WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review: Beneficial Effect of Naringenin in Neurological Disorders

Pratibha B. Bembde [a*], Vaishnavi V. Karekar [a], Swaliha I. Patel [b], Shubhangi H. Gosavi [c], Ankita V. Sharma [d], Sarita B. Soni [e], Mr. Prashant D. Mali [f]

[a,b,c,d,e,f] *Sinhgad College of Pharmacy Vadgaon (B.K) Pune, 411046, India*

A B S T R A C T

Neuropathological diseases and brain aging are primarily caused by neurodegeneration. Cerebrovascular and neurodegenerative diseases account for around 2/1000 of all deaths worldwide and have a mortality rate of about 8%. Effective management of these neurological disorders continues to be a global challenge despite a variety of medicines. Thus, An important class of natural polyphenolic substances known as flavonoids has been shown to have beneficial impacts on neurological diseases. It's intriguing to note that due to flavonoids' safety, improved pharmacokinetic profile, improved ability to cross the blood-brain barrier, cost-effectiveness their significance in treating various neurological illnesses has gained more attention. In this review, we have focused on the Naringenin's therapeutic potential as a neuroprotective drug. The overall neuroprotective properties of naringenin are reviewed, as well as many potential underlying processes. This major goal was to consider advancements in knowledge of the molecular mechanisms behind the creation of naringenin as a possible drug for neuroprotection.

Keywords: Anti-inflammatory, Anti-oxidant, Depression, Neuro-protective, , Naringenin.

1. Introduction:

Plants have been used by humans for a variety of purposes, including food and medicine, since antiquity. Many of today's pharmaceuticals are derived from natural sources. Natural products are high in phytochemicals, such as polyphenols, which are classified into flavonoids, lignans, stilbenes, and phenolic acids. Which provide a pool of antioxidants for long-term health. Plants are the source of more than 25% of drugs prescribed globally, and 121 active phytoconstituents are used to treat a variety of disorders (Dk et al., 2011),(Patel et al., 2011). Despite not being classified as nutrients, flavonoids are important components of the human diet in addition to their physiological roles in plants.

The term flavonoid is derived from the Latin word "flavus", meaning yellow. Flavonoids, which are primarily natural pigments, are found primarily in plants. Flavonoids are phytochemicals derived from plants that are responsible for the various colours of plant parts, such as yellow, orange, and red in flowers. More than 4,000 flavonoids, including flavanols, flavones, flavanols, flavanonols, flavanones, and isoflavones, have been identified in edible plants and are consumed on a regular basis (Galluzzo et al., 2015). Flavonoids have the same basic skeleton, the flavan- nucleus, which consists of two aromatic rings with six carbon atoms (rings A and B) connected by a hetero cycle with three carbon atoms (ring C) (Peng, Wang and Ren, 2005),(Lei et al., 2009),(Procházková, 2010),(Schijlen et al., 2004). Flavonoids, which are found in fruits and vegetables, have a number of health benefits (Han et al., 2008).

Among these, naringenin has recently received a lot of attention because several studies have suggested that several of its biological properties are medicinally important (Patel, Singh and Patel, 2014). Naringenin (4',5,7-trihydroxyflavonone) can be found primarily in citrus fruits (grapefruit and oranges) and tomatoes. It is derived from the aromatic amino acid phenylalanine and has been discovered in various conjugated forms, most notably as aglycone, neohesperidoside, and glycosylated forms. Naringenin is found in abundance in grapefruit and is used in perfumery, cosmetics, and various pharmaceutical formulations. It has hypocholesterolemic, antiestrogenic, hypolipidemic, antihypertensive, and anti-inflammatory properties (Bernini et al., 2003).

Neurodegeneration is the fundamental cause of both neuropathological disorders and brain aging. The most common causes of death worldwide are cerebrovascular and neurodegenerative illnesses, with a frequency of roughly 2/1000 and an approximate 8% global mortality rate (The et al., 1998). Devastating conditions include Alzheimer's disease, cerebrovascular impairment, dementia, seizure disorders, head injuries, and Parkinsonism can result from neuropsychiatric and neurodegenerative illnesses (Commenges et al., 2016). Neuroprotection refers to the methods used to protect the central nervous system against neuronal damage brought on by both acute and long-term neurodegenerative diseases (Kumar, 2016). The potential of flavonoids to induce antioxidant effects has been attributed to their ability to affect intracellular redox status or their ability to scavenge free radicals (Acids, 1996),(Vauzour, Paul and Spencer, 2007).

The bioactivity of flavonoids in vivo, particularly in the brain, where they are only found in very low concentrations, has been theorized to be unrelated to this conventional hydrogen-donating antioxidant activity (Vauzour et al., 2008). As an alternative, it has been suggested that their effects on the brain are influenced by their capacity to trigger neurogenesis, protect fragile neurons, and encourage neuronal regeneration. It is undeniable that flavonoids can have neuroprotective effects (at low concentrations) through their interactions with crucial neuronal intracellular signalling pathways that are crucial for regulating neuronal survival and differentiation, long-term potentiation (LTP), and memory (Biology, 2004)(Spencer, 2009).

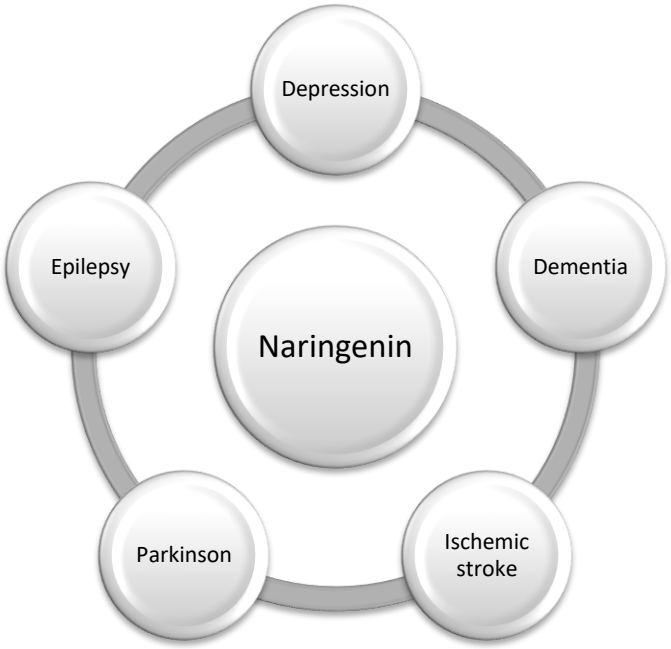

Fig. 1 Neuro-pharmacological properties of naringenin.

