti-inflammatory properties (32,33). Several studies have documented the neuroprotective and anti-neuroinflammatory potential of Moringa oleifera due to its rich phytochemical content with antioxidant and anti-inflammatory properties. MO is also reported to have neuroprotective potential mediated by the NF-kB/Nrf2/HO-1 signaling pathway (34).

5. Potential of Moringa oleifera in Alzheimer's Disease

Alzheimer's Disease is a progressive neurodegenerative disease often associated with memory impairment and cognitive decline, which can affect behavior, speech ability, visual-spatial skills, and motor systems. Alzheimer's is also classified as a multifactorial disease with etiopathology not fully understood. This neurodegenerative disease is characterized by the accumulation of amyloid plaques in the brain (35). Alzheimer's Disease results from disturbances in the function of the neurotransmitter acetylcholine. Acetylcholinesterase (AChE) is an enzyme that catalyzes the breakdown of acetylcholine (ACh) into inactive forms, namely acetate and choline. Disruption of AChE can be addressed by MO administration. MO extract, containing quercetin, is known to ameliorate memory impairments induced by cholinergic inhibitors in humans. Additionally, it has the ability to induce long-term potentiation

in the hippocampus, inhibit AChE enzyme, and facilitate calcium entry into nerve cells (36).

Research conducted by Nwidu et al. using in vitro methods with MO leaves showed that several compounds found in Moringa leaves, such as quercetin and kaempferol, have the ability to inhibit the activity of acetylcholinesterase enzyme, which has the potential to prevent Alzheimer's disease. Testing with MO ethanol extract showed an IC50 inhibition value against acetylcholinesterase of 0.2105 ppm. Additionally, MO ethanol extract detected the flavonoid compound quercetin at a concentration of 102.2 mg/g (37).

In vivo studies were also conducted using rats with hyperhomocysteinemia (HHcy) induction to mimic Alzheimer's-like pathology. HHcy administration leads to increased calpain activity, which can damage neurons and synapses. Additionally, HHcy is associated with increased production of amyloid-beta (Aβ), a hallmark of Alzheimer's, and tau hyperphosphorylation, which results in the formation of neurofibrillary tangles (NFTs), also associated with Alzheimer's. However, after MO administration, there was a reduction in ROS, preventing oxidative stress. MO also inhibited calpain activity, protecting neurons from damage, reducing Aβ production by inhibiting the activity of BACE1, an enzyme involved in Aβ formation, and reducing tau hyperphosphorylation by inhibiting GSK3β activity, one of the enzymes involved in tau phosphorylation. MO demonstrates neuroprotective effects and can inhibit several pathological mechanisms associated with HHcy, potentially protecting the brain from the development of diseases like Alzheimer's associated with this condition (8).

In another in vivo study, rats were used as an Alzheimer's model. In this research, the rats were administered colchicine at a dose of 15 µg/5µl and also given MO extract at a dose of 250 mg/kg body weight (38). The results of this study indicated that colchicine significantly interfered with the memory process, accompanied by a decrease in the levels of norepinephrine (NE) in the cerebral cortex, hippocampus, and caudate nucleus. Additionally, colchicine administration also led to a reduction in dopamine and serotonin levels. These alterations resulted in a decrease in beta and alpha wave patterns and an increase in biphasic peak wave patterns in the experimental Alzheimer's rat model observed in electroencephalogram (EEG) analysis (38,39).

Colchicine is known to cause lesions in the hippocampus, resulting in cognitive impairment and decreased ChAT, indicating its potential use as a candidate for modeling Alzheimer's disease. Colchicine can induce neurotoxicity and memory decline by inhibiting the cholinergic pathway, ultimately leading to a decrease in the number of cholinergic neurons and cholinergic rejuvenation, particularly in the hippocampal region of the brain. The memory impairment induced by colchicine may be attributed to the reduction in serotonin, dopamine, and norepinephrine levels in the caudate nucleus, hippocampus, and cerebral cortex (38,39). The administration of MO extract in this study showed a significant improvement in memory function and an increase in beta wave patterns in the experimental Alzheimer's animal model (38).

Mahaman et al. reported that MO also has anticholinesterase effects, increasing acetylcholine availability in the brain and improving cognitive function. Studies on APP/PS1 mice treated with MO methanol extract showed Aβ levels comparable to normal control mice through reductions in Beta-Secretase 1 (BACE1) and asparagine endopeptidase (AEP) and increases in insulin-degrading enzyme (IDE), neprilysin (NEP), and lipoprotein receptor-related protein-1 (LRP1) proteins. MO also enhanced synaptic plasticity by increasing downregulated GluN2B phosphorylation, PSD95 and synapsin1 synaptic proteins, dendritic spine quality and quantity, and reducing neurodegeneration in treated mice. However, further research is needed to understand the exact mechanism of MO's therapeutic effects in Alzheimer's disease (40).

Some commonly used animal models of Alzheimer's disease in research involve neurotoxins such as colchicine and amyloid-beta. These models have been utilized to study the pathogenic mechanisms of Alzheimer's disease and evaluate potential therapeutic strategies. MO has been found to have neuroprotective and anti-neuroinflammatory activities due to its phytochemical content with antioxidant and anti-inflammatory properties (38–40).

SIMPULAN

MO is a plant rich in bioactive compounds such as flavonoids, polyphenols, saponins, and tannins. These compounds have the potential as neuroprotective agents in addressing neurodegenerative diseases. Studies have revealed that MO has strong antioxidant effects, capable of combating oxidative stress involved in the pathogenesis of neurodegenerative diseases. In the context of Parkinson's disease, MO has been shown to reduce cataleptic symptoms and protect dopaminergic neurons, which are crucial in preventing a decline in dopamine production in the brain. In Alzheimer's disease, MO has demonstrated the ability to improve memory function, reduce oxidative stress, and inhibit the activity of AChE involved in neurotransmitter dysfunction. The results of research conducted by scientists can be summarized that MO can address neurodegenerative diseases through two main mechanisms: first, by increasing antioxidant activity that helps combat oxidative stress and inflammation damaging nerve cells; second, by inhibiting enzymes involved in the degradation of important neurotransmitters, such as AChE. However, further research is still needed to deeply understand the mechanisms and potential for more specific therapy of MO. The existing evidence suggests that the content and effects of MO have the potential as supportive supplements to slow down the progression of neurodegenerative diseases in the future.

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There are no conflicts of interest to declare in this research. The authors have no affiliations or connections with any entities or organizations that could influence the objectivity or results of this manuscript. The research was conducted in good faith and without any influence from parties that could affect the findings or conclusions presented in this manuscript.

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