https://doi.org/10.48047/AFJBS.6.12.2024.5034-5048

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Naringin(A Polyphenolic moiety) as a Neuroprotective Agent: A Comprehensive Clinical approach

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Article History
Volume 6, Issue 12, 2024
Received: June 10, 2024
Accepted: July 5, 2024
doi:
10.48047/AFJBS.6.12.2024.5034-5048

Abstract:
Neuroprotection is the conservation of design, capability and organization of neuronal tissues from harm brought about by different specialist as well as neurodegenerative sicknesses, Like Alzheimer infection (Promotion), Parkinson Illness (PD), Huntington Illness (HD), Numerous Sclerosis, Amyl Jungle Parallel sclerosis (ALS) and Spinal Line Injury (ALS). Naringin, a flavanone-7-O glycoside, between the flavanone naringenin and the disaccharide neo-Hesperides. This flavonoid glycoside is perceived as a non-harmful regular item with numerous bioactive impacts, including Hostile to malignant growth, Hostile to oxidative, Mitigating and Nephron-defensive. It was found that naringin can essentially work on mental, learning, memory brokenness in rodents with malathion memory hindrance. Our survey examines Neuro-pharmacological component for preventive and helpful impacts of naringin in neuro-degenerative illness. Furthermore, the audit looks at clinical proof affirming its neuroprotective capability. Different cell and creature models intended for neuroprotective infections have been led to assess the fundamental neuro-pharmacological component of naringin. Neuroprotective capability of this flavonoid is intervened by progress of brain development factors and endogenous enemy of oxidant guard capabilities, decreasing neuro-incendiary and apoptotic pathways. Regardless of the different pre-clinical examinations on the job of naringin in the neurodegenerative sickness, less in realized about its positive impact can altogether further develop cerebral blood stream, cognizance and memory execution. Further clinical preliminaries are additionally expected for affirming neuroprotective viability of this normal flavonoid and assessing its security profile.

Keywords: Naringin, Citrus Fruits, Neuroprotective mechanism, Alzheimer's disease, Parkinson disease, Neuroprotective.

INTRODUCTION-

The expression "neurological sickness" is frequently used to allude to anything that influences the sensory system. In the mind, spinal line, or different nerves, underlying, metabolic, or electrical dysfunctions might cause a wide scope of side effects. These side effects incorporate changed conditions of cognizance, spasms, solid shortcoming, unfortunate coordination, a deficiency of feeling, and an absence of sensation. Different side effects incorporate confusion, torment, and uneasiness. Broad review has lead to the revelation of a few neurological irregularities, some of which are fairly normal while others are generally phenomenal [1,2]. Neurodegenerative illnesses incorporate a few issues, including Alzheimer infection (Promotion), Parkinson Sickness (PD), Huntington infection (HD), Different Sclerosis and Spinal String Injury [1]. Alzheimer illness (Promotion), the most well-known neurodegenerative sickness is clinically portrayed by moderate memory impedance and mental. They are viewed as debilitating circumstances that influence a great many individuals overall [2]. Albeit the specific etiology of these ongoing sicknesses is completely obscure, the basic nerve degeneration-related pathologies including decompensated neuronal design/capability changes [3], disturbance in the combination of synapses [4], as well as unusual protein collection have been explained [5]. According to the pathophysiological perspective, the ubiquitin-proteasome framework and autophagy pathway, assume an essential part in debasement and end of deformed proteins and harmed organelles. Disturbance of these two significant intracellular proteolytic pathways is associated with the pathogenesis of NDs [6,7]. Notwithstanding these pathologies, mitochondrial brokenness, oxidative abuses, and neuroinflammation in the microglial cells are proposed to be embroiled in neurodegeneration [8]. Microglial cells are monocyte-like resistant cells which are considered as the gatekeeper of the sensory system. There are two aggregates of microglial cells relying upon the initiation state, either traditional M1 or elective M2 aggregate [9].

The initiated M1 microglial cells express cost like receptors (TLRs) as well as other supportive of incendiary cytokines like interferon γ (INF-γ), interleukin 1β (IL-1β) and cancer rot factor α (TNF-α) advance the axonal degeneration and apoptotic demise of neuronal cells [9]. Then again, M2 microglial cells express mitigating middle people, for example, IL-4, IL-10, IL-13, changing development factor β (TGF-β) and neurotrophic factors prompting neurogenesis, angiogenesis, and oligodendrogenesis (neuronal cells) and remyelination (arrangement of new myelin sheath around demyelinated axons) [10,11]. Citrus natural products are rich with naringenin and its forerunner, naringin [13]. As of late, developing interest has been centered around the expected helpful exercises of naringenin in neurological problems. Regardless of the promising impacts of naringenin to oversee NDs, there is an extraordinary test presented by unfortunate bioavailability and slight openness to the mind. Here in this survey, the job of naringenin in treating different neuronal problems is depicted. The nanostructured definitions of naringenin which are being researched to tackle its boundless pharmacokinetic impediment are likewise examined.

Naringin; Sources, Chemistry,Metabolism and therapeutic effects -

Chemistry of Naringenin and Its Sources- Naringenin is quite possibly of the most basic normally happening flavonoid (I). The essential construction of flavonoids (I) comprises of three rings (I, II, and III). Naringenin (II) has a sub-atomic recipe $C_{15}H_{12}O_5$ and is synthetically named as 2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl) 4H-1-benzopyran-4-one. Its atomic weight is 272.26 g·mol−1, and the liquefying point is 251 ◦C. This atom is insoluble in water and dissolvable in natural solvents as liquor [14]. Naringenin might be tracked down in two types of aglycone or its glycosidic structure (naringenin-7-O-glucoside) [15] (Figure 1). Naringin (III)

can likewise be viewed as naringin (naringenin-7-rhamnoglucoside) [16] and narirutin (naringenin-7-O-rutinoside) [17]. Naringenin glycosides relying upon their sugar moiety, connect by means of a glycosidic linkage at C7 to the flavonoid, and are severed by unambiguous chemicals, then, at that point, naringenin (aglycone) would be delivered [18].

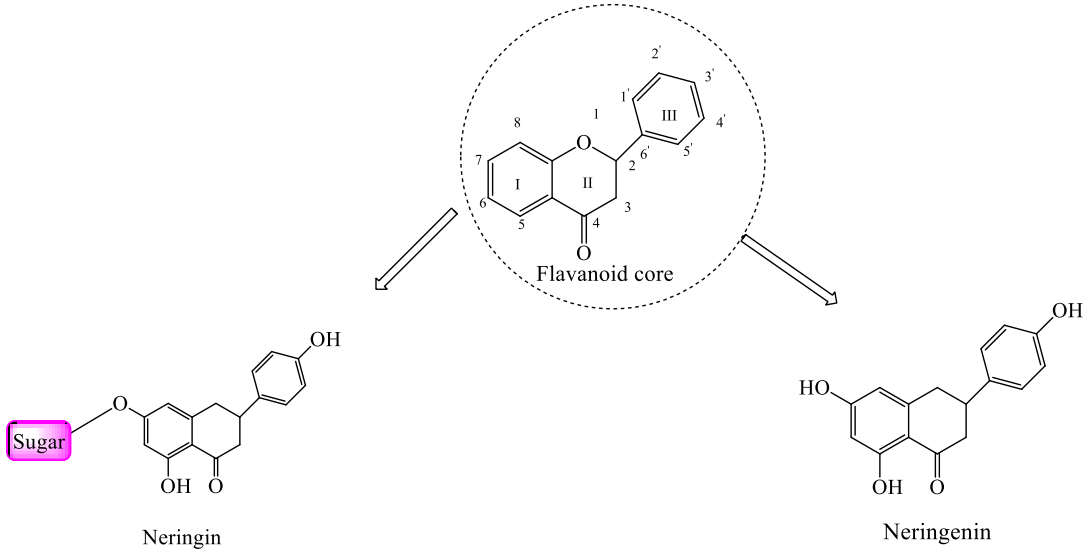

Figure 1. Structures of flavonoids (I); naringenin (II); and naringin (III).