Because of its powerful anti-oxidant and anti-inflammatory properties, naringenin has been shown in several studies to protect against a variety of neurological disorders. It has been shown to be helpful in the treatment of dementia (Prabhu and Prabhu, 2020), epilepsy (Mag et al., 2017), Parkinson's disease (Zbarsky et al., 2005), antidepressant effects (Yi et al., 2014), and ischemic stroke (Ren et al., 2019). (Fig.1). The purpose of this chapter is to present the neuroprotective effects of naringenin against various neurological disorders, as well as to describe the mechanism of naringenin's neuroprotective action.

2. Chemistry of Naringenin:

Naringenin is a flavanone that is found primarily in fruits (grapefruit and oranges) and vegetables. It has anti-cancer, anti-mutagenic, anti-inflammatory, anti-oxidant, anti-proliferative, and anti-atherogenic properties. Naringenin is a flavonoid that is thought to have a bioactive effect on human health. It is the most abundant flavone in grapefruit. A number of epidemiological studies (Weintraub, Yost and Rouseff, no date),(Cavia-saiz et al., 2010),(Choi et al., 1991),(Dou et al., 2013) have suggested an inverse relationship between flavonoid intake and oxidation effect. The chemical formula for Naringenin's molecular formula is 2, 3-dihydro-5, 7- dihydroxy-2-(4-hydroxyphenyl) - 4H-1- benzopyran-4-one (Figure 1). (C15 H12 O5). Naringenin is insoluble in water but soluble in organic solvents like alcohol. Naringenin is produced by hydrolysing glycone forms of this flavanone, such as naringin or narirutin (Madrigal-santillán et al., 2014). Naringin (naringenin-7-rhamnoglucoside), the bitter principle of grapefruit (Citrus paradisi), is found in the fruit's juice, flower, and rind and accounts for up to 10% of the dry weight. Naringin and other naringenin glycosides can be found in a variety of other foods and supplements (Disposition, 1995).

Naringenin's general chemical composition and atom arrangement are shown in Fig.2 Naringenin is made up of a distinctive 15 carbon skeleton that is linked together by three ring configurations. The chemical formula for naringenin is $C_{15}H_{12}O_5$, and its IUPAC name is (S)-5, 7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one. White crystalline powder, naringenin is soluble in all organic solvents and has a melting point between 3450°C and 3500°C. It is nearly insoluble in water. The flavonoid skeleton of ring "C" lacks the double bond between the carbon atoms at positions 2 and 3 that included in flavones and flavonols. The ring "C" has a hydroxyl group at position 4’ and is joined to the ring "B" at carbon position 2 with carbon position 1’. In contrast, the naringenin structure contains two additional hydroxy groups at carbon positions 5 and 7. At position 4 of the carbon atom, there is also one carbonyl group. As the centre of asymmetry (epimeric centre) in the structure of naringenin, carbon position 2 is capable of forming two stereoisomeric forms, both of which are referred to as 5,7,40-trihydroxyflavanone. Because the enzymatic activity catalysing the conversion of chalcones to flavanones is stereospecific [33, 34], the majority of the naringenin isolated from plants is in laevorotatory (Hollman and Hollman, 2009), (Kim et al., 2020)—or (2S)-flavanones.

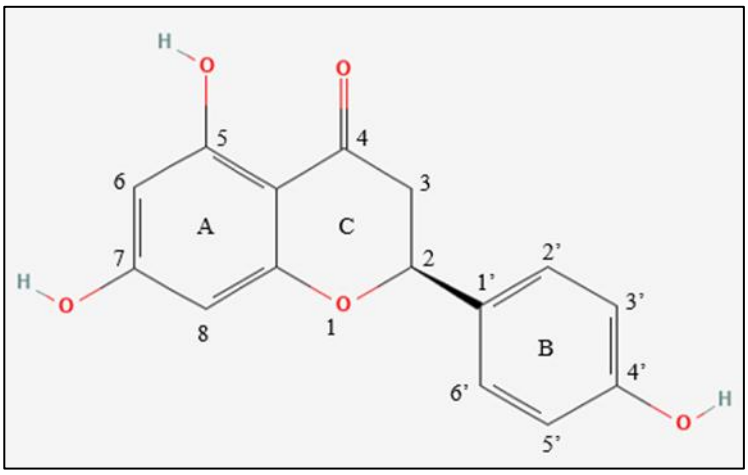

Fig. 2 The chemical structure and atom numbering for naringenin.

3. Properties of Naringenin:

Naringenin is also present in trace amounts in tomatoes and tomato-based products. Naringenin chalcone, which is transformed into naringenin during the production of tomato ketchup, is also present in fresh tomatoes, particularly tomato skin (Krause, 1992). Different flavonoids have a variety of biologic functions, according to in vitro research. These research have primarily used flavonoid glycosides or aglycones. Flavonoid metabolites were infrequently employed up until relatively recently, mostly due to the lack of information regarding their identity and the commercial availability of chemical standards for just a small number of possible metabolites (Erlund et al., 2018).

4. Source and Occurance of Naringenin:

Naringenin is present in citrus fruits like grapefruits (115–384mg/L), sour orange (>100mg/L), tart cherries, tomatoes (0.68 +/-_0.16mg/100g), Greek oregano (Vallverdú-queralt et al., 2013). It can also be found, though in smaller amounts, in bergamot, chocolate, water mint, Drynaria, and beans (Yang, Kuboyama and Tohda, 2017). Nearly all citrus fruits contain flavonoids, which are mostly obtained by dietary intake. However, the concentrations vary depending on the kind and variety of the fruit, the time of harvest, and the environmental conditions. The concentration of enzymes involved in biosynthesis determines the amount of naringenin in different parts of the fruit (Weintraub, Yost and Rouseff, no date).

