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The Role of Medicinal Plants in Treating Mild Cognitive Impairment: A Focus on Mitophagy Modulation

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ABSTRACT

Mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia, characterized by cognitive decline that is more pronounced than expected for age. While the exact mechanisms underlying MCI remain elusive, mounting evidence suggests that impaired mitophagy, a cellular process responsible for removing damaged mitochondria, may contribute to its development. Medicinal plants, rich in bioactive compounds, have shown promise in treating MCI. This review explores the potential of medicinal plants to ameliorate MCI by modulating mitophagy. We delve into the intricate interplay between mitophagy dysfunction and MCI, highlighting the pathways involved. Furthermore, we examine the reported effects of various medicinal plants on mitophagy, emphasizing their potential to restore mitochondrial homeostasis and protect cognitive function. Finally, we discuss future research directions and perspectives on the therapeutic potential of medicinal plants in MCI management.

Keywords: Mild cognitive impairment; mitophagy; Medicinal plants.

INTRODUCTION

Mild cognitive impairment (MCI) is a condition characterized by cognitive decline above that seen in normal aging, affecting six main cognitive domains: learning and memory, social functioning, language, visuospatial function, complex attention, and executive functioning [1]. With a prevalence of around 22% in those over 65 years of age [2, 3] and an annual progression rate to dementia of 5% to 10% [3], MCI poses a significant public health concern.

Recent studies have implicated mitophagy dysfunction as a potential risk factor in the pathophysiology of MCI [4]. There are various pathways to regulate the mitophagy mechanism. The PINK1-Parkin pathway is a crucial one in this context. Initially, PINK1-Parkin were recognized as proteins linked to Parkinson's disease. PINK1 is a serine/threonine kinase in mitochondria, and Parkin is a cytosolic E3 ubiquitin ligase. Upon mitochondrial damage, PINK1 accumulates on the outer mitochondrial membrane (OMM), leading to the phosphorylation of Parkin and its recruitment to the impaired mitochondria. Subsequently, this protein triggers autophagy receptors like P62/SQSTM1, ultimately resulting in the elimination of damaged mitochondria [5].

Medicinal plants have been used for centuries in traditional medicine systems worldwide for their therapeutic properties. They are a rich source of bioactive compounds, including polyphenols, alkaloids, and flavonoids, which have shown potential in treating various diseases [6-8]. Recent research has focused on the ability of medicinal plants to modulate mitophagy and their potential application in treating MCI.

This review aims to gather findings from researches that explores the effects of medicinal plants (or their active compounds) on cognitive disorders, with a focus on the role of these plants in regulating mitophagy.

Medicinal Plants and Their Effects on Mitophagy in Cognitive Disorders

As shown in Table 1, some medicinal plants can effect on mitophagy in cognitive disorders. In this section, they are discussed briefly.

Loganin

Loganin -derived from Corni Fructus- has shown promising results in a rat model of cognitive impairment. Zhou et al. (2023) demonstrated that loganin administration significantly elevated PTEN-induced kinase 1 (PINK1), PINK1-Parkin and optineurin (OPTN) levels, leading to improved mitophagy regulation. This treatment also reduced learning and memory deficits and β-amyloid (Aβ) protein deposition [9].

Panax notoginseng saponins (PNS)

It has been reported that PNS increase mitophagy in Aβ-damaged PC12 cells. Jiang et al. (2022) showed that PNS enhanced Parkin recruitment to mitophagy receptors in a PINK1 pathway-dependent manner [10]. Similarly, Ginsenoside Rg_1, another compound derived from ginseng, improved mitophagy by regulating LC3 II/I proteins, p62, and PINK1-Parkin proteins [11].

TSG (2,3,5,4'Tetrahydroxystilbene-2-O-β-D-glucoside)

TSG -derived from Polygonum multiflorum- has demonstrated anti-inflammatory effects in neuronal and glial cells. Gao et al. (2020) reported that TSG's protective effects against Aβ25-35-induced inflammation were mediated through the regulation of mitophagy via the AMPK/PINK1/Parkin pathway. Thus, inactivating the AMPK/PINK1/Parkin pathway led to inhibition of the protective effects of TSG on cell inflammation [12].

Senegenin

Senegenin -extracted from Polygala tenuifolia- has shown potential in reducing cell damage caused by Aβ1-42 through PINK1/Parkin-mediated mitophagy [13]. Tian et al. (2022) demonstrated its effectiveness in an Alzheimer's disease mouse model [14].

β-Asarone

β-Asarone -derived from Acorus tatarinowii- has been found to reduce Aβ1-42 levels and improve cognitive deficits in AD mice by regulating mitophagy through the PINK1-Parkin pathway [15].

6‴-feruloylspinosin

6‴-feruloylspinosin -a component of Ziziphus jujuba var spinosa seeds- has shown neuroprotective effects in both C. elegans and PC12 cells. Yang et al. (2020) reported that it reduces Aβ toxicity and increases mitophagy levels through the induction of the Pink1/Parkin pathway [16].

Resveratrol

A polyphenol found in grapes and red wine has emerged as a potential therapeutic agent for neurodegenerative diseases. It has been shown to promote mitophagy by activating the AMPK pathway, a key regulator of energy metabolism and autophagy. Resveratrol also exhibits antioxidant and anti-inflammatory properties, further contributing to its neuroprotective effects [17].

Astragalus mongholicus

While not directly studied in MCI, Liu et al. (2020) and Wen et al. (2020) demonstrated its ability to regulate mitophagy through the Pink1/Parkin pathway in diabetic nephropathy [18, 19]. Tohda et al. (2006) showed its positive effects on cognitive impairment caused by Aβ injection in rats [20].