TABLE 1.Various natural sources of naringin.

Plant Sources	Naringin content (µg/ml)	References
1. Citrus × aurantium L.	19.7	Kawaii et al. (1999)
2. Citrus × limon (L.)	22.3	Kawaii et al. (1999)
3. Citrus deliciosa Ten.	8.0	Dhuique-Mayer et al. (2005)
4. Citrus medica L.	18.6	Menichini et al. (2016)
5. Citrus × aurantium L.	230.0	Kawaii et al. (1999)
6. Citrus × aurantium L.	3383.6	de Lourdes Mata Bilbao et al. (2007)
7. Citrus × aurantium L.	21.0	Ooghe et al. (1994)

In Business grapefruit juice creation, the catalyst naringinase can be utilized to eliminate the sharpness made by naringin. In people naringin is used to the aglycone naringenin (not unpleasant) by naringinase present in the stomach. Notwithstanding the citrus natural products, it very well may be confined from other plant genera like Fabaceae, Rutaceae, Papilionaceae, Betulaceae, Lamiaceae, Zanthoxylum species and Acanthopanax Setchuenensis. Drynaria rhizome (Rutaceae) is a typical plant generally dispersed all through Southern China. The foundations of Drynaria rhizomes were routinely viewed as a medication against Osteoporosis and Bone resorption, while as of late it has expanding been utilized to treat neurodegenerative sicknesses like Promotion. North of 5000 normally happening flavonoids have been described from different plants. The Substance construction of naringin was first clarified in 1928 by Incubuses and Asahina. In one Review, Naringin was separated from C. aurantium rough strip remove after HPLC detachment and its design was affirmed by electrospray ionization mass spectrometry. Naringin has a place with the flavonoid family. Flavonoids comprises of 15-

Carbon particles in 3 rings, 2 of which should be benzene rings associated by a 3-carbon chain. Naringin contains the fundamental flavonoid structure alongside one rhamnose and one glucose unit connected to its aglycone segment, called naringin at 7-carbon position. The steric block given by the two sugar units makes naringin less strong than its aglycone partner, Naringenin.

Chemical Structure of Naringin, Naringenin & its derivatives-

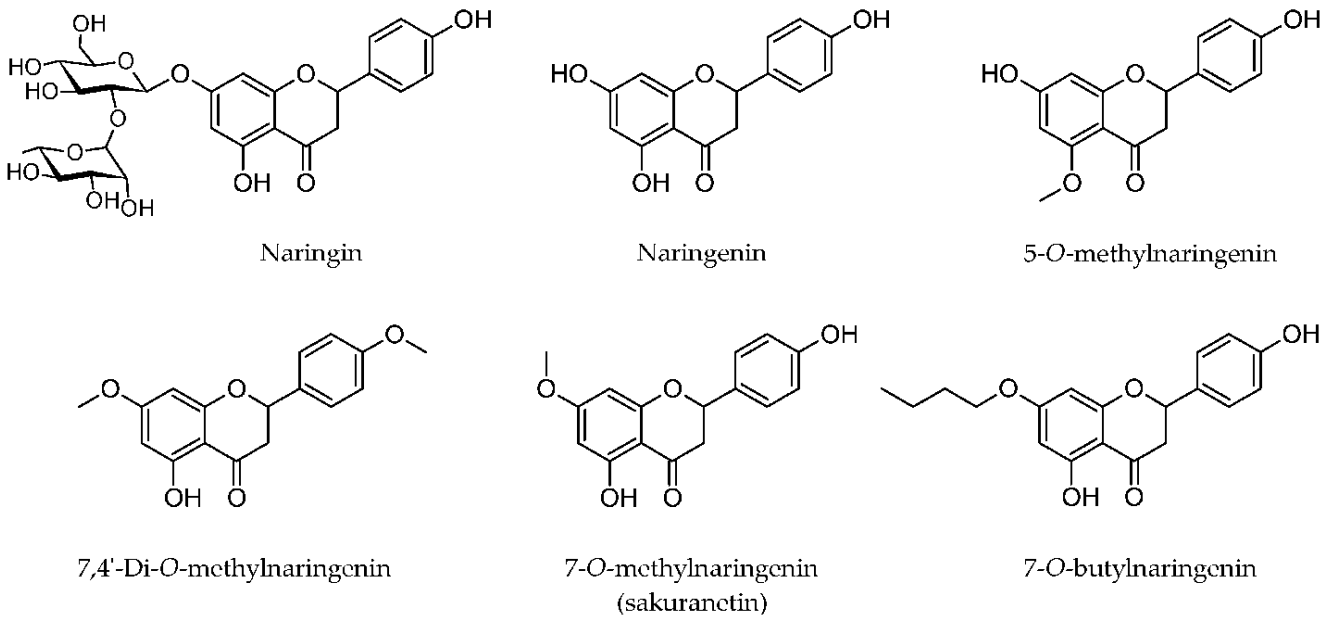

Figure:2 Different derivatives of polyphenols including Naringin, Naringenin.

Metabolism of Naringin

It very well may be hydrolyzed by rhamnosidase part action of naringinase, into naringenin and glucose. This occurs in two stages - First, Naringin is hydrolyzed by α-L-rhamnosidase movement of naringinase into rhamnose and prunin. The prunin shaped is then hydrolyzed by β-d glucosidase into naringin and glucose. Naringinase is a chemical that has a wide event in nature and plants, Yeast and organisms.

