



Physicochemical and Diverse Biological Properties of Hesperetin: A Review

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ABSTRACT

Citrus flavonoids are flavonoids found in citrus fruits, such as oranges, grapefruits, limes, mandarins, pomelos, and bergamots. The review was based on the physicochemical and diverse biological properties of Hesperetin. It is a trihydroxyflavanone with a methoxy substituent at the 4' position and three hydroxy groups at the 3', 5', and 7' locations. It functions as a plant metabolite, an antioxidant, and an anti-tumor agent. It has effective role in the management of various neurological disorders i.e., AD, PD etc. In conclusion. Hesperetin is a naturally occurring substance with low toxicity, ease of access, and promising future development and use. It is a major focus to perform some chemical modification of Hesperetin in order to find a synthetic product with a high degree of bioavailability and good pharmacological efficacy. We may observe from earlier research that there is insufficient clinical data regarding Hesperetin's therapeutic effects. Thus, further clinical research is still required to determine the proper dosage, bioavailability, effectiveness, and safety of hesperetin and its metabolites.

Keywords: Hesperetin, physicochemical, biological activities, flavonoids, toxicity.

INTRODUCTION

Citrus fruits, including oranges, grapefruits, limes, mandarins, pomelos, and bergamots, contain flavonoids known as citrus flavonoids [1][2]. Citrus flavonoids have demonstrated a number of advantageous characteristics, such as anti-inflammatory, anti-oxidant, and anti-apoptotic actions. Hesperetin is mostly found in the juices and has been proposed to have a variety of pharmacological effects. Hesperetin has been administered intraperitoneally as well as orally. Although the frequency of administration varies greatly, it is taken for 4 weeks at 50mg/kg daily [3].

Drug profile

Polymer : Hesperetin

Description: Hesperetin is a trihydroxyflavone chemically, having three hydroxy groups at positions 3, 5, and 7, as well as an extra methoxy replacement at position 4. Hesperetin is a trihydroxyflavanone with a methoxy substituent at the 4' position and three hydroxy groups at the 3', 5', and 7' locations. It functions as a plant metabolite, an antioxidant, and an anti-tumor agent. It belongs to the classes of monomethoxyflavanone, trihydroxyflavanone, 3'-hydroxyflavanones,

and 4'-methoxyflavanones. It is the conjugate acid of hesperetin (1-). Hesperetin belongs to the family of flavonoids called flavanones [4].

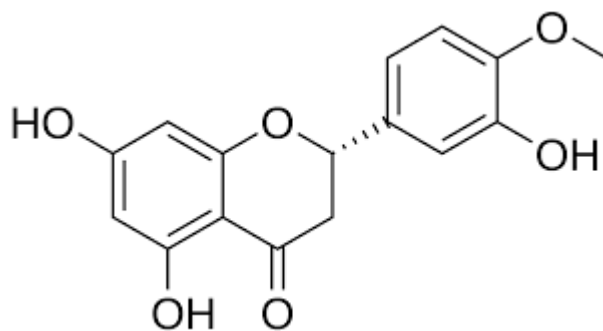


Fig 1. Structure of hesperetin

IUPAC : (2S)-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydrochromen-4-one

Log P : 2.6

Solubility : 273 mg/l

M.P. : 227.5 °C

Mol. formula: C₁₆H₁₄O₆

Mol. weight: 302.28 g/mol

Concerns about dietary flavonoid's ability to enter the CNS and pass through the blood-brain barrier are growing as interest in using them to treat oxidative stress-mediated neurodegeneration [5][6]. Flavonoids' physicochemical characteristics, including their molecular size, lipophilicity, solubility, and pKa values, determine how well they are absorbed after consumption [7]. Numerous studies have examined how flavonoids cross the blood-brain barrier, which has improved the quality of the research that has already been done [8][9]. Anthocyanin can cross the blood-brain barrier in rat and pig models, according to research on these animals [10][11][12].

