REVIEW ARTICLE

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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.

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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-

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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),

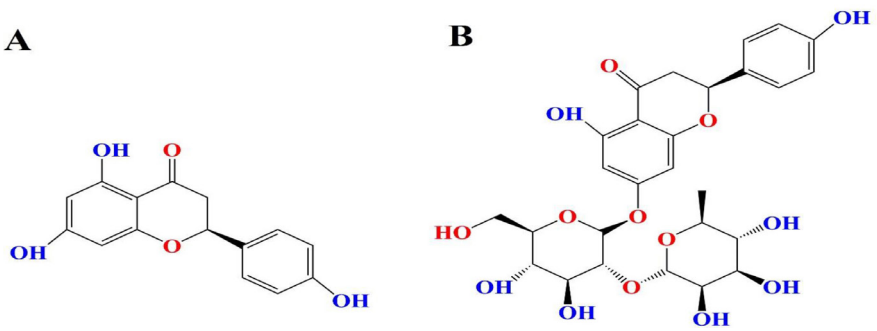

Figure 1. Chemical structure of (**A**) naringenin and (**B**) naringin. Grapes and citrus fruits are rich sources of naringenin (4', 5, 7-trihydroxyflavanone), which is converted to naringin (4′, 5, 7-trihydroxy flavanone-7-rhamnoglucoside) by glycosidation that contains more hydroxyl groups and offers 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 depended 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 IkB, 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 Cu^{2+}, Fe^{3+}, Al^{3+}, Zn^{2+}, and Mn^{2+}, 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 flavonoid 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]. Nrf-2 is a transcription factor activated under oxidative stress state that determines the fate of cells by maintaining cell redox homeostasis through cooperation with genes involved in responding to stress, such as the *mammalian target of rapamycin complex-1* (*mTORC1*) [77, 78].

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, rota-rod, 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.

References

1. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):459-80.
2. Deverman BE, Ravina BM, Bankiewicz KS, Paul SM, Sah DWY. Gene therapy for neurological disorders: progress and prospects. Nat Rev Drug Discov. 2018;17(9):641-59.
3. Espay AJ, Aybek S, Carson A, Edwards MJ, Goldstein LH, Hallett M, et al. Current Concepts in Diagnosis and Treatment of Functional Neurological Disorders. JAMA Neurol. 2018;75(9):1132-41.
4. Lee J, Jin C, Cho SY, Park SU, Jung WS, Moon SK, Park JM, Ko CN, Cho KH, Kwon S. Herbal medicine treatment for Alzheimer disease: A protocol for a systematic review and meta-analysis. Medicine (Baltimore). 2020;99(33):e21745.
5. Liang YT, Lin CY, Wang YH, Chou HH, Wei JC. Associations of Chinese Herbal Medicine Usage with Risk of Dementia in Patients with Parkinson's Disease: A Population-Based, Nested Case-Control Study. J Altern Complement Med. 2021;27(7):606-12.
6. Memariani Z, Abbas SQ, Ul Hassan SS, Ahmadi A, Chabra A. Naringin and naringenin as anticancer agents and adjuvants in cancer combination therapy: Efficacy and molecular mechanisms of action, a comprehensive narrative review. Pharmacol Res. 2021;171:105264.
7. Samare-Najaf M, Samareh A, Jamali N, Abbasi A, Clark CC, Khorchani MJ, Zal F. Adverse Effects and Safety of Etirinotecan Pegol, a Novel Topoisomerase Inhibitor, in Cancer Treatment: A Systematic Review. Curr Cancer Ther Rev. 2021;17(3):234-43.
8. Samare-Najaf M, Zal F, Safari S, Koohpeyma F, Jamali N. Stereological and histopathological evaluation of doxorubicin-induced toxicity in female rats' ovary and uterus and palliative effects of quercetin and vitamin E. Hum Exp Toxicol. 2020;39(12):1710-24.
9. Rostami S, Azhdarpoor A, Baghapour MA, Dehghani M, Samaei MR, Jaskulak M, et al. The effects of exogenous application of melatonin on the degradation of polycyclic aromatic hydrocarbons in the rhizosphere of Festuca. Environ Pollut. 2021;274:116559.
10. Jamali N, Zal F, Mostafavi-Pour Z, Samare-Najaf M, Poordast T, Dehghanian A. Ameliorative Effects of Quercetin and Metformin and Their Combination Against Experimental Endometriosis in Rats. Reprod Sci. 2021;28(3):683-92.
11. Samare-Najaf M, Zal F, Safari S. Primary and Secondary Markers of Doxorubicin-Induced Female Infertility and the Alleviative Properties of Quercetin and Vitamin E in a Rat Model. Reprod Toxicol. 2020 S;96:316-26.
12. Jamali N, Jalali M, Saffari-Chaleshtori J, Samare-Najaf M, Samareh A. Effect