Erigeron breviscapus (Scutellarin)

Wang et al. (2023) showed that Scutellarin enhances mitophagy by controlling the PINK1/Parkin pathway in myocardial ischemia [21]. Shin et al. (2018) and Zeng et al. (2018) demonstrated its positive effects on spatial cognitive impairment and Aβ formation in rat models [22, 23].

Berberidaceae (barberry family)

Abudureyimu et al. (2020) examined the impact of berberine, an active alkaloid found in Berberidaceae, on heart failure in rats and found that berberine treatment reduces heart hypertrophy, preserves heart function, and boosts mitophagy via the PINK1/Parkin pathway [24]. de Oliveira et al. (2016) examined the impact of berberine on spatial memory, learning, anxiety, acetylcholinesterase activity, and cell death in rats with AD (intraventricular streptozotocin (ICV-STZ) model) and demonstrated that this treatment enhances spatial memory and learning in rats [25].

Morinda officinalis (Indian mulberry)

Qiang et al. (2024) studied the effect of Monotropein (MON), the main natural compound in the root glycoside of Morinda officinalis, on colon damage caused by sepsis in rats and found that MON can induce mitophagy through the NFR2/PINK pathway and improve inflammation and apoptosis in colon tissues [26]. Zhang and Zhang (2022) investigated the potential neuroprotective effects of Morinda officinalis in Alzheimer's disease and found that the active components of this plant, such as oligosaccharides, anthraquinones, and iridoid glycosides, can inhibit neuroinflammation and oxidative stress [27].

Ziziphora bungeana

Liu et al. (2021) investigated the effect of Acacetin, the active compound of Ziziphora bungeana, on induced mitophagy in the H9C2 myocardial cell line. The results showed that Acacetin plays a role in reducing ischemia damage by strengthening mitophagy, mainly through the phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) (PI3K/Akt/mTOR) signaling pathway. Given the anti-inflammatory and antioxidant properties of this plant, it has been suggested that it may be effective in improving cardiac ischemias [28]. However, to our knowledge, the effects of this plant have not yet been studied in the field of MCI.

Tomatidine (found in unripe tomatoes)

A study investigated the effect of Tomatidine on the lifespan of C. elegans worms and found that Tomatidine delayed aging processes in the studied animal, mainly through the regulation of mitophagy induction (from the SKN-1/Nrf2 pathway) [29]. Xu et al. (2024) investigated the effect of Tomatidine on lung inflammation caused by blood infection (sepsis) in rats and found that Tomatidine improved lung damage, inflammatory responses, and activation of mitophagy in these animals [30].

FUTURE DIRECTIONS AND PERSPECTIVES

While promising, research on the effects of medicinal plants on mitophagy in MCI is still in its early stages. Further research is needed to: 1- Elucidate the precise pathways involved in mitophagy modulation by different medicinal plants. 2- Well-designed clinical trials are required to confirm the therapeutic benefits of medicinal plants in improving cognitive function and preventing MCI progression. 3- Explore the potential synergistic effects of combining different medicinal plants.

Table 1. Summary of Medicinal Plants and their Effects on Mitophagy in MCI.

Plant/Compound	Active Component	Effect on Mitophagy	Effect on Cognition	Reference
Corni Fructus	Loganin	Elevated PINK1-Parkin and OPTN levels	Reduced learning and memory deficits	[9]
Panax PNS	notoginseng	Increased mitophagy in Aβ-damaged cells	Not directly studied	[10, 11]
Polygonum multiflorum	TSG	Regulated mitophagy via AMPK/PINK1/Parkin	Reduced neuroinflammation	[12]
Polygala tenuifolia	Senegenin	Enhanced PINK1/Parkin-mediated mitophagy	Reduced Aβ1-42-induced damage	[14]
Acorus	β-Asarone tatarinowii	Regulated mitophagy via PINK1-Parkin	Improved cognitive deficits	[15]
Ziziphus jujuba var spinosa	6‴-feruloylspinosin	Increased mitophagy via Pink1/Parkin	Reduced Aβ toxicity	[16]
Astragalus mongholicus	Root decoction	Regulated mitophagy via Pink1/Parkin	Improved memory and axon regeneration	[20, 18, 19]
Erigeron breviscapus	Scutellarin	Enhanced mitophagy via PINK1/Parkin	Improved spatial cognition	[31, 21]
Morinda officinalis	Monotropein	Induced mitophagy via NFR2/PINK	Potential neuroprotective effects	[27, 26]
Curcumin (Curcuma longa)	Curcumin	Activates PINK1/Parkin pathway	Reduces oxidative stress, inflammation, and cognitive decline	[32]
Vitis vinifera	Resveratrol	Enhanced brain-derived cAMP response element-binding protein (CREB) pathway	Reduces oxidative stress, Restores the long-term potentiation (LTP)	[33]
Bacopa monnieri	Bacosides	Activates PI3K/Akt/mTOR pathway	Improves cognitive function and memory	[34]

CONCLUSION

Mitophagy plays a crucial role in maintaining neuronal health and function, and its impairment contributes to the pathogenesis of MCI. Medicinal plants, with their rich source of bioactive compounds, offer potential therapeutic interventions by modulating mitophagy and restoring mitochondrial homeostasis. Further research is needed to fully understand the mechanisms of action and therapeutic potential of medicinal plants in treating MCI. The development of safe and effective therapies based on medicinal plants holds promise for improving cognitive function and slowing down the progression of MCI.

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The author has no conflicts of interest to declare

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