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Neuroprotective effect of flavonoids: A systematic review

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Abstract

Neurodegenerative disorders such as Parkinson's and Alzheimer's disease are underpinned by neuronal damage corollary to the cascade of events pitched in by neuron inflammatory processes. Increase in cases of neurodegenerative diseases and ageing population indicates the need for developing new strategies to prevent or treat brain dysfunction and associated cognitive decline. Flavonoids have been documented for various health promoting effects. They exert multiple neuroprotective actions within the brain, such as protection of neurons from neurotoxins, suppression of neuron-inflammation and thus improve memory, learning and cognitive function. Two processes appear to be the basis of these effects. Firstly, they promote neuronal survival and synaptic plasticity by inhibition of apoptosis triggered by neurotoxic species due to interaction with critical protein and lipid kinase signaling cascades. Secondly they induce beneficial effects on the vascular system leading to changes in cerebrovascular blood flow capable of causing angiogenesis, neurogenesis and neuronal morphology. Limiting neurodegeneration and prevention or reversal of age-dependent loss in cognitive performance is possible by consumption of flavonoids-rich food throughout life. Thus flavonoids are strong candidates of being an important precursor molecule in the development of new generation of brain enhancing drugs. The present review accentuates current information on neuroprotective effects of flavonoids.

Keywords: flavonoids, neuro-inflammatory, neurodegeneration, rutin, apigenin, hesperidin, kaempferol

1. Introduction

Research on preventive action against age-related neurodegeneration and potential modulatory neuronal function of flavonoids has gained profound interest recently. Improvements in cognition by including flavonoids rich plant or food extract in humans and animal dietary supplementation have been reported indicating probable protection of vulnerable neurons, enhancement in existing neuronal function or stimulation of neuronal regeneration (Youdim *et al.* 2001) [92]. Studies have shown their neuroprotective potential in both, oxidative stress (Inanami *et al.* 1998) [27] and Ab- induced neuronal death models (Luo *et al.* 2002) [36]. Flavonoids rich ginkgo biloba extracts have been seen to exert beneficial and neuromodulatory effects regarding age-related dementias and Alzheimer's disease (Bastianetto *et al.* 2000) [6]. In case of lesioning with 6-hydroxydopamine; individual flavonoids such as the citrus flavanone tangeretin has been observed to maintain nigro-striatal integrity and functionality, suggestive of its potential use as neuroprotective agent against the underlying pathology associated with Parkinson's disease (Datla *et al.* 2001) [12]. Reversal of certain age related decline, prevention of cognitive loss and memory associated with aging are some more beneficial effects of flavonoids. Flavonoids are powerful antioxidants *in vitro*, but *in vivo*, due to extensive biotransformation and conjugation during their absorption from gastrointestinal tract (GI), in the liver and finally in cells, the antioxidative property is limited (Evans C *et al.* 1995) [15]. Phase I (hydrolyzing and oxidizing) and phase II (conjugating and detoxifying) reactions in small intestine and liver use dietary flavonoids (and other polyphenols) as substrate leaving them de-glucosylated and metabolized into glucuronoids, sulphates and O- methylated derivatives (Spencer *et al.* 1999) [73]. Further breakdown of flavonoids into simple phenolic acids is induced by enzymes of the gut microflora in the colon, which then probably undergoes absorption and further metabolized in the liver. Antioxidant potential of circulating metabolites of flavonoids, such as sulphates, glucuronoids and conjugated O- methylated forms, or intracellular metabolites like flavonoids-GSH adducts, is significantly lesser relative to forms found in plants (Spencer *et al.* 2001) [60]. Reduction in effectiveness of such conjugates and metabolites in scavenging reactive oxygen and nitrogen species in the circulation is reported in comparison to their parent aglycones (Silva *et al.* 1998 and Shirai *et al.* 2001) [13, 64]. Flavonoids must cross the blood brain barrier (BBB), which controls entry of xenobiotics into the brain, in order to access the brain.