Moreover, the majority of neurological diseases develop in later life, and in the next years, there will likely be an increase in the number of people suffering from conditions i.e., multiple sclerosis, PD, & AD. Even though these problems are becoming more common, it is difficult to create therapeutic approaches to treat neurodegenerative conditions, and existing neurodegeneration care is still mostly ineffective [13]. A complicated multifactorial process known as neurodegeneration results in the progressive loss of the structure and functions of brain and spinal cord neurons, which in turn leads to neuronal malfunction and memory impairment [14][15]. Neurodegenerative disorders have a number of pathophysiological causes, but the most significant ones include mitochondrial dysfunction, oxidative stress, neuroinflammation, and the buildup of aberrant proteins. [16] The development of neurodegenerative illnesses and the roles of several elements are depicted in a straightforward graphic [17].

Neurodegenerative diseases are caused by oxidative stress and neuroinflammation. Numerous causes, including as the buildup of aberrant proteins, disruptions in the equilibrium between peroxidation and polyunsaturated fatty acids, and increased Ca²⁺ trafficking throughout neurons, can result in oxidative stress [18]. Increased oxidative stress triggers a number of metabolic processes that cause oxidative damage to other components, including proteins, lipids, and DNA, which results in the death of neuronal cells and neurodegeneration [19][20]. The brain's intricate immunological response to injury causes neuroinflammation, or inflammation of the CNS, which can have major repercussions linked to neurodegenerative illnesses by activating glial cells and releasing inflammatory cytokines [21].

Phytonutrients derived from various plant sources have recently drawn more interest due to their potential to strengthen the immune system. Flavonoids are a broad collection of natural substances among phytonutrients that have been thoroughly researched for the prevention and treatment of a number of neurological illnesses [22][23][24]. Fruits and vegetables with varying phenolic structures include flavonoids. The flavonoids, which are utilized in a variety of pharmaceutical and medicinal supplements [25][26]. They can lower the concentration of compounds that actively contribute to the production of ROS, scavenge ROS, and activate antioxidant-producing enzymes.

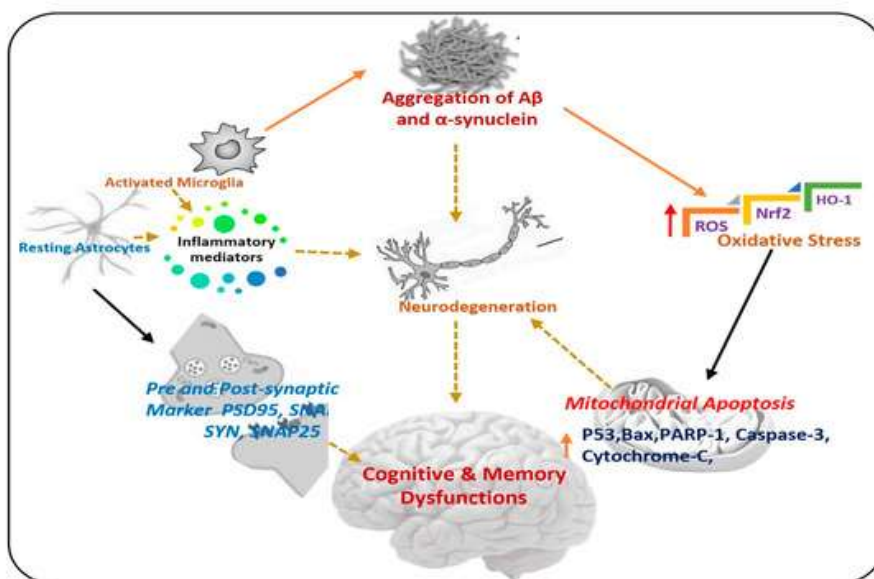


Fig 2. Pathophysiology of neurodegenerative diseases

In Chinese traditional medicine, hesperetin is a significant bioactive molecule with anti-carcinogenic and antioxidant qualities. Orange and grape juices, which contain 200-590 mg/L of hesperetin, are consumed on a daily basis. Numerous biological functions have been demonstrated by HSD and its aglycone, hesperetin. Hesperetin, for instance, has vitamin-like properties and can reduce fragility, leakiness, and capillary permeability (vitamin P) [27].