Name of source	***Amount***
Citrus aurantium	*19.7µg/mL*
Citrus reticulata	*3383.6µg/mL*
Citrus clementina	*8.0µg/mL*
Citrus bergamia	*22.3µg/mL*
Citrus paradisi	*230.0µg/mL*

Table 1:- Dietary sources of naringenin.

The maximum concentration is seen in the solid tissues, whereas juice also includes some flavanones. The primary flavonoid in grapefruits, oranges, and tomatoes is naringin (Naringenin-7-neohesperidoside). There is also a trace quantity of naringenin in tomatoes. The first reports of naringenin came from grapefruit leaves and celery seeds. When tomato ketchup is made, the naringenin-chalcone found in tomato skin is transformed into naringenin (Erlund et al., 2018). Intestinal bacteria convert naringenin from its inert form, "Naringin," into the active form, "Naringenin" (Mag et al., 2017). Naringenin distribution varies throughout the fruit depending on the levels of biosynthetic enzymes present.

5. Bioavailability, Safety and Toxicity of Naringenin:

With different subgroups and compounds, the bioavailability of flavonoids changes dramatically. This is mostly because of variations in their chemical properties, such as polarity, etc. Additionally, analytical techniques that enable the precise estimation of bioavailability analysis of flavanones like naringenin have just lately been accessible. The amount of naringenin found in the urine of six people in the study by Fuhr and Kummert (Disposition, 1995) ranged from 5 to 59%, but other studies found urine concentrations of 5% (Weintraub, Yost and Rouseff, no date), 14 to 15% (Lee and Reidenberg, 1998), and 1-6% following a single intake of an average 500 mg of naringenin in juice or as a supplement. Naringenin's renal clearance is also reported

to be dose-dependent (Manach, Morand and Re, 2003). Naringenin's plasma availability was dramatically reduced if administered after an overnight fast, to the point where the existing analytical techniques were unable to detect it. Along with physiological variables like body weight, composition, gastrointestinal motility, etc., the bioavailability also varies depending on molecular variables like the enzymes participating in the biotransformation process. In the study by (Erlund et al., 2018), naringenin demonstrated good bioavailability from grapefruit and orange juices, exhibiting a plasma concentration of 0.6 + 0.4 umol/L from orange juice and 6.0 + 5.4 umol/L from grapefruit juice after 24 hours of ingestion. However, inter-individual variation in bioavailability was quite striking. The data from the study by Felgines et al. (Ibrahim et al., 2011) on the bioavailability of naringenin and its glycosides in rats demonstrated that the flavanones are efficiently absorbed after feeding to rats and that their bioavailability is related to that of their glycosidic counterpart.

6. Neuroprotective Effects of Naringenin:

6.1:- Effects of Naringenin as an Antioxidant:

Cells are negatively affected by oxidative stress in one of two ways: either by losing some of their natural ability to fight off free radicals or by producing more of them. These oxidants, also known as reactive oxygen species, lead to cell degeneration by oxidising lipids, proteins, and nucleic acids that are already present in the cell. Numerous plant extracts have strong anti-oxidant properties against the oxidative environment that has been produced inside the cell. Citrus fruits contain a variety of chiral isoforms of naringenin, which has numerous advantageous qualities including anti-oxidation, hepatoprotection, and anti-inflammation. Molecular pathways, however, are still in their infancy. In mice with streptozotocin-induced diabetes, naringenin significantly increased the activity of the pancreatic antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione-S-transferase as well as the levels of the plasma antioxidant profile, including reduced glutathione, vitamin C, and vitamin E (Dharan, Thomas and Geraldine, 2012). Rats fed naringenin and its metabolites, such as -hydroxyphenylpropionic acid (PHPP) and -hydroxybenzoic acid, showed a considerable increase in the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx). Additionally, these derivatives had a strong hypocholesterolemic impact and decreased hepatic and plasma thio-barbituric acid reactive substances (TBARS), which indicated that they had an anti-lipid peroxidative activity (Li et al., 2013). Any substance that could lessen liver and kidney damage can be a good candidate for treating lead toxicity. Lead toxicity mostly has harmful effects on the kidney and liver. By raising the levels of reduced glutathione, superoxide dismutase, catalase, and glutathione peroxidase in rat kidney and liver homogenates, lead-induced oxidative stress was significantly attenuated. A study was recently conducted to clarify the chemical mechanism underlying naringenin's antioxidation property in intestinal cell lines. The higher amounts of miR-17-3p had an impact on the target mRNA levels of two antioxidant enzyme genes, manganese-dependent superoxide dismutase (MnSOD) and glutathione peroxidase 2 (GPx2), according to a micro- RNome investigation in an intestinal cell line (Caco-2) (Curti et al., 2017).

Therefore, naringenin's antioxidative and anti-inflammatory activities may be caused by an epigenetic response on the antioxidative enzymes. Naringenin has a strong anti-oxidative stress-relieving capacity, which helps to ameliorate the neuro- behavioural abnormalities that result from social defeat stress (SDS) in mice. On the induction of SDS, it was observed that excessive acetylcholine release and inflammatory cascade activation result in behavioural abnormalities. The increased levels of tumour necrosis factor (TNF-Alpha), interleukin-1 (IL-1), malondialdehyde (MDA), and acetylcholinesterase (AChE) activity in the brain tissues, however, were able to be reduced by naringenin (Jarikr, Orhode and Aderibigbe, 2020). Naringenin administration in SDS mice was accompanied by a decrease in lipid peroxidation as indicated by MDA concentrations and an increase in GSH (reduced glutathione) levels. Pesticides have a negative impact on brain tissue, leading to neurotoxicity and neuronal cell death. Carbaryl, like many other herbicides containing carbamates, inhibits acetylcholinesterase's to cause ongoing neuroexcitation. Carbaryl causes a cascade of cell apoptosis and raises ROS. By using the DCFH-DA (20,70-dichlorofluorescein-diacetate) assay, naringenin has been reported to inhibit the production of reactive oxygen species (ROS) (Prakash et al., 2013). While upregulating the anti-apoptotic gene Bcl2 and downregulating the apoptosis-related enzymes BAX and Caspase-3, it could protect the mitochondrial membrane's integrity and membrane potential. Therefore, naringenin's antioxidative function may aid in reducing pesticide and insecticide toxicities, which are rather common in today's society. By upregulating ROS production, which causes biological molecules to be oxidised, iron causes neurotoxicities. It also increases calcium overload by activating calcium channels. In iron-treated rats, naringenin co-administration increased the antioxidative profile by increasing non-enzymatic antioxidants like total thiols and ascorbic acid as well as enzymatic antioxidants like superoxide dismutase and catalase, with a concomitant increase in the activity of acetylcholinesterase and Na+/K+ ATPase in the cerebral cortex (Fetoui and Gdoura, 2014). On naringenin administration, there was also a reversal of histomorphological changes in the cerebral cortex. Since iron-mediated neurotoxicity was being attenuated, the rise in antioxidative state revealed crosslinks.