of cinnamon supplementation on blood pressure and anthropometric parameters in patients with type 2 diabetes: A systematic review and meta-analysis of clinical trials. Diabetes Metab Syndr. 2020;14(2):119-25.
13. Jamali N, Kazemi A, Saffari-Chaleshtori J, Samare-Najaf M, Mohammadi V, Clark CCT. The effect of cinnamon supplementation on lipid profiles in patients with type 2 diabetes: A systematic review and meta-analysis of clinical trials. Complement Ther Med. 2020;55:102571.
14. Li S, Jiang J, Fang J, Li X, Huang C, Liang W, Wu K. Naringin protects H9C2 cardiomyocytes from chemical hypoxia induced injury by promoting the autophagic flux via the activation of the HIF 1α/BNIP3 signaling pathway. Int J Mol Med. 2021;47(6):102.
15. Jamali N, Soureshjani EH, Mobini GR, Samare-Najaf M, Clark CCT, Saffari-Chaleshtori J. Medicinal plant compounds as promising inhibitors of coronavirus (COVID-19) main protease: an in silico study. J Biomol Struct Dyn. 2021:1-12.
16. Benameur T, Soleti R, Porro C. The Potential Neuroprotective Role of Free and Encapsulated Quercetin Mediated by miRNA against Neurological Diseases. Nutrients. 2021;13(4):1318.
17. Aihaiti Y, Song Cai Y, Tuerhong X, Ni Yang Y, Ma Y, Shi Zheng H, Xu K, Xu P. Therapeutic Effects of Naringin in Rheumatoid Arthritis: Network Pharmacology and Experimental Validation. Front Pharmacol. 2021;12:672054.
18. Benavente-García O, Castillo J. Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. J Agric Food Chem. 2008;56(15):6185-205.
19. Yonekura-Sakakibara K, Higashi Y, Nakabayashi R. The Origin and Evolution of Plant Flavonoid Metabolism. Front Plant Sci. 2019;10:943.
20. Cavia-Saiz M, Busto MD, Pilar-Izquierdo MC, Ortega N, Perez-Mateos M, Muñiz P. Antioxidant properties, radical scavenging activity and biomolecule protection capacity of flavonoid naringenin and its glycoside naringin: a comparative study. J Sci Food Agric. 2010;90(7):1238-44.
21. Jucá MM, Cysne Filho FMS, De Almeida JC, Mesquita DDS, Barriga JRM, Dias KCF, et al. Flavonoids: biological activities and therapeutic potential. Nat Prod Res. 2020;34(5):692-705.
22. Chen YC, Shen SC, Lin HY. Rutinoside at C7 attenuates the apoptosis-inducing activity of flavonoids. Biochem Pharmacol. 2003;66(7):1139-50.
23. Chen R, Qi QL, Wang MT, Li QY. Therapeutic potential of naringin: an overview. Pharm Biol. 2016;54(12):3203-10.
24. Lather A, Sharma S, Khatkar A. Naringin derivatives as glucosamine-6-phosphate synthase inhibitors based preservatives and their biological evaluation. Sci Rep. 2020;10(1):20477.
25. Şekeroğlu G, Fadıloğlu S, Göğüş F. Immobilization and characterization of naringinase for the hydrolysis of naringin. Eur Food Res Technol. 2006;224(1):55-60.
26. Wang J, Ye X, Lin S, Liu H, Qiang Y, Chen H, Jiang Z, et al. Preparation, characterization and in vitro and in vivo evaluation of a solid dispersion of Naringin. Drug Dev Ind Pharm. 2018;44(11):1725-32.
27. Gelen V, Şengül E. Antioxidant, anti-inflammatory and antiapoptotic effects of Naringin on cardiac damage induced by cisplatin. Indian J Tradit Know. 2020;19(2):459-65.
28. Hussain K, Ali I, Ullah S, Imran M, Parveen S, Kanwal T, et al. Enhanced antibacterial potential of naringin loaded β cyclodextrin nanoparticles. J Clust Sci. 2022;33(1):339-48.
29. Li P, Wang S, Guan X, Cen X, Hu C, Peng W, Wang Y, Su W. Six months chronic toxicological evaluation of