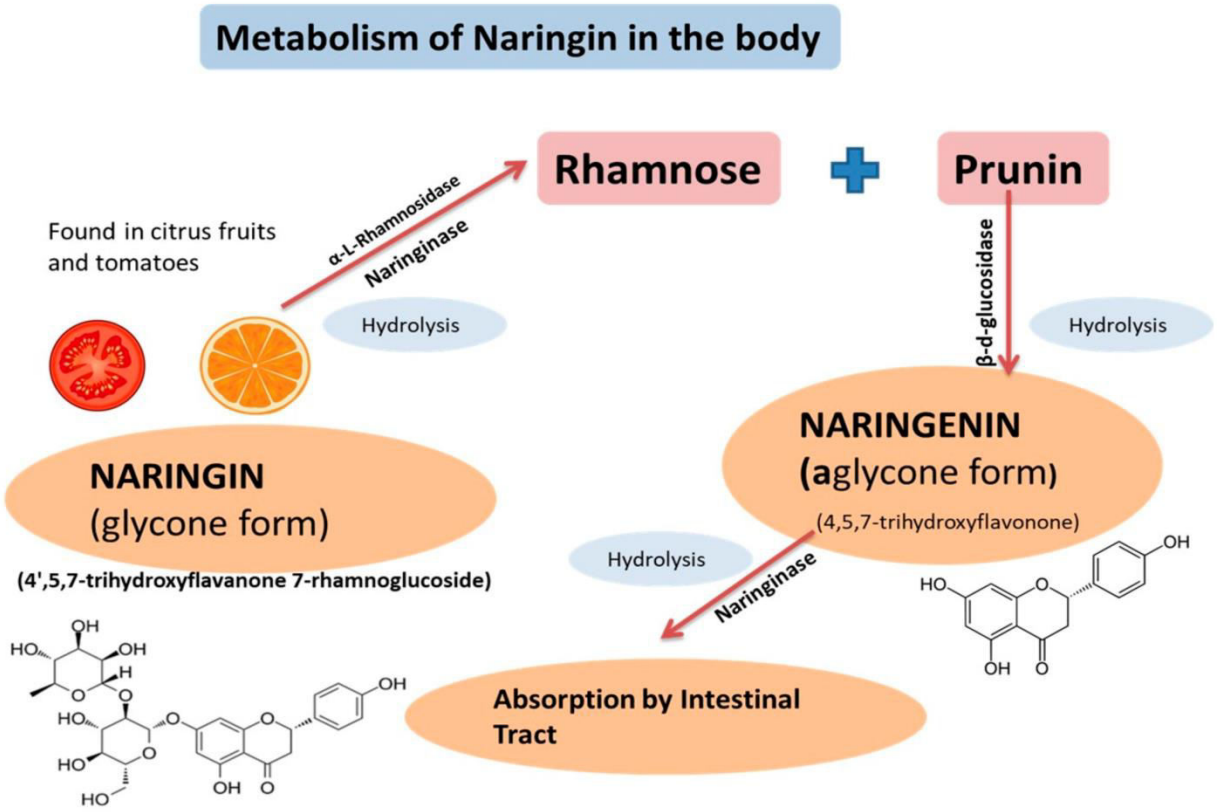

Figure3. Naringin is hydrolyzed by naringinase and α-L-rhamnosidase into prunin and rhamnose. With the help of β-d-glucosidase, prunin then is hydrolyzed into "Naringenin," which is absorbed into the intestinal tract after being hydrolyzed by naringinase.

Naringin and Neuroprotection: Mechanisms of Action Based on Animal Studies

Botanical Sources

Flavonoids are phenolic compounds related with a great many organic capabilities. There are in excess of 4000 distinct flavonoids known to science, the majority of which are found in their regular, unaltered plant-based structures. Flavonoids can be a dietary enhancement [19,20]. Grapefruit and other citrus natural products get their particular unpleasant taste from flavonoid naringin. Albeit the quantity of flavonoids taken from food might be huge and the flavonoids show likely natural activity, they certainly stand out than flavanols and isoflavones [28,29]. Generally speaking, the scientists zeroed in on flavanols and isoflavones — intracellular cycling of naringenin, hesperidin, and its glycosylated subsidiaries, naringenin, hesperidin, and rutin. Grapefruit, bergamot, sharp orange, tart cherry, tomato, chocolate, Greek oregano, water mint, and beans are food varieties and plants that contain norepinephrine or its glycosides [29,30].

Parkinson's Infection

Parkinson's sickness (PD) is a degenerative neurological illness that outcomes in debilitated engine capability due to dopaminergic neuropathy in the substantia nigra [21-22]. Hereditary inclination might assume a part in creating mitochondrial harm and oxidative pressure; notwithstanding, extra sub-atomic courses exist. As of late, oxidative pressure has been examined as a likely system in neurodegeneration, which is just a single illustration of numerous similitudes among Promotion and PD. The cell reinforcement properties of flavonoids, alkaloids,

and other polyphenols are coming to the front. Plant synthetic compounds might tweak proteins and metabolic flagging pathways to lessen ROS creation. Bioactive metabolite flavonoids have against oxidative activities on the liver's metabolic pathway [23-25]. The cancer prevention agent and neuroprotective properties of naringin have been examined. Asahina and Inubuse tracked down the plans for naringin in 1928 [26,27]. Naringenin is connected to naringin through the C-7 hydroxyl bunch. Metabolites of naringenin might be tracked down in stages I and II of the medication's digestion. Glucose is the wellspring of naringin's unpleasant flavor. It responds with potassium hydroxide or other fundamental substances to frame 1,3-diphenylpropan1-one, which has a fragrance suggestive of menthol [28-30]. It has been shown that naringin may kill ROS, search superoxide, smother xanthine oxide, decline lipid peroxidation, and reduction the porousness of oxygen-invigorated K+ erythrocytes. Naringin's cancer prevention agent possibilities might support treating nervous system science and diabetes. Degeneration of nerve cells in the striatum and substantia nigra standards compacta kills dopamine-delivering synapses, prompting Parkinson's sickness [31].

Uneasiness and Sorrow

Uneasiness and sorrow are two of the most widely recognized psychological maladjustments, the two of which have complex beginnings at the convergence of a few natural frameworks. Li et al. played out the principal concentrates on the stimulant impacts of naringin and naringenin. The synthetic substances were tried on mice models of melancholy welcomed on by constant erratic gentle pressure (CUMS) [32]. Nervousness might cause various awkward physical and profound side effects, including however not restricted to: bothering, fretfulness, exhaustion, trouble focusing, a hustling heart, chest torment, and a resentful stomach. Tension arrives in various structures, and each is dealt with diversely [33]. The serotonergic and noradrenergic frameworks have been associated with mind-set issues like sadness and uneasiness. The serotonergic framework has extensive consequences for mental cycles in the mind, notwithstanding its part in controlling temperament and hunger. Memory and center are just two of the mental capabilities that are constrained by the noradrenergic framework. Expansions in serotonin (5-HT) and norepinephrine (NE) receptors, actuation of cerebrum determined neurotrophic factor (BDNF), and diminished blood corticosterone are guessed to underlie NRG's stimulant like impacts [34,35].