6.2:- Effect of Naringenin on Depression:

Depression is a form of extreme nervous tension that is steadily becoming more prevalent around the world. There are sporadic periods of mood swings, anhedonia, abnormal sleep and movement patterns, energy deficits, digestive system problems, etc. Depression is thought to have an underlying etiology that involves inhibition of noradrenergic (NE), dopaminergic (Patel, Singh and Patel, 2014), and serotonergic (5-HT) neurons in the brain. The therapeutic action of phytochemicals such polyphenols, flavonoids, and others as antidepressants has been thoroughly investigated. In an experimental mouse model administered serotonin and noradrenaline inhibitors, the antidepressant effects of the flavonoid naringenin were determined, and the neuropharmacological mechanism was examined. When compared to the control group, naringenin significantly improved outcomes through the noradrenergic and serotonergic systems in the brain (Patel, Singh and Patel, 2014). The same group also elaborated the mechanism of naringenin action and showed that brain-derived neurotrophic factor (BDNF) regulates the anti-depressant like the action of naringenin in chronic unpredictable mild stress.

It was further proved that the antidepressant action of naringenin was completely inhibited by an inhibitor of BDNF receptor tropomyosin related kinase receptor B (TrkB) (Yi et al., no date). Another study states the mechanism of antidepressant action of naringenin to be mediated by elevation of serotonin (5-HT), nor-epinephrine, brain- derived neurotrophic factor (BDNF) and glucocorticoid receptors (Bahramsoltani et al., 2015). Decreased immobility time only in the mouse tail suspension test in naringenin treated groups might be via noradrenergic and serotonergic pathways. Naringenin's antidepressant effects have been attributed, in part, to its ability to reduce neuroinflammatory damage to glial cells by blocking proinflammatory mediators including the STAT-1 transcription factor and p38 signalling cascades. According to the research done by Stafford et al. (Stafford et al., 2008), naringenin has been demonstrated to traverse the blood-brain barrier (BBB) and exercise its effects on the central nervous system. This means that it has some affinity for benzodiazepine site $GABA_A$ receptors.

6.3:- Effects of Naringenin on Epilepsy:

Epilepsy is a neurological condition characterised by episodes of epileptic seizures. It can be brought on by a variety of conditions, including hypertension-related strokes, brain tumours, meningitis, brain abscesses, hyperpyrexia, allergies to specific medications, and hereditary susceptibility. Status epilepticus, a type of ongoing seizure, is often brought on by an increase in oxidative and nitrosative stress or by a drop in ATP levels in brain cells, which causes neuronal deterioration. Naringenin significantly reduced oxidative stress and elicited an antiepileptic response in the pilocarpine-induced epileptic model (Mag et al., 2017). The treatment of naringenin to these rats resulted in behavioural parameters characterised by a decrease in the frequency and intensity of seizures and a return of the normal histoarchitecture of the dentate gyrus and hippocampus. The antioxidative enzymes SOD, glutathione reductase (The et al., 1998), and catalase (Ibrahim et al., 2011) were restored upon naringenin treatment, and TBARS content was decreased. Naringenin is a possible candidate for treating epileptic shocks since it is known to pass the blood-brain barrier fast and effectively (Pinho-ribeiro et al., 2016). Naringenin produced an antioxidative impact, an elevation of GABA receptor-mediated action, and a concurrent downregulation of glutaminergic activity in pentylenetetrazole-induced seizures. These effects resulted in a notable decrease in seizure duration and mortality (Khodayar et al., 2017). The duration of hind limb tonic extensions was reduced by 200 mg/kg body weight of naringenin, demonstrating the anticonvulsant impact of this substance. Naringenin reduced excitatory neurotransmission by inhibiting the activity of kainic acid (Park et al., 2016) receptors. Status epilepticus is indicated by morphological changes involving granule cell dispersions in the dentate gyrus of the hippocampal region. Granule cell dispersions are reduced after naringenin treatment (Ross and Kasum, 2002). Treatment of epilepsy-induced morphological changes may be due to naringenin's inhibitory action on the release of pro-inflammatory cytokines such tumour necrosi1s factor (TNF), interleukin-1 (IL-1), and mammalian target of rapamycin complex 1 (mTOR).

6.4:- Effect of Naringenin on Amyloidosis:

Amyloidosis is characterised by an increase in protein amyloid (A) deposits that disrupt calcium-mediated signalling and increase oxidative stress, resulting in death in a variety of organs, including nerve tissues. Numerous neurological conditions, including Parkinson's disease, Huntington's disease, cerebral amyloid angiopathy, and Alzheimer's disease (AD), are brought on by an elevated A level. Inducing neuronal death in nerve cell lines (PC12) is brought on by an increase in ROS generation that results in lipid peroxidation. By scavenging free radicals, naringenin from *Citrus junos* stops PC12 cells from producing A. As a result, it halts neuronal degeneration in numerous disorders, including AD (Chem, 2004). The hallmarks of Alzheimer's disease include dementia and a decline in learning and cognition. Animals treated with naringenin have improved behavioural impairments following A protein injections. Animals treated with naringenin (Ghofrani, Joghataei and Mohseni, 2015) demonstrated noticeably increased performance on memory and recognition tests such the Y-maze task, passive avoidance test, and radial arm maze (Bahramsoltani et al., 2015). Naringenin administration significantly reduced hippocampal levels of malondialdehyde (MDA), which links the antioxidative activity to treating AD. Memory and cognition are severely impacted by AD, and naringenin treatment significantly improves learning ability in AD model animals. The expression of amyloid 40, 42, and a decrease in tau protein phosphorylation are all significantly downregulated (Yang, Ma and Liu, 2013). Additionally, oxidative stress is lessened as evidenced by a decrease in MDA concentration and an increase in SOD activity. Scopolamine is used to generate amnesia, namely as a model for Alzheimer's disease, in experimental investigations on dementia and to determine the antiamnestic action of particular substances. In both people and animals, scopolamine causes aberrant learning and behaviour by acting as an anticholinergic drug. Scopolamine-induced behavioural, histomorphological, and neurochemical alterations are responsive to naringenin's anti-amnesia and antidementia properties. By reducing the activity of Acetylcholinesterase's, Naringenin reversed the aberrant scopolamine-induced behavioural alterations that occurred simultaneously with an increase in the neurotransmitter acetylcholine (Prabhu and Prabhu, 2020). Naringenin's antioxidative impact in brain tissues, as evidenced by decreased lipid peroxidation and increased GSH content, may also help to protect against neuroinflammatory behaviours by TNF-dependent signalling (Prabhu and Prabhu, 2020). Streptozocin is known to promote neurodegeneration at sub-diabetogenic levels and acts as a model for Alzheimer's disease. Streptozotocin injection intracerebroventricularly alters behaviour and increases oxidative stress. The antioxidative profile of these cells could be restored by naringenin, and the production of the cholinesterase enzyme in the neurons could be restored (Khan et al., 2012). It is necessary to do additional research to clarify the molecular neuroprotective mechanisms involved in naringenin's ability to reverse neurodegeneration. The effectiveness of naringenin as a prospective medication for the treatment of cognitive deficits needs to be examined. Another chronic neurological disease, Parkinson's disease exhibits dementia, depression, a slowing of the initiation of voluntary movements, and sleep problems. In Parkinson's disease, amyloid plaques are frequently present. The degradation of dopaminergic neurons, an increase in free radicals, and an inhibition of mitochondrial respiration are all brought on by 6-hydroxydopamine. This antidopaminergic action is identical to that seen in Parkinson's disease. Naringenin significantly raised the amounts of dopamine and tyrosine hydroxylase positive cells in the 6-hydroxydopamine-induced PD model (Zbarsky et al., 2005). This results in neuroprotection in the substantia nigra, which may be caused by naringenin's capacity to function as a strong antioxidant and reduce oxidative stress. However, much more research is required to understand the underlying molecular mechanism. None of the medications that are now on the market can stop the brain degradation brought on by these illnesses, and

the rising prevalence of dementia is a grave concern. These ailments are becoming more prevalent, and naringenin, which has potent anti-inflammatory and cytoprotective properties, may be able to help. In the neurodegenerative model of Alzheimer's disease, Yang et al. (Yang, Ma and Liu, 2013) investigated the preventive effects of naringenin against elevated levels of Amyloid beta (AB). Treatment with naringenin improved learning and memory functions and elevated insulin and insulin receptor mRNA expression in the cerebral cortex and hippocampus. In addition, streptozotocin-induced tau hyperphosphorylation in the cerebral cortex and hippocampus was reversed by naringenin. Additionally, naringenin greatly reduced the levels of amyloid beta in the brain, which had increased in STZ-treated mice. And the brain's enhanced expression of inulin and insulin receptors was the cause of this.

6.5. Effect of Naringenin on Neuroinflammatory Diseases:

Dementia and cognition response dysregulation are caused by neuroinflammation in the central nervous system, which is caused by microglial activation (CNS). Many autoimmune diseases, including autoimmune encephalomyelitis, are common in humans. Alternative herbal medicine, in addition to conventional treatments, can help to improve such disorders. On naringenin feeding, there was a reduction in pro-inflammatory mediators such as CD4 T class of cells such as Th1, Th9, and Th17 cells as well as their associated transcription factors T-bet, PU.1, and RORt. There was also less cell infiltration in the CNS and lymph nodes, as well as less demyelination of spinal tissue. Naringenin's anti-inflammatory and antioxidant properties may aid in its neuroprotective abilities. LPS is responsible for inducing inflammation in tissues, including nervous tissue. In an animal model, the protective effect of naringenin against LPS-induced cognitive failure was investigated. Naringenin reduced MDA synthesis while increasing catalase, SOD, and glutathione (GSH) synthesis and improving spatial response as measured by object discrimination and passive avoidance tests. Naringenin's ability to reduce neuroinflammation could be attributed to its ability to inhibit the release of proinflammatory substances such as TNF-Alpha, cyclooxygenase-2 (COX2), nuclear factor-kappa B (NF-kB), toll-like receptor 4, inducible nitric oxide synthase (iNOS), and glial fibrillary acidic protein (GFAP) (Khajevand-khazaei, Ziaee and Motevalizadeh, 2018). Furthermore, a decrease in AChE activity was observed, which may aid in the reduction of excitotoxicity during neuroinflammation. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a key regulator of antioxidative response, was also increased following naringenin treatment, indicating that reducing oxidative stress is responsible for preventing neuroinflammation and neuronal degeneration. Naringenin can be used to treat amnesia in Alzheimer's disease by inhibiting the release of acetylcholine from nerve endings. Naringenin from *Citrus junos* inhibits the enzyme acetylcholinesterase, alleviating amnesia caused by scopolamine as measured by passive avoidance and the Y-maze test (Chem, 2004). The molecular mechanism by which naringenin produced neuroprotection has received less attention. MiRNome studies have revealed that miR-223 plays a dominant role in granulocyte activation, production, and migration in response to inflammatory stimuli. Naringenin treatment significantly reduced the expression of miR-223, NLRP, and IL-1 in rats induced with spinal cord injury (SCI) (Shi et al., 2016). This reflects the fact that naringenin can treat spinal cord injuries by eliciting an anti-inflammatory response in brain cells and inhibiting neuroinflammation.