naringin in Sprague-Dawley rats. Food Chem Toxicol. 2014;66:65-75.
30. Akamo AJ, Rotimi SO, Akinloye DI, Ugbaja RN, Adeleye OO, Dosumu OA, et al. Naringin prevents cyclophosphamide-induced hepatotoxicity in rats by attenuating oxidative stress, fibrosis, and inflammation. Food Chem Toxicol. 2021;153:112266.
31. Ge X, Zhou G. Protective effects of naringin on glucocorticoid-induced osteoporosis through regulating the PI3K/Akt/mTOR signaling pathway. Am J Transl Res. 2021;13(6):6330-41.
32. Syed AA, Reza MI, Shafiq M, Kumariya S, Singh P, Husain A, et al. Naringin ameliorates type 2 diabetes mellitus-induced steatohepatitis by inhibiting RAGE/NF-κB mediated mitochondrial apoptosis. Life Sci. 2020;257:118118.
33. Zhao Y, Liu S. Bioactivity of naringin and related mechanisms. Pharmazie. 2021;76(8):359-63.
34. Lutz MW, Sprague D, Barrera J, Chiba-Falek O. Shared genetic etiology underlying Alzheimer's disease and major depressive disorder. Transl Psychiatry. 2020;10(1):88.
35. Sachdeva AK, Kuhad A, Chopra K. Naringin ameliorates memory deficits in experimental paradigm of Alzheimer's disease by attenuating mitochondrial dysfunction. Pharmacol Biochem Behav. 2014;127:101-10.
36. Thomas GEC, Leyland LA, Schrag AE, Lees AJ, Acosta-Cabronero J, Weil RS. Brain iron deposition is linked with cognitive severity in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2020;91(4):418-25.
37. Wang DM, Yang YJ, Zhang L, Zhang X, Guan FF, Zhang LF. Naringin Enhances CaMKII Activity and Improves Long-Term Memory in a Mouse Model of Alzheimer's Disease. Int J Mol Sci. 2013;14(3):5576-86.
38. Kumar A, Dogra S, Prakash A. Protective effect of naringin, a citrus flavonoid, against colchicine-induced cognitive dysfunction and oxidative damage in rats. J Med Food. 2010;13(4):976-84.
39. Prabhakar O. Naringin Attenuates Aluminum Induced Cognitive Deficits in Rats. Indian J Pharm Educ Res. 2020;54:674-81.
40. Ramalingayya GV, Nampoothiri M, Nayak PG, Kishore A, Shenoy RR, Mallikarjuna Rao C, Nandakumar K. Naringin and Rutin Alleviates Episodic Memory Deficits in Two Differentially Challenged Object Recognition Tasks. Pharmacogn Mag. 2016;12(Suppl 1):S63-70.
41. Wu BW, Guo JD, Wu MS, Liu Y, Lu M, Zhou YH, Han HW. Osteoblast-derived lipocalin-2 regulated by miRNA-96-5p/Foxo1 advances the progression of Alzheimer's disease. Epigenomics. 2020;12(17):1501-13.
42. Kaur G, Prakash A. Involvement of the nitric oxide signaling in modulation of naringin against intranasal manganese and intracerbroventricular β-amyloid induced neurotoxicity in rats. J Nutr Biochem. 2020;76:108255.
43. Kumar A, Prakash A, Dogra S. Naringin alleviates cognitive impairment, mitochondrial dysfunction and oxidative stress induced by D-galactose in mice. Food Chem Toxicol. 2010;48(2):626-32.
44. Sachdeva AK, Chopra K. Naringin mitigate okadaic acid-induced cognitive impairment in an experimental paradigm of Alzheimer's disease. J Funct Foods. 2015;19:110-25.
45. Wang D, Gao K, Li X, Shen X, Zhang X, Ma C, Qin C, Zhang L. Long-term naringin consumption reverses a glucose uptake defect and improves cognitive deficits in a mouse model of Alzheimer's disease. Pharmacol Biochem Behav. 2012;102(1):13-20.
46. Wang DM, Yang YJ, Zhang L, Zhang X, Guan FF, Zhang LF. Naringin Enhances CaMKII Activity and Improves Long-Term Memory in a Mouse Model of Alzheimer's Disease. Int J Mol Sci. 2013;14(3):5576-86.
47. Yang W, Zhou K, Zhou Y, An Y, Hu T, Lu J, Huang S, Pei G. Naringin Dihydrochalcone Ameliorates Cognitive

