Neuropharmaceutical Properties of Naringin Against Alzheimer's and Parkinson's Diseases

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Abstract

Neurological complications are considered the leading cause of disability and the second cause of death worldwide. Although the most common neurological disorders affecting a large population are Alzheimer's (AD) and Parkinson's diseases (PD), no definitive treatment has been propounded in the clinic. As in recent years, special attention has been paid to medicinal herbal products as one of the ways to meet the challenges of treating diseases. This review study aimed to introduce the naringin neuroprotective effects as an abundant flavonoid in grapes and citrus fruits on the most common neurological disorders, including AD and PD. For this purpose, the specified keywords were searched in PubMed, Web of Science, Scopus, Embase, and Google Scholar, and the results were entered into the study after a concise overview. The findings show naringin can confront neurological disorders through several mechanisms such as modulating stress response pathways, preventing apoptosis, oxidative stress, and neuroinflammation, excessive chelating amounts of metal ions, thereby improving cognitive impairment and memory loss induced by neurological disorders. However, further studies, particularly on human, are critical for the final confirmation of obtained findings.

Keywords: Flavonoids; Parkinson's Disease; Naringenin; Naringin; Alzheimer's Disease; Neurological Disorder

Introduction

Globally, neurological disorders are considered the leading cause of disability and the second cause of death. Notably, the neurological caused disability and death burden in the present decade is increasing due to global population growth and aging. Hence it is recognized as a public health challenge. The statistics revealed that despite a diminution in communicable neurological disorders over the past three decades, there was an approximately 40% increment in the absolute number of deaths and a 15% growth in disability-adjusted life-years [1]. Although promising research and develop-
ments for early detection and treatment are underway in the current clinic, there is no absolute cure for most neurological disorders and deducing an effective treatment protocol still poses a significant clinical challenge. In recent years, researchers have looked at different ways, such as gene therapy or applying other synthetic and/or herbal compounds to test their promising efficacy against various neurological disorders [2-5]. Indeed, herbal medicine is considered one of the most important options to meet the current challenges that health care providers have faced, such as cancer [6, 7], environmental and pharmacological toxicities [8, 9], infertility [10, 11], diabetes [12, 13], cardiovascular complications [14], infectious diseases [15], neurological diseases [16], and immunological disorders [17]. Therefore, representing a medicinal plant with the potential to prevent neurological disorders is an essential component of current research in managing diseases related to the nervous system. The present study aimed to provide a concise introduction to naringin and assess its neuroprotective properties against the most common neurological complications, including Alzheimer’s (AD) and Parkinson’s disease (PD).

Search Strategy
Data collection was carried out in Web of Science, Scopus, Embase, Google Scholar, and PubMed databases using the keywords include "flavonoids", "PD", "naringenin", "naringin", "AD", "cognitive impairment", and "neurological disorder" without language and time restriction. The title and abstract of all articles were recognized, and those introducing a relationship between the naringin, and AD and/or PD were finally selected.

A Concise Characterization of Naringin and Its Therapeutic Properties
Flavonoids are low-molecular-weight polyphenolic compounds and a source of bioactive chemicals in most plant-based foods consumed by humans regularly [18, 19]. Numerous studies have demonstrated that these natural compounds contain a wide range of biological and pharmacological properties attributed to their capability of inhibition or modulation certain enzymes and their antioxidant properties. The flavonoids' antioxidant properties appear due to the scavenging of free radicals, ascribed to the flavonoids structure and the attached phenolic hydroxyl groups. The free radicals scavenging activity is undeniably related to the structure of flavonoids, which depends on the degree of hydroxylation and polymerization, structural class, and other conjugations [20, 21]. Moreover, glycosylation routinely occurs in the flavonoid metabolism, leading to adding sugar moieties into the structure, followed by an increment of their hydrophilic properties [22].