The complex neuroinflammatory response is linked to a number of neurodegenerative disorders, the most prominent of which are Parkinson's and Alzheimer's. Inhibiting the activity of microglial cells may be considered a significant neuroprotective strategy and may aid in the treatment of a variety of neuronal disorders. In an experiment, naringenin significantly reduced microglial activation and proinflammatory cytokine release. Inhibiting phosphorylation of kinases involved in signal transduction pathway activation, such as Akt and mitogen-activated protein kinases (MAPKs), may aid in the suppression of neuroinflammation in BV2 microglial cells (Park, Kim and Choi, 2012). Naringenin treatment increased the expression of suppressors of cytokine signalling (SOCS)-3 in microglia, resulting in a decrease in iNOS and COX-2 expression via the adenosine monophosphate-activated protein kinase (AMPK) and protein kinase C (PKC) signalling pathways (Signaling et al., 2015). The mechanistic understanding of the anti-inflammatory effects suggests that naringenin inhibits the nuclear factor-B (NF-kB) p65 subunit's translocation into the nucleus. This may be followed by a decrease in the expression of pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF- Alpha, as well as some inflammation-specific enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Park, Kim and Choi, 2012). Naringenin's anti-neuroinflammatory action was also deduced, as there was a significant inhibition of TNF-Alpha and iNOS expression glial induced with LPS (Vafeiadou et al., 2009). In addition, naringenin inhibited p38 mitogen-activated protein kinase (MAPK) phosphorylation and signal transducer and activator of transcription-1 (STAT-1) transcription factor in LPS/IFN-stimulated glial cells, resulting in neuroprotective effects in the glial cells. Naringenin treatment significantly reduces ischemia-induced neuronal inflammation and brain cell death. This is accomplished by increasing the antioxidative profile, decreasing the synthesis of myeloperoxidase, nitric oxide, and cytokines, and decreasing the expression of NF-kB (Raza et al., 2013). This results in a significant reduction in neuroinflammatory response in microglial cells. Naringenin has a significant nociceptive response to a variety of stimuli as well as anti-inflammatory properties. Naringenin has the ability to reduce by inhibiting carrageenan-induced oxidative stress (Pinho-ribeiro et al., 2016). The proposed mechanism for analgesic activity is NF-kB signalling inhibition with downstream proinflammatory cytokine downregulation (IL-33, TNF- Alpha, and IL-1). Naringenin also reduces carrageenan-induced hyperalgesia via the NO-cGMP-PKG-ATP dependent opening of the K+ channel signalling pathway, resulting in K+ efflux and decreased conductance of other ions across neuronal membranes, resulting in decreased neuronal hyperexcitability (Pinho-ribeiro et al., 2016). As a result, naringenin can aid in the treatment of many inflammation-related neuronal derangements, and further research is required to evaluate the more vivid molecular signalling cascades undertaken by naringenin.

7. Conclusion:

According to epidemiological studies, mental illness is becoming a growing concern as the population ages. As a result, current research has focused on the development of potent neuroprotective agents with increased efficacy and fewer side effects. The use of phytochemicals, particularly flavonoids, in disease prevention and treatment is well known. Flavonoids are naturally found in fruits and vegetables. A wide range of flavonoids found in nature each have unique physical, chemical, and physiological properties. Flavonoids are dietary components with biochemical and pharmacological effects that can

be used in drug development. Massive research is being conducted on flavonoids as neuroprotective agents as a result of mounting evidence. Naringenin (4,5,7-trihydroxyflavanone), a major flavone glycoside found in citrus fruits, is an important neuroprotective agent. Naringenin exhibits neuroprotection via various mechanisms and has received a lot of attention. We documented from the available literature that naringenin reduces oxidative stress and neurotoxicity in neural tissues in the current manuscript. Furthermore, available research indicates that naringenin reduces neuro-inflammation and epilepsy. We also came across numerous reports claiming that naringenin is an effective anti-amyloidogenic, anti-depressant, and neurotrophic agent. Mechanistic studies revealing the molecular mechanisms underlying naringenin's remarkable neuroprotective properties should also be conducted. Before naringenin can be used in clinical trials, extensive toxicity studies must be completed. Clinical trials should be carried out to assess its beneficial effects on brain disorders.

References

Acids, P. (1996) 'Review Article', 20(7), pp. 933–956.

Bahramsoltani, R. et al. (2015) 'Phytochemical constituents as future antidepressants : a comprehensive review'. Available at: https://doi.org/10.1515/revneuro-2015-0009.

Bernini, R. et al. (2003) 'Conversion of naringenin and hesperetin by heterogeneous catalytic Baeyer – Villiger reaction into lactones exhibiting apoptotic activity', 44, pp. 4823–4825.

Biology, F.R. (2004) 'Serial Review : Flavonoids and Isoflavones (Phytoestrogens): Absorption , Metabolism , and Bioactivity Serial Review Editor : Catherine Rice-Evans', 36(7), pp. 838–849. Available at: https://doi.org/10.1016/j.freeradbiomed.2004.01.001.

Cavia-saiz, M. et al. (2010) 'Antioxidant properties , radical scavenging activity and biomolecule protection capacity of flavonoid naringenin and its glycoside naringin : a comparative study', (November 2009), pp. 1238–1244. Available at: https://doi.org/10.1002/jsfa.3959.

Chem, F. (2004) 'Effect of Antioxidant Flavanone , Naringenin , from Citrus junos on Neuroprotection', pp. 1520–1525.

Choi, S.U.E. et al. (1991) 'Antihypeiuipidemic effect of flavonoids from', 54(1), pp. 218–224.

Commenges, A.D. et al. (2016) 'Intake of Flavonoids and Risk of Dementia Published by : Springer Stable URL : http://www.jstor.org/stable/3581727 Accessed : 03-07-2016 05 : 11 UTC', 16(4), pp. 357–363.

Curti, V. et al. (2017) 'Enantioselective Modulatory Effects of Naringenin Enantiomers on the Expression Levels of miR-17-3p Involved in Endogenous Antioxidant Defenses'. Available at: https://doi.org/10.3390/nu9030215.

Dharan, M., Thomas, P. and Geraldine, P. (2012) 'streptozotocin – nicotinamide-induced experimental diabetic rats Antihyperglycemic and antioxidant effects of a flavanone , naringenin , in streptozotocin – nicotinamide-induced experimental diabetic rats', (June 2015). Available at: https://doi.org/10.1007/s13105-011-0142-y.