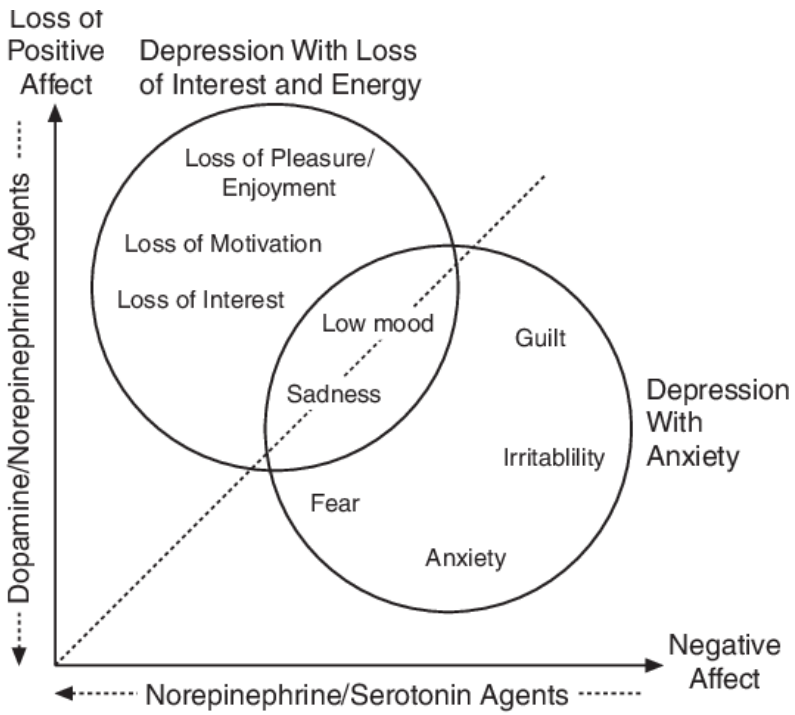

Figure:4 Relation between Catechol neurochemicals and depression.

It inhibits monoamine oxidase, which may also help those who are depressed. Increased rearing activity, decreased immobility, and increased social communication was seen in mice administered NRG intraperitoneally (at doses of 2.5, 5, and 10 mg/kg), which is consistent with anti-depressant-like and anxiolytic-like effects. Reductions were seen in nitrosative stress, lipid peroxidation, and cholinergic transmission. Mental diseases, often known as mental illnesses or psychiatric disorders, are characterized by persistent patterns of thinking or behavior that significantly impair an individual's capacity to function in everyday life. Both the frequency and length of time that these symptoms will persist are unknown at this time. Various diseases and disorders have been identified, and each has its signs. In some instances, seeking the assistance of a clinical psychologist or psychiatrist specializing in evaluating and managing mental health conditions may be beneficial [36–39]. Chronic illnesses and ailments may benefit from consuming a diet high in NG-rich fruits and vegetables. Animal pharmacokinetic studies have shown that NG rapidly undergoes intermediate glucuronide metabolism in the liver and readily crosses the blood–brain barrier (BBB). NG's high permeability across the BBB has been attributed to its association with a broad range of CNS effects. However, the oral bioavailability of naringenin is limited by its metabolism in the liver and its degradation by bacterial enzymes in the colon. Lowered levels of inflammatory mediators were seen in rats, including TNF-α, cyclooxygenase-2, and inducible nitric oxide synthase (iNOS). Studies of naringenin's effects on the brain and spinal cord show it may help treat various neurological disorders [40-42]

Cerebral Ischemia

Cerebral ischemia is a disorder that may trigger a cascade of unfavorable biochemical responses in the brain, leading to malfunction of key brain regions and, commonly, neuropathy [43,44]. An inflammatory reaction and the production of ROS following an ischemia event may damage brain tissue and lead to neuronal death [45]. Ischemiainduced damage involves several kinases,

including mitogen-activated protein kinases, extracellular signal-regulated kinases, signal transducers and activators of transcription 1, calcium/calmodulin-dependent kinases, etc. ROS initiate the caspase cascade and encourage the synthesis of pro-inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha, all of which contribute to cell death. Although progress has been made, a full understanding of the molecular mechanisms behind post-ischemic neuronal damage remains elusive. However, naringin and naringenin have been shown to have a neuroprotective effect after ischemia [46–49].

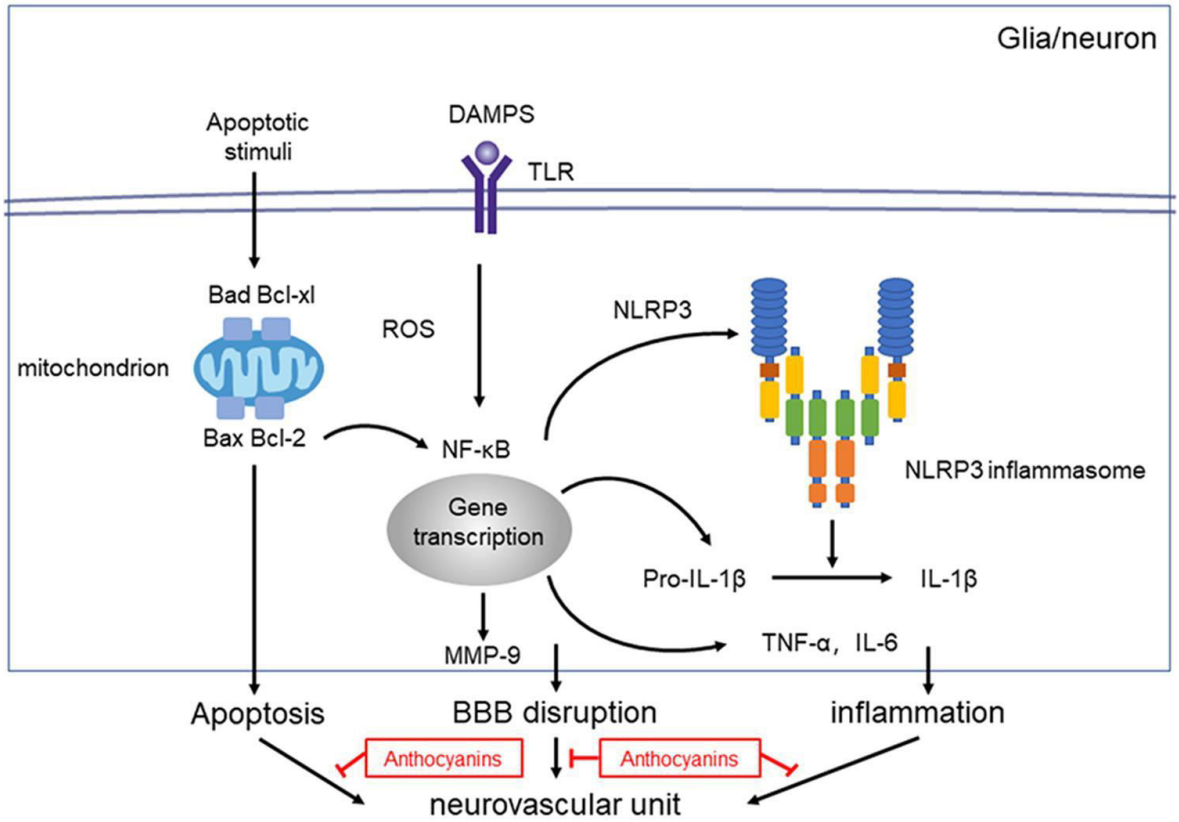

Figure:5 Proposed instruments of anthocyanin's impact on NVU brokenness after ischemic stroke. Injury to the neurovascular unit results in one or the other demise or injury to endothelial cells, neurons, microglia and so on. Following hypoxia and ischemia, receptive oxygen species (ROS) are produced and NF-κB are actuated, which enacts the NLRP3 irritation pathway, and triggers the statement of IL-1β.