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Relevant *in vitro* and *in situ* models have shown the passing of flavonones such as naringenin, hesperetin and their *in vivo* metabolites, along with some dietary anthocynins pelargonidin-3-glucoside and cyanidine-3-rutinoside across the BBB. Compound lipophilicity governs the degree of their BBB penetration (Youdim *et al.* 2003) [191], meaning less polar O-methylated metabolites may be capable to greater brain uptake than the more polar flavonoid glucuronoides. Suggestive of evidence, certain drug glucuronoides may cross the BBB and exert pharmacological effects (Kroemer *et al.* 1992) [133], indicating specific *in vivo* uptake mechanism for glucuronoides. Their interaction with specific efflux transporters expressed in the BBB, such as P-glycoprotein may also be a factor for their brain entry (Lin *et al.* 2003) [34], difference in *in situ* flux of quercetin and naringenin into the brain seems to be depending on this factor (Youdim *et al.* 2004) [90]. Post oral administrative entry of epigallocatechin gallate (Suganuma *et al.* 1998) [166], epicatechin and anthocyanins (D. Vauzour 2008) [20] in brain has been seen in animals, whilst flavanones have been found in brain after their intravenous administration (Peng *et al.* 1998) [46]. Likewise different regions of rat and pig brains of blueberry fed animals have shown anthocyanins, with 11 intact ones found in the cortex and cerebellum (Kim *et al.* 2001) [31].

2. Prevention of neurodegenerative disease

Sensory dysfunction and functional loss in neurodegenerative diseases is a result of loss of central nervous system (CNS) (Mattson *et al.* 2004) [43]. The neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS) *etc.* (Saxena *et al.* 2011) [70]. Show pathological signs which are ageing, disability and mortality. Prominent AD symptoms are irreversible memory impairment, cognitive and behavioral disturbances (Allan *et al.* 2002) [3]. Neuronal degeneration is caused by pathologic processes including oxidative stress, inflammation, mitochondrial dysfunction, apoptosis and genetic factors (Fu W *et al.* 2015) [18]. Peroxidation reactions highly affect central nervous system which contains high level of polyunsaturated fatty acids. Neural cells are more susceptible to oxidative damage than other tissues because antioxidant activity of the brain is lower than other tissues. High levels of ascorbate in general and iron in certain regions of human brain is seen but CNS is not particularly enriched in antioxidant defense. Free radicals such as singlet oxygen, superoxide, peroxy radicals and hydroxyl radicals are called reactive oxygen species (ROS). Various diseases like diabetes, asthma, carcinogenesis, arthritis, cancer, rheumatism and various neurodegenerative diseases are corollary to the damage caused by ROS to cellular functions. Cells or organisms protect themselves from these damages by the help of antioxidants. Loss in balance between ROS production and antioxidant defense causes oxidative stress. All medicinal plants are protected from oxidative damage due to presence of antioxidant compound. Prevention and therapy of various neurodegenerative diseases and neuronal dysfunction is aided essentially by natural products extracted from medicinal plants. Delay in neurodegeneration and improvement in memory and cognitive functions by use of polyphenolic and alkaloid compounds isolated from plants is suggested by various studies (Floyd *et al.* 1992) [19]. Flavonoids exert multiple neuroprotective actions within the brain, such as protection of neurons from neurotoxins, suppression of neuro-inflammation and thus improve memory, learning and cognitive function (Sharma *et al.* 2015) [69]. Flavonoids exert

anti-ageing and rejuvenating effects by activating various signaling pathways and thus protect the brain. Two processes appear to be the basis of these effects. Firstly, they promote neuronal survival and synaptic plasticity by inhibition of apoptosis triggered by neurotoxic species due to interaction with critical protein and lipid kinase signaling cascades. Secondly they induce beneficial effects on the vascular system leading to changes in cerebrovascular blood flow capable of causing angiogenesis, neurogenesis and neuronal morphology (Chonodrohianni *et al.* 2010) [7]. Prevention of age-related neurodisorders is a result of modulatory neuronal function of flavonoids (Rodriguez *et al.* 2014) [54]. Limiting neurodegeneration and prevention or reversal of age-dependent loss in cognitive performance is possible by consumption of flavonoids-rich food throughout life. Thus flavonoids are strong candidates of being an important precursor molecule in the development of new generation of brain enhancing drugs (Fariaa *et al.* 2012) [17].