Figure 1 depicts the chemical structure of naringenin (4', 5, 7-trihydroxyflavanone), a well-known type of flavonoids abundantly present in typical diet mainly found in citrus fruits that possess favorite properties such as anti-inflammatory, antioxidant, antiproliferative, antimutagenic, and chemopreventive activities. Naringin (4′, 5, 7-trihydroxy flavanone-7-rhamnoglucoside),

Figure 1. Chemical structure of (A) naringenin and (B) naringin. Grapes and citrus fruits are rich sources of naringenin (4', 5, 7-trihydroxyflavanone), which is converted to naringin (4′, 5, 7-trihydroxy flavanone-7-rhamnoglucoside) by glycosidation that contains more hydroxyl groups and offers more therapeutic properties.
A flavonoid extracted from the naringenin and the disaccharide neohesperidose, is extensively present as one of the key effector molecules in Chinese herbal medicines (e.g., Drynariae rhizoma, Citri Grandis Exocarpium, C. Fructus, and Aurantii Fructus). It is well established that naringin is the main component of grapefruit far more than the other components [23-26]. According to previous studies, naringin has several biological activities, including antibacterial, anti-inflammatory, antioxidant, and antiapoptotic [27, 28]. Furthermore, naringin possesses very low toxicity, and its oral administration (1250 mg/kg/day) for six consecutive months showed no adverse effects in Sprague–Dawley rats [29]. Although naringin has become an outstanding candidate for treating diabetic complications, osteoporosis, bone injury, hepatic injury, and neurodegenerative disorders [30-33], the latest attempts at delivering naringin were restricted to the field of bone repair and regeneration [26]. Therefore, in the following sections, studies that evaluated the neuroprotective properties of naringin to determine its promising ability to treat or prevent the most common neurological disorders were reviewed.

Neuroprotective Properties of Naringin

1. AD

AD is the most common progressive neurodegenerative disorder, pathologically characterized by senile plaques (extracellular amyloid-beta [Aβ] deposition in brain tissues), intracellular neurofibrillary tangles of hyperphosphorylated tau protein, and advanced involvement of cognitive alterations that primarily consist of memory loss, particularly in the elderly population. The prevalence of AD varies depending on several factors, including age, genetics, comorbidities, and the education level of the society population [34-36]. As there is no absolute cure in the current clinical practice against AD, researchers in recent years have conducted multiple studies to evaluate the neuroprotective properties of naringin to suggest a promising therapeutic strategy for AD. Along with several in vitro investigations, the previous studies mainly focused on naringin neuropharmaceutical properties on behavioral, biochemical, and histomorphological parameters of animal AD models [37]. In the following, studies were reviewed to understand the mechanisms involved in AD improvement upon treatment with naringin.