Alzheimer's Disease

Alzheimer's illness (Promotion) is the most well-known kind of dementia in the industrialized world and is an extreme general medical condition [50]. A few different sub-atomic cycles caused Promotion, yet its careful pathophysiology is still inadequately perceived. In a few pre-clinical examinations, naringin and a portion of its subsidiaries, for example, naringenin, changed these pathways in manners that could be utilized to treat Promotion [51,52]. The illness is brought about by the passing of cholinergic neurons in the cerebrum and the arrangement of Amyloid-β (Aβ) plaques outside the body [53]. Memantine, a main bad guy of the NMDA glutamate receptor, separates at a lot more slow rate than acetylcholinesterase (Throb) inhibitors, for example, donepezil Aricept, which is much of the time used to treat the side effects of Promotion [54,55]. Synaptic brokenness, in which neural connections are harmed, cells are

killed, and mental debilitations happen, comes about because of consuming excessively. This brokenness can be fixed altogether with the legitimate treatment. It is fundamental to comprehend how Aβ is presently responsible for creating and putting away recollections and how this influences synaptic versatility in the mind organization. Proof recommends that calcium/calmodulin free protein kinase II (CaMKII) is a basic synaptic objective for Aβ-incited synaptic wretchedness [56,57]. A few plant animal categories high in flavonoids have been utilized in customary medication for many years. Epidemiological and dietary investigations on the two individuals and creatures have shown that these flavonoids safeguard against and dial back neurodegeneration, particularly in regards to the mental degradation that goes with maturing [58]. The flavonoid glycoside naringin, found in citrus natural products in enormous sums, is viable against numerous illnesses and conditions, like malignant growth, irritation, ulcers, osteoporosis, and apoptosis. Naringin has been displayed to further develop conduct and thinking in creature models of epilepsy brought about by kainic corrosive and Huntington's sickness brought about by 3-nitropropionic corrosive [59].

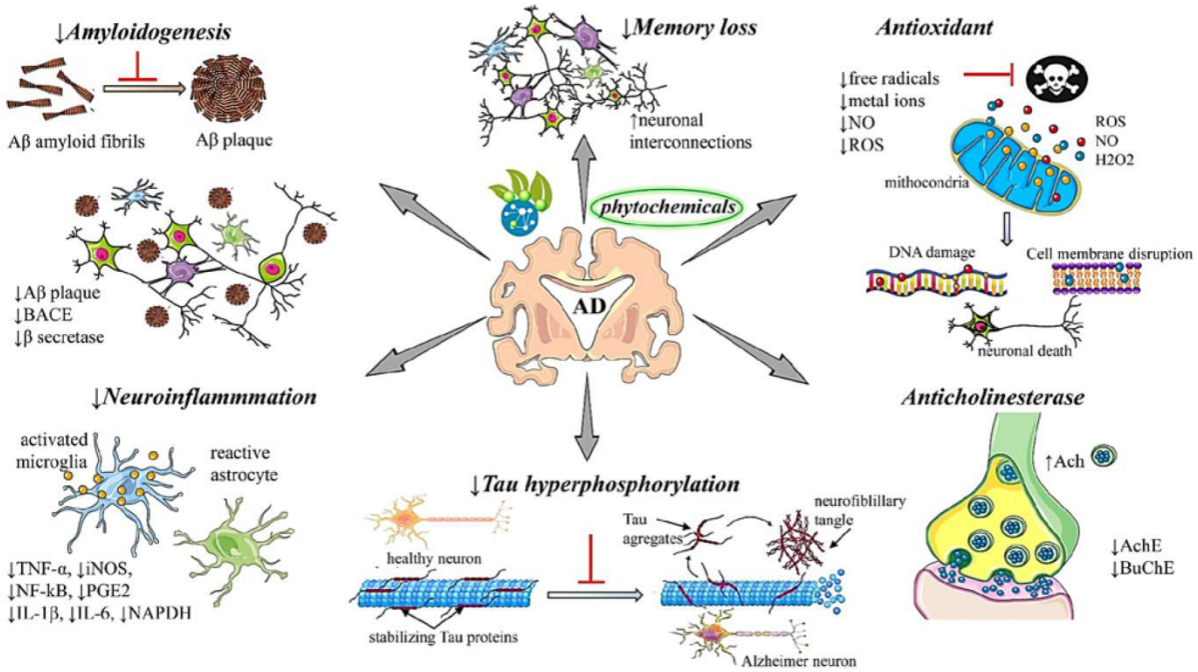

Figure: 6 Summed up plans with the most delegate neuroprotective systems of activities and impacts of phytochemicals in Alzheimer's illness. Shortened forms and images: ↑ increment, ↓ decline, acetylcholine. (ACh), acetylcholinesterase (Throb), amyloid beta (Aβ), beta-site amyloid forerunner protein separating compound 1 (BACE1), butyrylcholinesterase (BuChE), inducible nitric oxide synthase (iNOS), cancer putrefaction factor (TNF)- α, interleukin (IL), nitric oxide (NO), atomic variable kappa-light-chain-enhancer of initiated B cells (NF-kB), Prostaglandin E2 (PGE2), nicotinamide adenine dinucleotide phosphate. (NADPH), receptive oxygen species (ROS), cancer corruption factor-alpha (TNF-α).

Schizophrenia

Schizophrenia is a significant weakening illness of grown-ups in each general public, influencing around 1-1.5% of worldwide populace. The frequency of schizophrenia is higher among guys than female at a proportion of 1.4 to1.0 .Schizophrenia is the seventh most expensive problems on the planet It is a disorder including positive and negative side effects, and mental issues. Positive side effects, including visualizations and daydreams are the premier element of this

disorder. Pessimistic side effects incorporate the inability to communicate feelings and indifference. Mental issues emerge before the presence of psychosis and can go about as better indicator of the sickness. Dissimilar to other degenerative sicknesses, its beginning happens during early adulthood or late youth. Schizophrenia dominatingly happens during second and third ten years of the life, yet it can likewise influence older people It builds the gamble of other mind problems like Parkinson's sickness, mental imbalance, Alzheimer's infection and different sclerosis.