Pharmacokinetics profile

Following extraction, the absorption, distribution, and metabolism of bioactive chemicals are the other key elements that contribute to their effectiveness. Hesperetin has been shown to undergo an enzymatic process that transforms it into hesperetin 7-O-glycoside after 20 minutes of ingestion. Here, beta-glucosidase hydrolyzes the flavone aglycone in the colon or small intestine. According to a human investigation, consuming orange and grapefruit juices orally significantly raises the peak plasma concentration of hesperetin [28].

Pharmacological properties

Five million of the 6.8 million people with dementia diagnoses had Alzheimer's disease, making it the most prevalent form of dementia. Memory and cognitive loss are caused by the brain's aberrant production of amyloid-beta in AD. Increased oxidative stress, neuroinflammation, and neurodegeneration are caused by the buildup of A β . For the treatment and prevention of AD, there isn't a viable medicine at the moment. Natural antioxidants called flavonoids lower the amyloid-beta load and oxidative stress in animal models of AD [29].

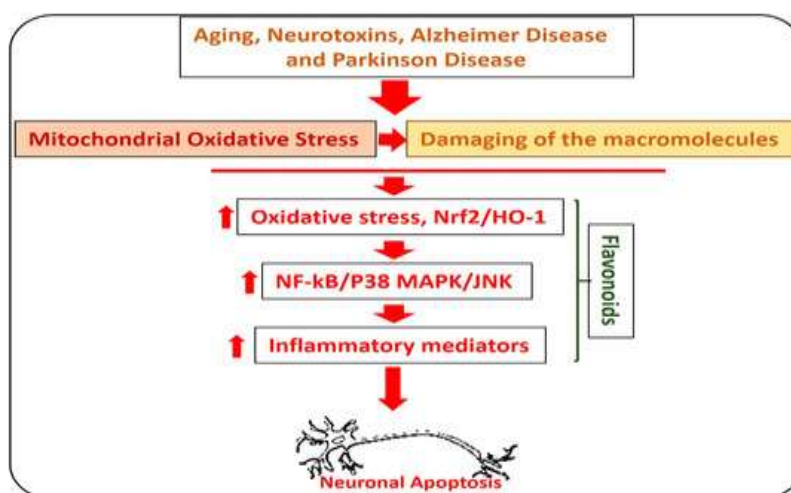


Fig 3. Flavonoids' function in the treatment of neurodegenerative illnesses

Although the precise origin of Parkinson's disease is unknown, oxidative stress, environmental pollutants, aberrant protein buildup, and α -synuclein accumulation are all contributing factors. Furthermore, studies on animals and cellular models of Parkinson's disease have demonstrated the positive benefits of berries that contain a range of flavonoids [30].

Psychiatric disorders, uncontrollable movements, dementia, and cognitive impairments are some of the symptoms of Huntington's disease (HD), another neurodegenerative illness. In terms of genetics, it is linked to the Huntingtin gene's cytosine adenine guanine trinucleotide repeat expansion. Although there is currently no cure for HD, preclinical research has revealed that a number of flavonoids, such as naringin and hesperidin in a rat model of HD, have promise protective benefits against HD [31]

In a transgenic mouse model of ALS, ginkgo biloba extract administration has also demonstrated encouraging results, improving motor function and lengthening survival time. In a mouse model of ALS, the dietary flavone genistein has also demonstrated encouraging therapeutic effects [32]. According to the aforementioned lines of evidence, flavonoids may provide neuroprotection by controlling several facets of neurodegeneration.