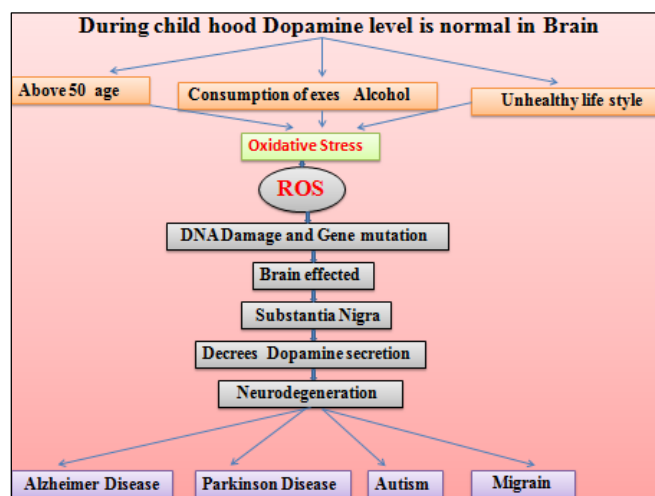


Fig 1: During child hood Dopamine level is always normal in brain. Due to Above age 50, due to consumption of exes alcohol, due to unhealthy life style oxidative stress will caused in brain. ROS(Reactive Oxygen Species) goes beyond the limit which can be stabilized by the action of antioxidants is called oxidative stress DNA damage and Gene mutation occur then Brain will effected as a results of oxidative stress substantia nigra decrees the dopamine secretion that is called Neurodegeneration. Neurodegeneration caused Alzheimer disease, Parkinson disease, Autism and Migrain

Many of currently available drugs were originally isolated from plants or their constituents. Potential of anticholinesterase (Anti-Che) isolated from plants in treatment of Alzheimer's disease has been investigated. Improvement of neuron-inflammation, convulsion, anxiety *etc.* was achieved by using plants and their isolated components, due to their anti-inflammatory and antioxidant activity, also presence of various complex chemical substances exhibit beneficial property for treatment of toxicity. Plant organs included in herbal medicine were: leaves, flowers, roots, stem and seeds were used as alternative and complimentary therapy. Neuroprotective characteristic is seen in some herbs which have curcumin, ginsenoside, polyphenols, resveratrol, triptolide *etc.*

3. Flavonoids regulate neuro-inflammatory proceses

The most common group of polyphenolic compounds in the human diet is flavonoids. It shares a common feature consisting of two aromatic carbon rings, benzopyran (A and C rings) and a benzene ring (B ring) and may be divided in

various subgroups based on the degree of the oxidation of the C-ring, the hydroxylation pattern of the ring structure and the substitution of the 3-position. Following are some important dietary group of flavonoids: 1) flavones (e.g. apigenin, luteolin), which are found in parsley and celery; 2) flavonols (e.g. kaempferol, quercetin), which are found in onions, leeks, broccoli; 3) isoflavones (e.g. daidzein, genistein), which are mainly found in soy and soy products; 4) flavanones/flavanonols (e.g. hesperetin, naringenin/astilbin, engeletin), which are mainly found in citrus fruit, herbs (oregano) and wine; 5) flavanols (e.g. (p)-catechin, (l)-epicatechin, epigallocatechin, epigallocatechin gallate (EGCG)), which are abundant in green tea, red wine, chocolate; and 6) anthocyanidins (e.g. pelargonidin, cyanidin, malvidin), whose sources include red wine and berry fruits. Further information regarding the structure and classes of flavonoids may be found in the thorough review by (Rodriguez-Mateos *et al.* 2014) [54]. Bioavailability and biological effects of flavonoids greatly depend on their biotransformation by the liver and by the gut microbiota and their bioaccessibility to the brain inspite of being good candidates for neuroprotection in terms of their ability to modulate neuroinflammation in the central nervous system (CNS). Although traversal of flavonoids and to some extent, their metabolites through the blood brain barrier has been reported in agreement to their degree of lipophilicity, but it does not seem to be the sole factor and role of efflux transporter in brain has to be considered (Rodriguez-Mateos *et al.* 2014) [54].