Disposition, D. (1995) 'HARMACOLOGY @ THERAPEUTICS DRUG DISPOSITION The fate of naringin in humans : A key to'.

Dk, P. et al. (2011) 'Pharmacologically screened aphrodisiac plant-A review of current scientific literature', Asian Pacific Journal of Tropical Biomedicine, 1(1), pp. S131–S138. Available at: https://doi.org/10.1016/S2221-1691(11)60140-8.

Dou, W. et al. (2013) 'Protective effect of naringenin against experimental colitis via suppression of Toll-like receptor 4 / NF- k B signalling British Journal of Nutrition', 4, pp. 599–608. Available at: https://doi.org/10.1017/S0007114512005594.

Erlund, I. et al. (2018) 'Human Nutrition and Metabolism Plasma Kinetics and Urinary Excretion of the Flavanones Naringenin and Hesperetin in Humans after Ingestion of Orange Juice and Grapefruit Juice 1', (September 2000), pp. 235–241.

Fetoui, H. and Gdoura, R. (2014) 'Protective Effects of Naringenin on Iron-Overload-Induced Cerebral Cortex Neurotoxicity Correlated with Oxidative Stress'. Available at: https://doi.org/10.1007/s12011-014-9948-0.

Galluzzo, P. et al. (2015) 'Antiestrogenic Effects by Regulating Estrogen Receptor', 149(September), pp. 2567–2575. Available at: https://doi.org/10.1210/en.2007-1173.

Ghofrani, S., Joghataei, M. and Mohseni, S. (2015) 'Naringenin improves learning and memory in an Alzheimer ' s disease rat model : Insights into the underlying mechanisms', (764), pp. 195–201.

Han, X. et al. (2008) 'Protective effects of naringenin-7- O -glucoside on doxorubicin-induced apoptosis in H9C2 cells', 581, pp. 47–53. Available at: https://doi.org/10.1016/j.ejphar.2007.11.048.

Hollman, P.C.H. and Hollman, P.C.H. (2009) 'Absorption , Bioavailability , and Metabolism of Flavonoids Absorption , Bioavailability , and Metabolism of Flavonoids', 0209. Available at: https://doi.org/10.3109/13880200490893492.

Ibrahim, M.H. et al. (2011) 'Effects of Nitrogen Fertilization on Synthesis of Primary and Secondary Metabolites in Three Varieties of Kacip Fatimah (Labisia Pumila Blume)', pp. 5238–5254. Available at: https://doi.org/10.3390/ijms12085238.

Jarikr, A., Orhode, V. and Aderibigbe, A.O. (2020) 'Repeated psychosocial stress causes glutamic acid decarboxylase isoform-67, oxidative-Nox-2 changes and neuroinflammation in mice: prevention by treatment with a neuroactive flavonoid, morin', Brain Research, p. 146917. Available at: https://doi.org/10.1016/j.brainres.2020.146917.

Khajevand-khazaei, M., Ziaee, P. and Motevalizadeh, S. (2018) 'Naringenin ameliorates learning and memory impairment following systemic lipopolysaccharide challenge in the rat', European Journal of Pharmacology, 826(June 2017), pp. 114–122. Available at: https://doi.org/10.1016/j.ejphar.2018.03.001.

Khan, M.B. et al. (2012) 'Neurochemistry International Naringenin ameliorates Alzheimer ' s disease (AD) -type neurodegeneration with cognitive impairment (AD-TNDCI) caused by the intracerebroventricular-streptozotocin in rat model', 61, pp. 1081–1093.

Khodayar, M.J. et al. (2017) 'Evaluation of the Effect of Naringenin on Pentylenetetrazole and Maximal Electroshock-Induced Convulsions in Mice', 12(1), pp. 1–5. Available at: https://doi.org/10.5812/jjnpp.31384.Research.

Kim, D.H. et al. (2020) 'nutrients Anti-Aging E ff ects of Calorie Restriction (CR) and CR Mimetics Based on the Senoinflammation Concept'.

Krause, M. (1992) 'o •• OH', pp. 29–32.

Kumar, V. (2016) 'Potential Medicinal Plants for CNS Disorders : an Overview', (August 2006). Available at: https://doi.org/10.1002/ptr.1970.

Lee, Y.S. and Reidenberg, M.M. (1998) 'A Method for Measuring Naringenin in Biological Fluids and Its Disposition from Grapefruit Juice by Man', 10021(212), pp. 314–317.

Lei, H.A.N. et al. (2009) 'Effect of Light on Flavonoids Biosynthesis in Red Rice Rdh', Agricultural Sciences in China, 8(6), pp. 746–752. Available at: https://doi.org/10.1016/S1671-2927(08)60274-6.

Li, P. et al. (2013) 'Acute and 13 weeks subchronic toxicological evaluation of naringin in Sprague-Dawley rats', 60, pp. 1–9. Available at: https://doi.org/10.1016/j.fct.2013.07.019.

Madrigal-santillán, E. et al. (2014) 'Review of natural products with hepatoprotective effects', 20(40), pp. 14787–14804. Available at: https://doi.org/10.3748/wjg.v20.i40.14787.

Mag, P. et al. (2017) 'Effect of Naringenin (A naturally occurring flavanone) Against Pilocarpine-induced Status Epilepticus and Oxidative Stress in Mice', pp. 154–160. Available at: https://doi.org/10.4103/0973-1296.203977.

Manach, C., Morand, C. and Re, C. (2003) 'Bioavailability in humans of the flavanones hesperidin and narirutin after the ingestion of two doses of orange juice', pp. 235–242.

Park, H.Y.E.Y., Kim, G. and Choi, Y.H. (2012) 'Naringenin attenuates the release of pro-inflammatory mediators from lipopolysaccharide-stimulated BV2 microglia by inactivating nuclear factor- κ B and inhibiting mitogen-activated protein kinases', pp. 204–210. Available at: https://doi.org/10.3892/ijmm.2012.979.