Since behavioral alterations simply characterize AD in animals, previous studies have demonstrated that naringin improves cognitive deficits in animal models of AD by conducting several behavioral tests, including platform-jumping, Morris water maze, memory consolidation, novel object recognition, y maze test, opened and closed field activity, radial arm maze, rota-rod, gross behavioral activity (locomotor activity), and passive avoidance [35, 38-47]. These behavioral modifications upon administration of naringin well reflect the neuroprotective effects of this flavonoid against the progression of AD and suggest it as a hopeful option for treating this neurological disorder. However, the exact mechanisms that naringin could improve the pathological alteration caused by AD are uncertain. Previous studies have attempted to study the neuroprotective properties of naringin against AD in various examinations, which can be reviewed at three levels, including histomorphological, molecular, and biochemical parameters. Previous studies have demonstrated that the nuclei of the hippocampal and hypothalamus in AD models were arranged unevenly and loosely [48]. Furthermore, AD models represented the disordered distribution of neurons, destroyed structure, altered morphology, and markedly decreased number of neuron cells. Additionally, the nuclei were shrunk, and the intercellular space was abnormally enlarged. Interestingly, Meng et al. suggested that naringin can ameliorate AD-induced alterations in the histoarchitecture of neuron cells [48]. Besides, transmission electron microscope assay showed promising neuroprotective properties of naringin in rat models of AD [41]. FOXO proteins, whose activation is neuroprotective, are critical regulators of the expression of stress response genes [49, 50]. Foxo1 is an essential mediator of autophagy, which was decreased in the hippocampus...
of vascular dementia animals, as its overexpression resulted in the prevention of AD progression. Moreover, Foxo1 is inhibited by miR-96-5p that is highly expressed in AD [41, 51]. Significantly, naringin inhibits miR-96-5p expression, induces Foxo1, and prevents AD progression [41]. β-site amyloid protein cleaving enzyme 1 (BACE1) can diminish amyloid proteins increasing Aβ production, which in turn, excessive deposition of Aβ causes nerve cell damage [52]. Meng et al. revealed that naringin could inhibit BACE1 expression and decrease the content of amyloid protein and the production of Aβ [48]. Tau protein stabilizes the structure of microtubules, but its atypical alteration disrupts the typical transport performance of neurons. In addition, hyperphosphorylation of the tau protein represents a double-helical structural alteration that raises the formation of neurofibrillary tangles and induces AD [53]. The phosphorylation of tau protein is done by a major regulatory enzyme called cyclin-dependent kinase 5 (CDK5) [54]. Interestingly, a recent study revealed that naringin decreased CDK5 expression, leading to reduced tau protein phosphorylation [48]. Furthermore, the administration of naringin increased the glutamate receptor-2 and N-methyl-D-aspartate receptor-1 expression and reduced the calcium/calmodulin-dependent protein expression. Kinase II (CaMKII) represents the ability of naringin to modulate the glutamate system by affecting this excitatory neurotransmitter's receptors [48]. The inhibition of CaMKII autophosphorylation plays a crucial role in long-term memory. Wang et al. proposed that naringin increased the CaMKII phosphorylation and enhanced the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic receptor phosphorylation and improved cognitive function in transgenic mouse modes of AD [46]. Importantly, evaluation of the levels of Caspase-3, Bad, and Bcl-2 demonstrated neuroprotective properties of naringin via preventing neuron apoptosis [48]. Other neuroprotective effects of naringin were affecting estrogen receptor pathways by increasing the protein expression of estrogen receptors α and β and activating the p38 mitogen-activated protein kinases pathway after binding with estrogen receptors [48]. Kaur et al. demonstrated that neuroprotective properties of naringin were mediated by its impact on nitric oxide signaling [42]. Elevated nitric oxide levels in AD models were coupled with increased hippocampal and cortical levels of NF-κB. Naringin administration inhibited the activation and translocation of protein kinase C, subsequent phosphorylation of IκB, and reduced hippocampal and cortical levels of NF-κB [44]. According to previous studies, most evaluations focus on biochemical parameters that can be reviewed in four levels consisting interaction with metals, change in acetylcholinesterase (AChE), protection against oxidative stress, and reducing the extent of neuroinflammation [55]. An excessive amount of metal ions promotes the rapid aggregation of Aβ peptides, which are implicated in AD and PD. Thereby, metal chelators can attenuate these detrimental effects [56]. Indeed, metals can change the morphology of Aβ and induce Aβ formation. Several studies revealed that naringin chelated excessive amounts of various metals, including Cu²⁺, Fe³⁺, Al³⁺, Zn²⁺, and Mn²⁺, thereby preventing aggregation of Aβ peptides [39, 42, 46]. Since cholinergic neurons represent a crucial duty in the central and peripheral nervous systems, which are implicated in attention span and cognitive ability, enhancing the levels of acetylcholine through inhibiting AChE is considered a major strategy for the amelioration of AD [57, 58]. Therefore, targeting and inhibiting AChE activity by naringin can be considered as one of the approaches to confronting AD [35, 39, 44, 59-61]. Neuroinflammation and oxidative stress are considered causative factors of AD progression. Abnormal neuroinflammation, such as activated astrocytes and microglia, is a typical hallmark of neurodegenerative diseases as the activated form of these immune cells surround Aβ plaques in the brains of patients with AD [62, 63]. Elevated secretion of cytokines such as interleukins (IL) and tumor necrosis factors (TNF) in the brain is thought to be a feature of AD patients. Several studies
have reported that naringin can attenuate inflammatory factors such as transforming growth factor-β1, IL-1β, TNF-α, and inactivated astrocytes and microglia in the hippocampus of AD animals [35, 44, 47]. Furthermore, several studies have determined the antioxidant properties of naringin by measuring the levels of reactive oxygen species (ROS), superoxide dismutase, reduced and oxidized glutathione, catalase, and nitric oxide in animal models of AD, resulting from chelating metals, regulating the expression of genes involved in the stress response process, and improving mitochondrial function [35, 38, 39, 42-44, 55, 60].