Alzheimer's Disease

Hesperetin's effects were examined in one study using a rat model of AD. The scientists came to the conclusion that by lowering the enhanced oxidative stress, hesperetin and hesperetin nanoparticles administered at doses of 10 & 20mg/kg for three weeks considerably improved learning and cognitive deficits. Additionally, they proposed that hesperetin nanoparticles work better than plain powdered hesperetin [33]. In a related investigation, our team assessed hesperetin's ability to prevent amyloid beta-induced AD. Gram-negative bacteria's outer membrane contains a biomolecule called LPS. A number of inflammatory genes and mediators are triggered by LPS's activation of transcription factors and targeting of the toll-like receptor [34]. We assessed hesperetin's effects using the LPS-induced neurodegenerative animal model of AD. Our results confirmed that hesperetin greatly decreased memory impairment and neurotoxicity brought on by LPS.

Parkinson's Disease

Another terrible neurological condition is Parkinson's disease. Dopaminergic neurons in the substantia nigra are lost in PD, resulting in cognitive and motor impairment. An environmental neurotoxin called 6-hydroxydopamine (6-OHDA) is utilized to cause Parkinson's disease-like symptoms in animals. Hesperetin was found to decrease oxidative stress. Additionally, they demonstrated that in the 6-OHDA-induced PD rats, hesperetin significantly decreased motor impairment [35].

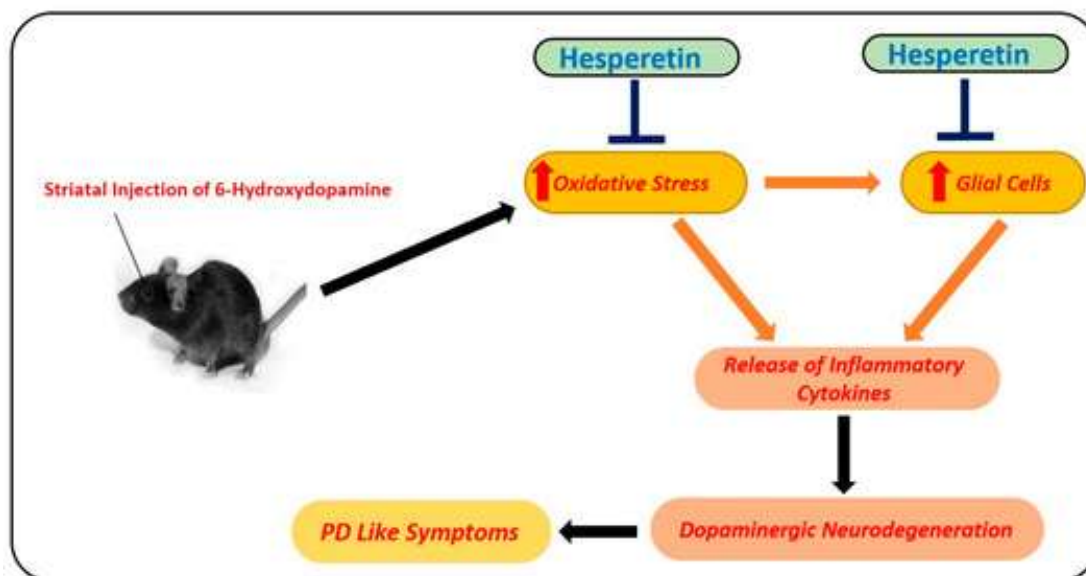


Fig 4. Hesperetin: management of PD in the mice brains

Against temporal lobe seizures

Another very common neurological condition is temporal lobe epilepsy, sometimes known as temporal lobe seizure. Temporal lobe seizures are commonly referred to as concentrated seizures with impaired awareness. In this instance, the patient remains aware of what is happening, but in severe situations, they lose their

ability to respond. The hands and lips may become motionless. Recurrent seizures have been linked to impairments in executive functioning, intellect, judgment, attention, and problem solving, according to several research. To induce seizures, kainic acid is administered to the mouse. Neuroinflammation and seizures are the main pathophysiological consequences of kainic acid. Dose-dependent oral hesperetin (5, 10, 20 mg/kg) delayed the onset of a seizure in epileptic mice by inhibiting the proinflammatory kinases in the hippocampus [36].