Deficits and Neuropathology in APP/PS1 Transgenic Mice. Front Aging Neurosci. 2018;10:169.
48. Meng X, Fu M, Wang S, Chen W, Wang J, Zhang N. Naringin ameliorates memory deficits and exerts neuroprotective effects in a mouse model of Alzheimer's disease by regulating multiple metabolic pathways. Mol Med Rep. 2021;23(5):332.
49. Estevez AO, Morgan KL, Szewczyk NJ, Gems D, Estevez M. The neurodegenerative effects of selenium are inhibited by FOXO and PINK1/PTEN regulation of insulin/insulin-like growth factor signaling in Caenorhabditis elegans. Neurotoxicology. 2014;41(100):28-43.
50. Zhao Y, Yang J, Liao W, Liu X, Zhang H, Wang S, Wang D, Feng J, Yu L, Zhu WG. Cytosolic FoxO1 is essential for the induction of autophagy and tumour suppressor activity. Nat Cell Biol. 2010;12(7):665-75.
51. Jiang X, Niu X, Guo Q, Dong Y, Xu J, Yin N, et al. FoxO1-mediated autophagy plays an important role in the neuroprotective effects of hydrogen in a rat model of vascular dementia. Behav Brain Res. 2019;356:98-106.
52. Kimura A, Hata S, Suzuki T. Alternative Selection of β-Site APP-Cleaving Enzyme 1 (BACE1) Cleavage Sites in Amyloid β-Protein Precursor (APP) Harboring Protective and Pathogenic Mutations within the Aβ Sequence. J Biol Chem. 2016;291(46):24041-53.
53. Hampel H, Blennow K, Shaw LM, Hoessler YC, Zetterberg H, Trojanowski JQ. Total and phosphorylated tau protein as biological markers of Alzheimer's disease. Exp Gerontol. 2010;45(1):30-40.
54. Saito T, Oba T, Shimizu S, Asada A, Iijima KM, Ando K. Cdk5 increases MARK4 activity and augments pathological tau accumulation and toxicity through tau phosphorylation at Ser262. Hum Mol Genet. 2019;28(18):3062-71.
55. Rabbito A, Dulewicz M, Kulczyńska-Przybik A, Mroczko B. Biochemical Markers in Alzheimer's Disease. Int J Mol Sci. 2020;21(6):1989.
56. Ben-Shushan S, Miller Y. Neuropeptides: Roles and Activities as Metal Chelators in Neurodegenerative Diseases. J Phys Chem B. 2021;125(11):2796-811.
57. Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM. Alzheimer's disease: Targeting the Cholinergic System. Curr Neuropharmacol. 2016;14(1):101-15.
58. Ahmad SS, Akhtar S, Jamal QM, Rizvi SM, Kamal MA, Khan MK, Siddiqui MH. Multiple Targets for the Management of Alzheimer's Disease. CNS Neurol Disord Drug Targets. 2016;15(10):1279-89.
59. Liu MY, Zeng F, Shen Y, Wang YY, Zhang N, Geng F. Bioguided Isolation and Structure Identification of Acetylcholinesterase Enzyme Inhibitors from Drynariae Rhizome. J Anal Methods Chem. 2020;2020:2971841.
60. Mani VM, Asha S, Sadiq AM. Pyrethroid deltamethrin-induced developmental neurodegenerative cerebral injury and ameliorating effect of dietary glycoside naringin in male wistar rats. Biomed Aging Pathol. 2014;4(1):1-8.
61. Orhan I, Kartal M, Tosun F, Sener B. Screening of various phenolic acids and flavonoid derivatives for their anticholinesterase potential. Z Naturforsch C J Biosci. 2007;62(11-12):829-32.
62. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388-405.
63. McGeer EG, McGeer PL. Inflammatory processes in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(5):741-9.
64. Burke RE, O'Malley K. Axon degeneration in Parkinson's disease. Exp Neurol. 2013;246:72-83.
65. Geibl FF, Henrich MT, Oertel WH. Mesencephalic and extramesencephalic dopaminergic systems in Parkinson's