2. PD
PD is characterized by clinical symptoms such as instability, rigidity, bradykinesia, and tremor at rest [64, 65]. The neurodegeneration of the nigrostriatal dopaminergic system, followed by dopamine deficiency in the striatum, has been suggested as the cause of PD [65, 66]. Due to the insufficiency of current clinical pharmaceutics applied in patients with PD, the most important of which are high toxicity and destructive adverse effects, establishing an efficient alternative is an essential component in the management of PD. So far, several studies have been conducted to evaluate the efficacy of naringin against PD in rodents through assessment of alteration in behavioral, biochemical, and histological/stereological observations [67-69]. Behavioral paradigms usually include narrow beam walk test for measuring hind-limb impairment, open field test to assess locomotor and emotional reactivity, rota-rod test to monitor motor coordination ability, bar catalepsy test to evaluate catalepsy behavior, grip strength test to estimate neuromuscular strength, actophotometer to measure locomotor activity, and footprint analysis, which is an indicator to the animal gait [67-69]. Biochemical analysis commonly determines the levels of dopamine and metabolites in the striatum, the levels of oxidative stress and inflammatory markers, mitochondrial performance, and the expression of related genes [70-73]. Concerning behavioral paradigms affected by PD, Garabadu and Agrawal demonstrated that naringin remarkably attenuated rotenone-induced behavioral deficits by evaluating actophotometer, open field, bar catalepsy, narrow beam walk, rota-rod, grip strength, and footprint estimations tests [74]. Previous studies determined that the impairment in behavioral function is involved in the pathogenesis of PD [75]. Hence, attenuative properties of naringin against rotenone-induced PD introduced this flavonone as a promising neuropharmaceutic in the management of PD. Interestingly, the authors revealed that treatment with trigonelline, an alkaloid inhibitor of the nuclear factor erythroid 2–related factor 2 (Nrf-2) [76], abolished the neurotherapeutic properties of naringin on rotenone-induced alterations in the behaviors of the animals [74]. Hence, it suggests that naringin exerts neuroprotective effects against PD through Nrf-2 mediated pathways [74]. Indeed, Kim et al. revealed that naringin activated mTORC1, a critical survival factor for dopaminergic neurons [79]. Given the involvement of Nrf-2 and mTORC1 in the battle against oxidative damage, the antioxidant properties of naringin, and the role of ROS in the pathogenesis of PD, it could be assumed that the protective properties of naringin against this neurological disorder are related to the regulation of redox homeostasis. The reported results regarding restored antioxidant enzyme activity in PD models upon treatment with naringin are logical proof for this claim [74].