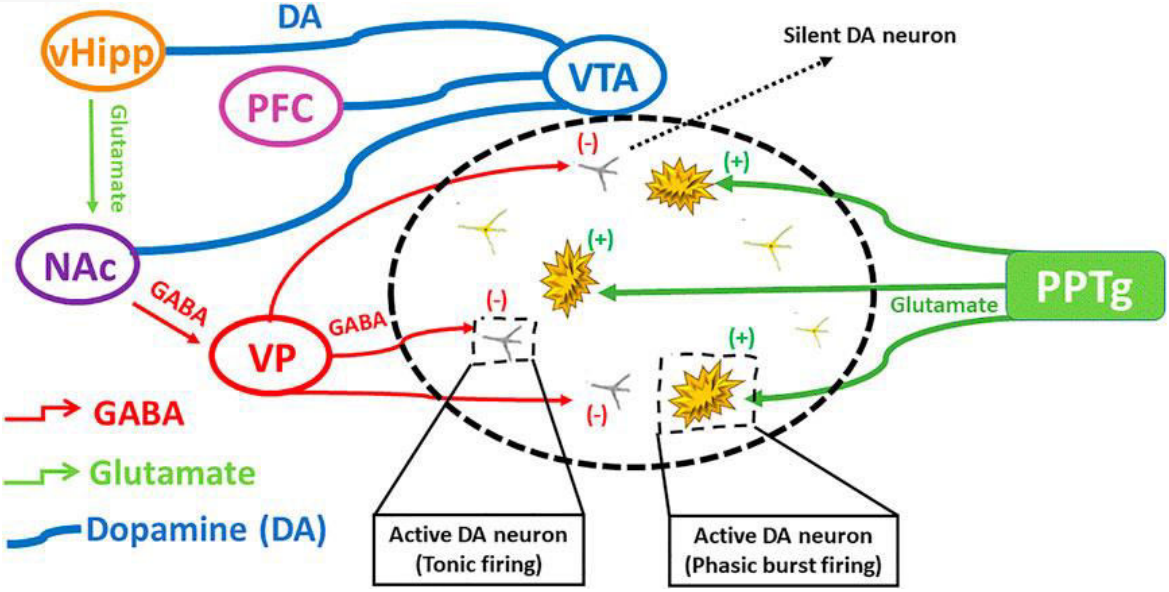

Figure:7 The interplay of different neuronal signals involved in schizophrenia. Ventral hippocampus regulates dopamine levels by excitatory projections towards ventral pallidum, that regulates GABAergic transmission producing silent DA neurons, influencing on DA rapid burst firing and tonic firing. Modified from (Grace and Gomes 2019).

Schizophrenia and apoptosis have been associated by means of both inherent (mitochondrial passing) and outward (demise receptor) pathways [60]. Cytochrome C interfaces with proapoptotic and against apoptotic proteins to set off the arrival of actuated caspase-3 (principally Bax and Bcl-2). Diabetes was forestalled in streptozotocin-treated rodents by organization of naringin, which restrained the creation of fiery and oxidative pressure middle people [61]. Diminished free extreme creation, diminished arrival of supportive of fiery cytokines (like interleukin-6 and TNF-α), and down-guideline of provocative proteins, for example, NF-κB have all been connected to its calming impacts in diabetic, ongoing bronchitis, and walker carcinosarcoma rodents. To assess if naringenin safeguards between endothelial tight intersections, we dissected the articulation and limitation of ZO-1, impeding, claudin-1, and claudin-2 across trial gatherings. ZO-1 protein articulation was essentially diminished in the TNF-α treated bunch contrasted with the benchmark group ($p < 0.05$) [62-63].

Conclusion and future space for discussion

Albeit innovative advances have significantly accelerated research on phytochemicals, we actually have far to go before we accumulate more conclusive proof with respect to the neuro-restorative advantages of home grown medications. Our information and other analysts' information persuade us to think that naringin and naringenin might be advantageous as neuro-restorative drugs as a result of their capacity to modify a few flagging pathways. The results so

far are in accordance with this hypothesis. In spite of the impediments of continuous clinical examinations, naringenin and naringin are promising treatments for different neurological circumstances, including Promotion, PD, cerebral ischemia, nervousness, wretchedness, schizophrenia, and a few other ongoing neurodegenerative illnesses. Given these hindrances, it is fundamental that pharmacokinetic research on naringin and naringenin organization be played out, that more precise measurements plans for various ailments be created, and that imaginative medication conveyance systems be created to support bioavailability in medical care circumstances.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest

Abbreviations

PD	Parkinson's disease
TRP	Transient receptor potential
NO	Nitric oxide
cGMP	Cyclic guanosine monophosphate
PKG	Protein kinase G
MAPK	Mitogen-activated protein kinase
GDNF	Growth differentiation and neurotrophic factor
AD	Alzheimer's disease
Aβ	Amyloid-β
AChE	Acetylcholinesterase
CaMKII	Calcium/calmodulin-dependent protein kinase II
GSH	Reduced glutathione
GPx	Glutathione peroxidase
GST	Glutathione-S-transferase
SOD	Superoxide dismutase
ROS	Reactive oxygen species
LPO	Lipid peroxidation
MDA	Malondialdehyde
5-HT	Serotonin
NE	Norepinephrine
BBB	Blood–brain barrier
iNOS	Inducible nitric oxide synthase

REFERENCES

1. Hardy, J.; Gwinn-Hardy, K. Genetic classification of primary neurodegenerative disease. Science 1998, 282, 1075–1079.
2. Thrall, J.H. Prevalence and costs of chronic disease in a health care system structured for treatment of acute illness. Radiology 2005, 235, 9–12.
3. Sweeney, M.D.; Sagare, A.P.; Zlokovic, B.V. Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat. Rev. Neurol. 2018, 14, 133–150. [CrossRef] [PubMed]
4. Singh, A.K.; Kashyap, M.P.; Tripathi, V.K.; Singh, S.; Garg, G.; Rizvi, S.I. Neuroprotection through rapamycin-induced activation of autophagy and PI3K/Akt1/mTOR/CREB signaling against amyloid-β-induced oxidative stress, synaptic/neurotransmission dysfunction, and neurodegeneration in adult rats. Mol. Neurobiol. 2017, 54, 5815–5828.
5. Giráldez-Pérez, R.M.; Antolín-Vallespín, M.; Muñoz, M.D.; Sánchez-Capelo, A. Models of α-synuclein aggregation in Parkinson's disease. Acta Neuropathol. Commun. 2014, 2, 176.
6. Nah, J.; Yuan, J.; Jung, Y.-K. Autophagy in neurodegenerative diseases: From mechanism to therapeutic approach. Mol. Cells 2015, 38, 381–389.
7. Guo, F.; Liu, X.; Cai, H.; Le, W. Autophagy in neurodegenerative diseases: Pathogenesis and therapy. Brain Pathol. 2018, 28, 3–13.
8. Vallee, A.; Lecarpentier, Y.; Guillevin, R.; Vallee, J.N. Effects of cannabidiol interactions with Wnt/beta-catenin pathway and PPARgamma on oxidative stress and neuroinflammation in Alzheimer's disease. Acta Biochim. Biophys. Sin. 2017, 49, 853–866.
9. Tang, Y.; Le, W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. Mol. Neurobiol. 2016, 53, 1181–1194.
10. Cherry, J.D.; Olschowka, J.A.; O'Banion, M.K. Arginase 1+ microglia reduce Aβ plaque deposition during IL-1β-dependent neuroinflammation. J. Neuroinflammation 2015, 12, 203.
11. Hu, X.; Leak, R.K.; Shi, Y.; Suenaga, J.; Gao, Y.; Zheng, P.; Chen, J. Microglial and macrophage polarization-new prospects for brain repair. Nat. Rev. Neurol. 2015, 11, 56–64.
12. Zhang, B.; Wei, Y.Z.; Wang, G.Q.; Li, D.D.; Shi, J.S.; Zhang, F. Targeting MAPK Pathways by Naringenin Modulates Microglia M1/M2 Polarization in Lipopolysaccharide-Stimulated Cultures. Front. Cell. Neurosci. 2018, 12, 531.
13. Zobeiri, M.; Belwal, T.; Parvizi, F.; Naseri, R.; Farzaei, M.H.; Nabavi, S.F.; Sureda, A.; Nabavi, S.M. Naringenin and its nano-formulations for fatty liver: Cellular modes of action and clinical perspective. Curr. Pharm. Biotechnol. 2018, 19, 196–205.
14. Hernández-Aquino, E.; Muriel, P. Naringenin and the liver. In Liver Pathophysiology; Elsevier: Amsterdam, The Netherlands, 2017; pp. 633–651.
15. Yen, F.-L.; Wu, T.-H.; Lin, L.-T.; Cham, T.-M.; Lin, C.-C. Naringenin-loaded nanoparticles improve the physicochemical properties and the hepatoprotective effects of naringenin in orally-administered rats with CCl 4-induced acute liver failure. Pharm. Res. 2009, 26, 893–902.