Against Ischemic-Reperfusion Injury

The acceleration of cellular death and loss of function once blood supply to ischemic cells is restored is known as ischemia-reperfusion injury (IRI). For the ischemic tissues to heal, blood flow must be restored. Nevertheless, this reperfusion damages the organ more, disrupting its normal function and compromising its viability [37]. The mice were given either water-soluble hesperetin (0.3ml, 200mg/kg/day) or normal saline (NS, 0.3ml/day) to assess the effects of hesperetin against ischemia-reperfusion (I/R) injury. Furthermore, by downregulating microglial cells like Iba-1, hesperetin lessened the inflammatory consequences [38].

Against Cd-Induced Neurodegeneration

Cadmium is a heavy metal and environmental pollutant that accumulates in the bodies of both humans and animals. An accumulation of cadmium can change the permeability of the blood-brain barrier, causing oxidative stress and neurodegeneration, among other health problems. The scientists tested the effects of hesperetin (40 mg/kg) on cadmium-induced neurotoxicity and memory impairment in rats over a three-week period. [39].

Cellular Models of Neurodegeneration

Serine/threonine kinases, ERK1 and ERK2, are involved in the regulation of several activities, such as RNA production and processing, immunological responses, cell proliferation, apoptosis, and nervous system function [40]. Hesperetin significantly raised the level of ERK1/2 phosphorylation in a dose dependent manner [41][42]. In PC12 cells, H₂O₂ produces cytotoxicity, which results in cell damage, decreased mitochondrial membrane potential, decreased levels of antioxidant enzymes like glutathione peroxidase and catalase, cytochrome C release into the cytosol, caspase-3 activation, reactive oxygen species, and glutathione depletion. It's interesting to note that hesperetin treatment dramatically reduced these effects [43]. The results showed that the increased oxidative stress and mitochondrial dysfunction were restored by hesperetin. At varying concentrations, hesperetin protected over half of the cells among the seven flavonoids that were utilized. Additionally, it was observed that hesperetin had no action against CK-1 δ and medium potency against GSK-3 β , indicating the necessity for more thorough research.

Hesperidin and hesperetin treatments of the cortical rat neuronal cells treated with H₂O₂ and l-glutamate had comparable outcomes. The results demonstrated that hesperetin outperforms hesperidin as an antioxidant [44]. Hesperetin may shield neuronal cells from neurodegeneration based on the different pharmacological activities shown in these research. Hesperetin's effectiveness against both in vitro and in vivo neurodegenerative disease models is supported by the in vitro results.

Anti-oxidative

In the treatment of neurodegenerative diseases, agents that combat high ROS levels are gaining the most attention [45]. Numerous substances that are natural or derived from plants are currently demonstrating effectiveness in the treatment of neurodegenerative diseases [46]. via scavenging the raised ROS and enhancing the body's natural antioxidant defense systems, hesperetin has demonstrated remarkable antioxidant effects. Hesperetin was used in a prior work to relieve oxidative damage that H₂O₂ had caused in RPE-19 cells [47]. By strengthening the antioxidant system and reducing lipid peroxidation, the results demonstrated that orange juice and hesperetin protected oxidative stress [48]. Another study used sodium selenite (20 μ mol/kg body weight) to cause cataracts in rats, after which the rodents were given hesperetin injections. Despite having less of an impact on systemic antioxidant levels, the results indicated that hesperetin and its derivatives decreased oxidative stress in the cataract lens [49][50][51]. Mice treated with 7,12-dimethylbenz (a) anthracene (34mg/kg in maize oil twice a week for 2 weeks) showed similar results when given hesperetin (10 & 50mg/kg for 5 weeks). In this case, hesperetin significantly decreased the amount of protein oxidation and lipid peroxidation [52][53]. Overall, the results point to hesperetin as a potent antioxidant flavonoid that may alleviate oxidative damage by lowering high oxidative stress.