It is believed that in PD models, the function, integrity, and bioenergetics of mitochondria in the substantia nigra pars compacta are disrupted [72, 73]. Mitochondrial dysfunction has been linked to inflammation and redox imbalance, among the most critical risk factors for PD [80]. Previous studies have demonstrated that the administration of naringin to animal models of PD restores mitochondrial activity via attenuating decreased mitochondrial complex-I, -II, -IV, and -V activities, preventing microglial activation, and
reducing the level of inflammatory responses [74, 79, 81]. Furthermore, naringin is able to modulate dopamine levels and its metabolites in striatum and substantia nigra pars compacta, thereby protecting against rotenone-induced dopaminergic toxicity in animal models of PD [74]. Similarly, naringin is suggested as a beneficial natural compound to prevent 6-hydroxydopamine-induced nigrostriatal dopaminergic degeneration, which is involved in PD [79]. The ability of naringin to impart dopaminergic neurons the capability of glia-derived neurotrophic factor production as a neurotherapeutic agent against PD reveals that it is an appropriate candidate to prevent dopaminergic degeneration in the adult brain [81]. Aging, a significant risk factor for multiple human diseases, including AD and PD, is accompanied by constant alterations in morphology and function [82]. Zhu et al. revealed that naringin could extend the lifespan of a well-known nematode, *Caenorhabditis elegans*, and alter the expression levels of DAF-16, which in turn led to a delay in the progression of aging-related AD and PD [83]. Animal studies revealing naringin neuroprotective properties against PD are shown in Table-1.

| Table 1. Animal Studies Revealing Naringin Neuroprotective Properties Against Parkinson's Disease (PD) |
|---|---|---|---|---|---|
| PD Induction | Sample Size | Dose | Duration | Findings | Ref |
| The rotenone was injected through an intracerebroventricular route into SNpc | Wistar albino male rats | 80 mg/kg | 14 days | -Naringin-attenuated rotenone-induced behavioral abnormalities were evaluated by several examinations including actophotometer, OFT, bar catalepsy, narrow beam walk, rotorod, grip strength, and footprint analysis. -Naringin decreased dopaminergic toxicity in the striatum and SNpc rats, improved mitochondrial function, and reduced apoptosis in the animal SNpc. -The neuroprotective properties of naringin were suggested to be mediated by the Nrf pathway | [74] |
| 6-OHDA was unilaterally injected into the striatum | C57BL/Mice | 80 mg/kg | 7 days | Naringin protected the nigrostriatal dopaminergic projection, induced the activation of mTORC1, and inhibited microglial activation. | [79] |
| MPP⁺ was unilaterally injected into the medial forebrain bundle of the brains | Female Sprague Dawley Rats | 8 or 80 mg/kg | 7 days | Naringin increased the level of GDNF in dopaminergic neurons, activated mTORC1, and attenuated the levels of TNF-α in microglia. | [81] |
| N/A | *Caenorhabditis elegans* | 50 μM | 7 days | Naringin extended the lifespan of *C. elegans*, increased the thermal and oxidative stress tolerance, reduced the accumulation of lipofuscin, delayed the progress of PD via *DAF-16*. | [83] |

**PD:** Parkinson’s disease; **SNpc:** Substantia nigra pars compacta; **OFT:** Open field test; **Nrf:** Nuclear factor erythroid–related factor; **6-OHDA:** 6-hydroxydopamine; **C57BL:** C57 black 6; **mTORC1:** Mammalian target of rapamycin complex 1; **MPP⁺:** 1-Methyl-4-phenylpyridinium; **GDNF:** Glia-derived neurotrophic factor; **TNF-α:** Tumor necrosis factor-alpha; **N/A:** Not Applicated; **DAF-16:** The sole ortholog of the forkhead box protein
**Conclusion**

The findings show naringin can confront neurological disorders through several mechanisms such as modulating stress response pathways, preventing apoptosis, oxidative stress, and neuroinflammation, excessive chelating amounts of metal ions, thereby improving cognitive impairment and memory loss induced by neurological disorders. However, further studies, particularly on human specimens, are critical for the final confirmation of obtained findings.

**Conflict of Interest**

The authors have no conflict of interest to declare.

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