16. Jiménez-Moreno, N.; Cimminelli, M.J.; Volpe, F.; Ansó, R.; Esparza, I.; Mármol, I.; Rodríguez-Yoldi, M.J.; Ancín-Azpilicueta, C. Phenolic Composition of Artichoke Waste and Its Antioxidant Capacity on Differentiated Caco-2 Cells. Nutrients 2019, 11, 1723.
17. Hernández-Aquino, E.; Muriel, P. Beneficial effects of naringenin in liver diseases: Molecular mechanisms. World J. Gastroenterol. 2018, 24, 1679–1707.
18. Cook, N.C.; Samman, S. Flavonoids—Chemistry, Metabolism, Cardioprotective Effects, and Dietary Sources. J. Nutr. Biochem. 1996, 7, 66–76.
19. Choudhury, R.; Chowrimootoo, G.; Srai, K.; Debnam, E.; Rice-Evans, C.A. Interactions of the Flavonoid Naringenin in the Gastrointestinal Tract and the Influence of Glycosylation. Biochem. Biophys. Res. Commun. 1999, 265, 410–415.
20. Croft, K.D. The Chemistry and Biological Effects of Flavonoids and Phenolic Acids A. Ann. N. Y. Acad. Sci. 1998, 854, 435–442.
21. Scalbert, A.; Williamson, G. Dietary Intake and Bioavailability of Polyphenols. J. Nutr. 2000, 130, 2073S–2085S.
22. Pietta, P.; Minoggio, M.; Bramati, L. Plant Polyphenols: Structure, Occurrence and Bioactivity. Stud. Nat. Prod. Chem. 2003, 28, 257–312.
23. Burke, R.E.; O'Malley, K. Axon Degeneration in Parkinson's Disease. Exp. Neurol. 2013, 246, 72–83.
24. Savitt, J.M.; Dawson, V.L.; Dawson, T.M. Diagnosis and Treatment of Parkinson Disease: Molecules to Medicine. J. Clin. Investig. 2006, 116, 1744–1754.
25. Shulman, J.M.; De Jager, P.L.; Feany, M.B. Parkinson's Disease: Genetics and Pathogenesis. Annu. Rev. Pathol. Mech. Dis. 2011, 6, 193–222.
26. Dexter, D.T.; Jenner, P. Parkinson Disease: From Pathology to Molecular Disease Mechanisms. Free Radic. Biol. Med. 2013, 62, 132–144.
27. AlDakheel, A.; Kalia, L.V.; Lang, A.E. Pathogenesis-Targeted, Disease-Modifying Therapies in Parkinson Disease. Neurotherapeutics 2014, 11, 6–23.
28. Olanow, C.W.; Tatton, W.G. Etiology and Pathogenesis of Parkinson's Disease. Annu. Rev. Neurosci. 1999, 22, 123.
29. Zbarsky, V.; Datla, K.P.; Parkar, S.; Rai, D.K.; Aruoma, O.I.; Dexter, D.T. Neuroprotective Properties of the Natural Phenolic Antioxidants Curcumin and Naringenin but Not Quercetin and Fisetin in a 6-OHDA Model of Parkinson's Disease. Free Radic. Res. 2005, 39, 1119–1125.
30. Golechha, M.; Chaudhry, U.; Bhatia, J.; Saluja, D.; Arya, D.S. Naringin Protects against Kainic Acid-Induced Status Epilepticus in Rats: Evidence for an Antioxidant, Anti-Inflammatory and Neuroprotective Intervention. Biol. Pharm. Bull. 2011, 34, 360–365.
31. Ahmed, S.; Khan, H.; Aschner, M.; Hasan, M.M.; Hassan, S.T.S. Therapeutic Potential of Naringin in Neurological Disorders. Food Chem. Toxicol. 2019, 132, 110646.
32. Raza, S.S.; Khan, M.M.; Ahmad, A.; Ashafaq, M.; Islam, F.; Wagner, A.P.; Safhi, M.M. Neuroprotective Effect of Naringenin Is Mediated through Suppression of NF-KB Signaling Pathway in Experimental Stroke. Neuroscience 2013, 230, 157–171.
33. Harrison, W.T.A.; Yathirajan, H.S.; Sarojini, B.K.; Narayana, B.; Anilkumar, H.G. Do C—H· · · O and C—H· · · π Interactions Help to Stabilize a Non-Centrosymmetric Structure for Racemic 2, 3-Dibromo-1, 3-Diphenylpropan-1-One? Acta Crystallogr. Sect. C Cryst. Struct. Commun. 2005, 61, o728–o730.
34. Gopinathan, G.; Teravainen, H.; Dambrosia, J.M.; Ward, C.D.; Sanes, J.N.; Stuart, W.K.; Evarts, E.V.; Calne, D.B. Lisuride in Parkinsonism. Neurology 1981, 31, 371.