Anti-neuroinflammatory

The primary cause of the development of neurodegenerative diseases is inflammation [54]. Numerous cells, including activated microglia and astrocytes, are involved in the process of neuroinflammation. Various investigations have been carried out thus far to emphasize the anti-inflammatory properties of hesperetin. Hesperetin's ability to prevent amyloid beta-induced neuroinflammation and neurodegeneration was examined in one study. All of our research points to hesperetin lowering AB-induced oxidative stress, which in turn lowers activated astrocytes and microglial cells [55][56].

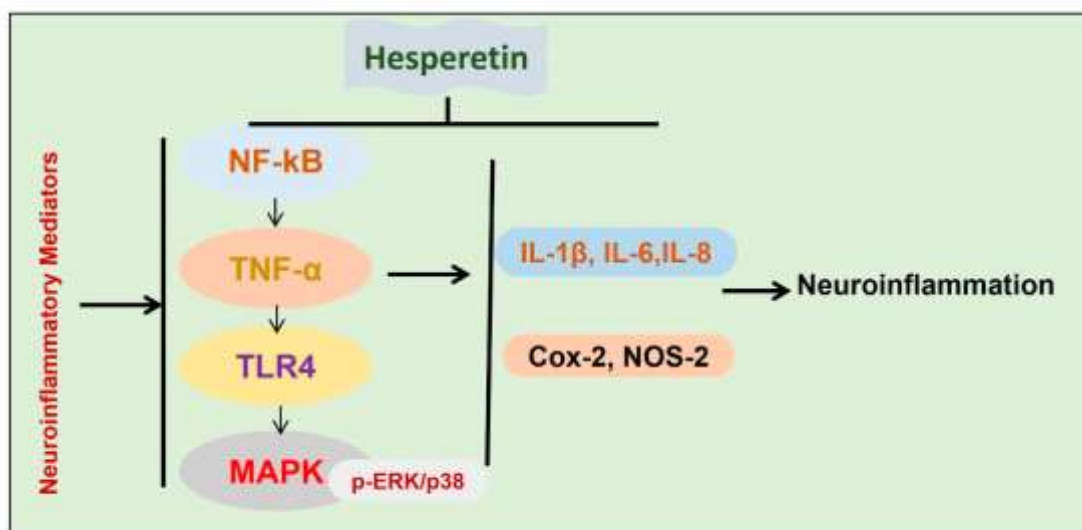


Fig 5. Hesperetin as anti-inflammatory agent to combat neurodegenerative diseases

Overall, the results showed that hesperetin may have neuroprotective benefits in neurodegenerative disease models against activated inflammatory mediators.

CONCLUSION

There is a connection and interaction between oxidative stress and the inflammatory response. Oxidative damage is exacerbated by inflammation, which is brought on by oxidative stress and raises ROS production. Through the elimination of ROS and free radicals, hesperetin improves cellular antioxidant defense. Through p53, hesperetin prevents cancer cells from going through the G1/S phase. Recent research has demonstrated the antiviral, antibacterial, antifungal, and antiparasitic properties of hesperetin and hesperidin. While their precise mode of action remains unclear, a number of theories have been put up, including interference with microbial enzymes, breakdown of bacterial membranes, and activation of the human immune system.

In conclusion. Hesperetin is a naturally occurring substance with low toxicity, ease of access, and promising future development and use. It is a major focus to perform some chemical modification of Hesperetin in order to find a synthetic product with a high degree of bioavailability and good pharmacological efficacy. We may observe from earlier research that there is insufficient clinical data regarding Hesperetin's therapeutic effects. Thus, further clinical research is still required to determine the proper dosage, bioavailability, effectiveness, and safety of hesperetin and its metabolites.

CONFLICT OF INTEREST

Authors declare for none conflict of interest.

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