Park, J. et al. (2016) 'Naringenin ameliorates kainic acid-induced morphological alterations in the dentate gyrus in a mouse model of temporal lobe epilepsy', pp. 22–23. Available at: https://doi.org/10.1097/WNR.0000000000000678.

Patel, D.K. et al. (2011) 'Pedalium murex Linn .: An overview of its phytopharmacological aspects', Asian Pacific Journal of Tropical Medicine, 4(9), pp. 748–755. Available at: https://doi.org/10.1016/S1995-7645(11)60186-7.

Patel, K., Singh, G.K. and Patel, D.K. (2014) 'REVIEW A Review on Pharmacological and Analytical Aspects of Naringenin'. Available at: https://doi.org/10.1007/s11655-014-1960-x.

Peng, L., Wang, B. and Ren, P. (2005) 'Reduction of MTT by flavonoids in the absence of cells', 45, pp. 108–111. Available at: https://doi.org/10.1016/j.colsurfb.2005.07.014.

Pinho-ribeiro, F.A. et al. (2016) 'Naringenin reduces inflammatory pain in mice', Neuropharmacology [Preprint]. Available at: https://doi.org/10.1016/j.neuropharm.2016.02.019.

Prabhu, J. and Prabhu, K. (2020) 'Saraswatarishta Reverses Neuronal Injury in Brain Tissues of Scopolamine - induced Rat Model', pp. 269–273. Available at: https://doi.org/10.4103/JASI.JASI.

Prakash, V. et al. (2013) 'Neuroprotective role of naringenin on carbaryl induced neurotoxicity in mouse neuroblastoma cells', 4(3). Available at: https://doi.org/10.4103/0976-500X.114599.

Procházková, D. (2010) 'CHARLES UNIVERSITY IN PRAGUE FACULTY OF PHARMACY IN HRADEC KRÁLOVÉ Department of Biochemical Sciences Antioxidant and prooxidant properties of flavonoids Bachelor thesis'.

Raza, S.S. et al. (2013) 'NEUROPROTECTIVE EFFECT OF NARINGENIN IS MEDIATED THROUGH SUPPRESSION OF NF-kB SIGNALING PATHWAY IN EXPERIMENTAL STROKE', 230, pp. 157–171.

Ren, L. et al. (2019) 'AC SC', Journal of Ethnopharmacology, p. 112044. Available at: https://doi.org/10.1016/j.jep.2019.112044.

Ross, J.A. and Kasum, C.M. (2002) 'D IETARY F LAVONOIDS : Bioavailability , Metabolic Effects , and Safety', pp. 19–34. Available at: https://doi.org/10.1146/annurev.nutr.22.111401.144957.

Schijlen, E.G.W.M. et al. (2004) 'Modification of flavonoid biosynthesis in crop plants', 65, pp. 2631–2648. Available at: https://doi.org/10.1016/j.phytochem.2004.07.028.

Shi, L. et al. (2016) 'Naringenin inhibits spinal cord injury-induced activation of neutrophils through miR-223', Gene, 592(1), pp. 128–133. Available at: https://doi.org/10.1016/j.gene.2016.07.037.

Signaling, C. et al. (2015) 'Naringenin Suppresses Neuroinflammatory Responses Through Inducing Suppressor of Cytokine Signaling 3 Expression', (January). Available at: https://doi.org/10.1007/s12035-014-9042-9.

Spencer, J.P.E. (2009) 'The impact of flavonoids on memory : physiological and molecular considerations'. Available at: https://doi.org/10.1039/b800422f.

Stafford, G.I. et al. (2008) 'Review on plants with CNS-effects used in traditional South African medicine against mental diseases', 119, pp. 513–537. Available at: https://doi.org/10.1016/j.jep.2008.08.010.

The, G. et al. (1998) 'A Prospective Community-Based Study of Stroke in Germany—The Erlangen Stroke Project (ESPro)', pp. 2501–2506.

Vafeiadou, K. et al. (2009) 'The citrus flavanone naringenin inhibits inflammatory signalling in glial cells and protects against neuroinflammatory injury', Archives of Biochemistry and Biophysics, 484(1), pp. 100–109. Available at: https://doi.org/10.1016/j.abb.2009.01.016.

Vallverdú-queralt, A. et al. (2013) 'A comprehensive study on the phenolic profile of widely used culinary herbs and spices: rosemary, thyme, oregano, cinnamon, cumin and bay', FOOD CHEMISTRY [Preprint], (2014). Available at: https://doi.org/10.1016/j.foodchem.2013.12.106.

Vauzour, D. et al. (2008) 'The neuroprotective potential of flavonoids : a multiplicity of effects', pp. 115–126. Available at: https://doi.org/10.1007/s12263-008-0091-4.

Vauzour, D., Paul, J. and Spencer, E. (2007) 'The reaction of flavonoid metabolites with peroxynitrite', (January). Available at: https://doi.org/10.1016/j.bbrc.2006.09.131.

Weintraub, R.A., Yost, A. and Rouseff, R.L. (no date) 'Flavanone absorption after naringin , hesperidin , and citrus administration', pp. 34–40.

Yang, W., Ma, J. and Liu, Z. (2013) 'Effect of naringenin on brain insulin signaling and cognitive functions in ICV-STZ induced dementia model of rats'. Available at: https://doi.org/10.1007/s10072-013-1594-3.

Yang, Z., Kuboyama, T. and Tohda, C. (2017) 'A Systematic Strategy for Discovering a Therapeutic Drug for Alzheimer ' s Disease and Its Target Molecule', 8(June), pp. 1–13. Available at: https://doi.org/10.3389/fphar.2017.00340.

Yi, L. et al. (2014) 'Progress in Neuro-Psychopharmacology & Biological Psychiatry BDNF signaling is necessary for the antidepressant-like effect of naringenin', 48, pp. 135–141. Available at: https://doi.org/10.1016/j.pnpbp.2013.10.002.

Yi, L. et al. (no date) 'Author ' s personal copy Progress in Neuro-Psychopharmacology & Biological Psychiatry BDNF signaling is necessary for the antidepressant-like effect of naringenin'.

Zbarsky, V. et al. (2005) 'Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson ' s disease', 39(October), pp. 1119–1125. Available at: https://doi.org/10.1080/10715760500233113.