disease. J Neural Transm (Vienna). 2019;126(4):377-96.
66. Darbinyan LV, Hambardzumyan LE, Simonyan KV, Chavushyan VA, Manukyan LP, Badalyan SA, et al. Protective effects of curcumin against rotenone-induced rat model of Parkinson's disease: in vivo electrophysiological and behavioral study. Metab Brain Dis. 2017;32(6):1791-803.
67. Islam MS, Quispe C, Hossain R, Islam MT, Al-Harrasi A, Al-Rawahi A, Martorell M, Mamurova A, Seilkhan A, Altybaeva N, Abdullayeva B, Docea AO, Calina D, Sharifi-Rad J. Neuropharmacological Effects of Quercetin: A Literature-Based Review. Front Pharmacol. 2021;12:665031.
68. Prasad EM, Hung SY. Behavioral Tests in Neurotoxin-Induced Animal Models of Parkinson's Disease. Antioxidants (Basel). 2020;9(10):1007.
69. Su CF, Jiang L, Zhang XW, Iyaswamy A, Li M. Resveratrol in Rodent Models of Parkinson's Disease: A Systematic Review of Experimental Studies. Front Pharmacol. 2021;12:644219.
70. Ay M, Luo J, Langley M, Jin H, Anantharam V, Kanthasamy A, et al. Molecular mechanisms underlying protective effects of quercetin against mitochondrial dysfunction and progressive dopaminergic neurodegeneration in cell culture and MitoPark transgenic mouse models of Parkinson's Disease. J Neurochem. 2017;141(5):766-82.
71. Panneton WM, Kumar VB, Gan Q, Burke WJ, Galvin JE. The neurotoxicity of DOPAL: behavioral and stereological evidence for its role in Parkinson disease pathogenesis. PLoS One. 2010;5(12):e15251.
72. Rasheed MSU, Tripathi MK, Patel DK, Singh MP. Resveratrol Regulates Nrf2-Mediated Expression of Antioxidant and Xenobiotic Metabolizing Enzymes in Pesticides-Induced Parkinsonism. Protein Pept Lett. 2020;27(10):1038-45.
73. Sharma S, Raj K, Singh S. Neuroprotective Effect of Quercetin in Combination with Piperine Against Rotenone- and Iron Supplement-Induced Parkinson's Disease in Experimental Rats. Neurotox Res. 2020;37(1):198-209.
74. Garabadu D, Agrawal N. Naringin Exhibits Neuroprotection Against Rotenone-Induced Neurotoxicity in Experimental Rodents. Neuromolecular Med. 2020;22(2):314-30.
75. Medeiros-Linard CFB, Andrade-da-Costa BLDS, Augusto RL, Sereniki A, Trevisan MTS, Perreira RCR, et al. Anacardic Acids from Cashew Nuts Prevent Behavioral Changes and Oxidative Stress Induced by Rotenone in a Rat Model of Parkinson's Disease. Neurotox Res. 2018;34(2):250-62.
76. Fouzder C, Mukhuty A, Mukherjee S, Malick C, Kundu R. Trigonelline inhibits Nrf2 via EGFR signalling pathway and augments efficacy of Cisplatin and Etoposide in NSCLC cells. Toxicol In Vitro. 202;70:105038.
77. Clerici S, Boletta A. Role of the KEAP1-NRF2 Axis in Renal Cell Carcinoma. Cancers (Basel). 2020;12(11):3458.
78. Tao J, Krutsenko Y, Moghe A, Singh S, Poddar M, Bell A, et al. Nuclear factor erythroid 2-related factor 2 and β-Catenin Coactivation in Hepatocellular Cancer: Biological and Therapeutic Implications. Hepatology. 2021;74(2):741-59.
79. Kim HD, Jeong KH, Jung UJ, Kim SR. Naringin treatment induces neuroprotective effects in a mouse model of Parkinson's disease in vivo, but not enough to restore the lesioned dopaminergic system. J Nutr Biochem. 2016;28:140-6.
80. Urrutia PJ, Mena NP, Núñez MT. The interplay between iron accumulation, mitochondrial dysfunction, and inflammation during the execution step of neurodegenerative disorders. Front Pharmacol. 2014;5:38.
81. Leem E, Nam JH, Jeon MT, Shin WH, Won SY, Park SJ, Choi MS, Jin BK, Jung UJ, Kim SR. Naringin protects the nigrostriatal dopaminergic projection through induction of GDNF in a

neurotoxin model of Parkinson's disease. J Nutr Biochem. 2014;25(7):801-6.
82. Gentile G, La Cognata V, Cavallaro S. The contribution of CNVs to the most common aging-related neurodegenerative diseases. Aging Clin Exp Res. 2021;33(5):1187-95.
83. Zhu Q, Qu Y, Zhou XG, Chen JN, Luo HR, Wu GS. A Dihydroflavonoid Naringin Extends the Lifespan of C. elegans and Delays the Progression of Aging-Related Diseases in PD/AD Models via DAF-16. Oxid Med Cell Longev. 2020;2020:6069354.