35. Li, M.; Fu, Q.; Li, Y.; Li, S.; Xue, J.; Ma, S. Emodin Opposes Chronic Unpredictable Mild Stress Induced Depressive-like Behavior in Mice by Upregulating the Levels of Hippocampal Glucocorticoid Receptor and Brain-Derived Neurotrophic Factor. Fitoterapia 2014, 98, 1–10.
36. Mitra, S.; Anjum, J.; Muni, M.; Das, R.; Rauf, A.; Islam, F.; Emran, T.B.; Semwal, P.; Hemeg, H.A.; Alhumaydhi, F.A. Exploring the Journey of Emodin as a Potential Neuroprotective Agent: Novel Therapeutic Insights with Molecular Mechanism of Action. Biomed. Pharmacother. 2022, 149, 112877.
37. Mitra, S.; Lami, M.S.; Uddin, T.M.; Das, R.; Islam, F.; Anjum, J.; Hossain, M.J.; Emran, T.B. Prospective multifunctional roles and pharmacological potential of dietary flavonoid narirutin. Biomed. Pharmacother. 2022, 150, 112932.
38. Halbreich, U.; Kahn, L.S. Role of Estrogen in the Aetiology and Treatment of Mood Disorders. CNS Drugs 2001, 15, 797–817.
39. Yang, J.; Yuan, L.; Wen, Y.; Zhou, H.; Jiang, W.; Xu, D.; Wang, M. Protective Effects of Naringin in Cerebral Infarction and Its Molecular Mechanism. Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 2020, 26, e918772.
40. Sveinsson, O.A.; Kjartansson, O.; Valdimarsson, E.M. Cerebral Ischemia/Infarction-Diagnosis and Treatment. Laeknabladid 2014, 100, 393–401.
41. Olmez, I.; Ozyurt, H. Reactive Oxygen Species and Ischemic Cerebrovascular Disease. Neurochem. Int. 2012, 60, 208–212.
42. Tsung, A.; Klune, J.R.; Zhang, X.; Jeyabalan, G.; Cao, Z.; Peng, X.; Stolz, D.B.; Geller, D.A.; Rosengart, M.R.; Billiar, T.R. HMGB1 Release Induced by Liver Ischemia Involves Toll-like Receptor 4–Dependent Reactive Oxygen Species Production and Calcium-Mediated Signaling. J. Exp. Med. 2007, 204, 2913–2923.
43. Ma, L.L.; Song, L.; Yu, X.D.; Yu, T.X.; Liang, H.; Qiu, J.X. The Clinical Study on the Treatment for Acute Cerebral Infarction by Intra-Arterial Thrombolysis Combined with Mild Hypothermia. Eur. Rev. Med. Pharmacol. Sci. 2017, 21, 1999–2006.
44. Jeong, H.S.; Song, H.-J.; Kim, S.-B.; Lee, J.; Kang, C.W.; Koh, H.-S.; Shin, J.E.; Lee, S.H.; Kwon, H.J.; Kim, J. A Comparison of Stent-Assisted Mechanical Thrombectomy and Conventional Intra-Arterial Thrombolysis for Acute Cerebral Infarction. J. Clin. Neurol. 2013, 9, 91–96.
45. Bailey, D.G.; Arnold, J.M.O.; Strong, H.A.; Munoz, C.; Spence, J.D. Effect of Grapefruit Juice and Naringin on Nisoldipine Pharmacokinetics. Clin. Pharmacol. Ther. 1993, 54, 589–594.
46. Navipour, E.; Neamatshahi, M.; Barabadi, Z.; Neamatshahi, M.; Keykhosravi, A. Epidemiology and Risk Factors of Alzheimer's Disease in Iran: A Systematic Review. Iran. J. Public Health 2019, 48, 2133–2139.
47. Pedersen, W.A.; McMillan, P.J.; Kulstad, J.J.; Leverenz, J.B.; Craft, S.; Haynatzki, G.R. Rosiglitazone Attenuates Learning and Memory Deficits in Tg2576 Alzheimer Mice. Exp. Neurol. 2006, 199, 265–273.
48. Rajmohan, R.; Reddy, P.H. Amyloid-Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's Disease Neurons. J. Alzheimer's Dis. 2017, 57, 975–999.
49. Jin, H.; Wang, W.; Zhao, S.; Yang, W.; Qian, Y.; Jia, N.; Feng, G. Aβ-HBc Virus-like Particles Immunization without Additional Adjuvant Ameliorates the Learning and Memory and Reduces Aβ Deposit in PDAPP Mice. Vaccine 2014, 32, 4450–4456.

50. Gauthier, S.; Scheltens, P.; Cummings, J. Alzheimer's Disease and Related Disorders; CRC Press: Boca Raton, FL, USA, 2005; ISBN 0203931742.
51. Mimura, M.; Yano, M. Memory Impairment and Awareness of Memory Deficits in Early-Stage Alzheimer's Disease. Rev. Neurosci. 2006, 17, 253–266.
52. Fakhri, S.; Abbaszadeh, F.; Dargahi, L.; Jorjani, M. Astaxanthin: A Mechanistic Review on Its Biological Activities and Health Benefits. Pharmacol. Res. 2018, 136, 1–20.
53. Bao, X.-Q.; Li, N.; Wang, T.; Kong, X.-C.; Tai, W.-J.; Sun, H.; Zhang, D. FLZ Alleviates the Memory Deficits in Transgenic Mouse Model of Alzheimer's Disease via Decreasing Beta-Amyloid Production and Tau Hyperphosphorylation. PLoS ONE 2013, 8, e78033.
54. Mimura, M. Memory Impairment and Awareness of Memory Deficits in Early-Stage Alzheimer's Disease. Tohoku J. Exp. Med. 2008, 215, 133–140.
55. Obulesu, M.; Jhansilakshmi, M. Neuroinflammation in Alzheimer's Disease: An Understanding of Physiology and Pathology. Int. J. Neurosci. 2014, 124, 227–235.
56. Howes, O.; McCutcheon, R.; Stone, J. Glutamate and Dopamine in Schizophrenia: An Update for the 21st Century. J. Psychopharmacol. 2015, 29, 97–115.
57. Li, P.-F.; Dietz, R.; von Harsdorf, R. P53 Regulates Mitochondrial Membrane Potential through Reactive Oxygen Species and Induces Cytochrome C-Independent Apoptosis Blocked by Bcl-2. EMBO J. 1999, 18, 6027–6036.
58. Zou, W.; Xiao, Z.; Wen, X.; Luo, J.; Chen, S.; Cheng, Z.; Xiang, D.; Hu, J.; He, J. The Anti-Inflammatory Effect of Andrographis paniculata (Burm. f.) Nees on Pelvic Inflammatory Disease in Rats through down-Regulation of the NF-KB Pathway. BMC Complement. Altern. Med. 2016, 16, 483.
59. Stenvinkel, P.; Ketteler, M.; Johnson, R.J.; Lindholm, B.; Pecoits-Filho, R.; Riella, M.; Heimbürger, O.; Cederholm, T.; Girndt, M. IL-10, IL-6, and TNF-α: Central Factors in the Altered Cytokine Network of Uremia—The Good, the Bad, and the Ugly. Kidney Int. 2005, 67, 1216–1233.
60. Yao, Q.; Pecoits-Filho, R.; Lindholm, B.; Stenvinkel, P. Traditional and Non-Traditional Risk Factors as Contributors to Atherosclerotic Cardiovascular Disease in End-Stage Renal Disease. Scand. J. Urol. Nephrol. 2004, 38, 405–416.
61. Higley, M.J.; Picciotto, M.R. Neuromodulation by Acetylcholine: Examples from Schizophrenia and Depression. Curr. Opin. Neurobiol. 2014, 29, 88–95.
62. Futamura, T.; Toyooka, K.; Iritani, S.; Niizato, K.; Nakamura, R.; Tsuchiya, K.; Someya, T.; Kakita, A.; Takahashi, H.; Nawa, H. Abnormal Expression of Epidermal Growth Factor and Its Receptor in the Forebrain and Serum of Schizophrenic Patients. Mol. Psychiatry 2002, 7, 673–682.