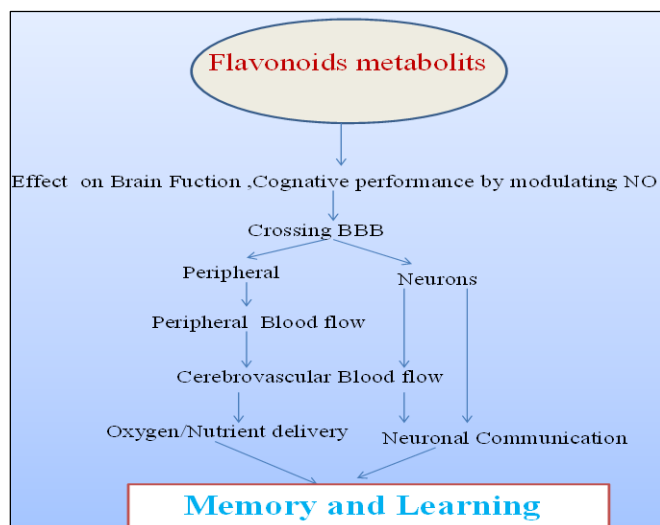
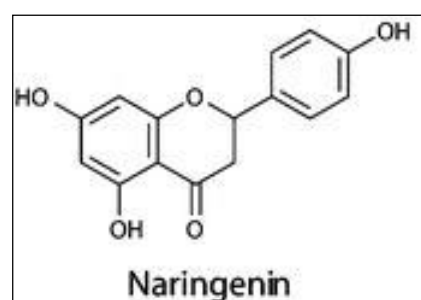
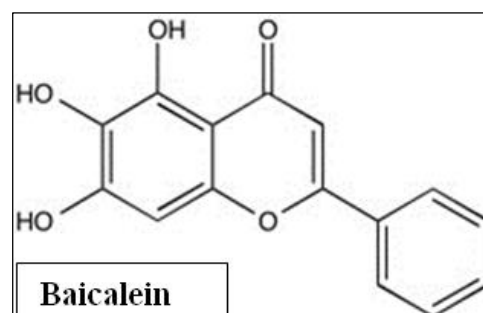
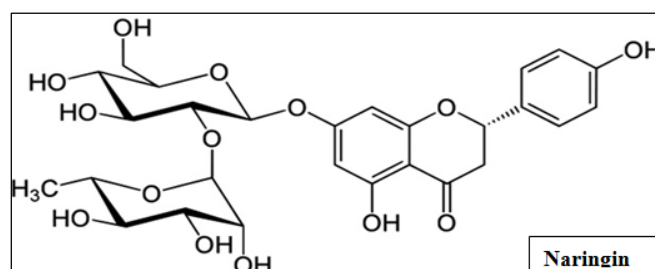
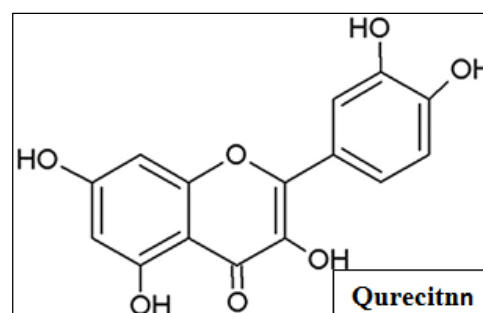
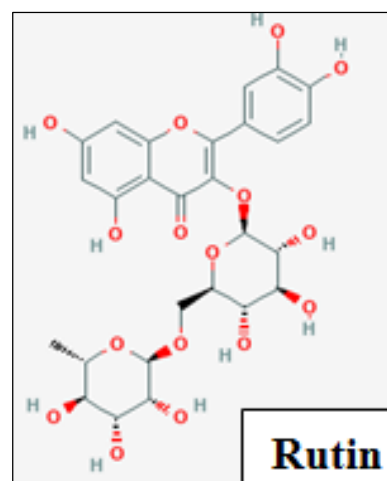


Fig 2: Mechanisms underpinning the effects dietary flavonoids on memory and learning (Williams and Spencer, 2012). Circulating flavonoid metabolites might indirectly affect brain function and cognitive performance by modulating Nitric-Oxide (NO) dependent cerebrovascular function at the level of the cerebral endothelium or (Spencer, 2008) [20] by crossing the Blood Brain Barrier (BBB), some flavonoid metabolites may act centrally by modulating neuronal receptors (e.g. TrkB, NMDA), signaling kinases (e.g. Akt, ERK1/2) and neurotrophins (e.g. BDNF) leading to changes in synaptic function.

4. Effect of flavonoids on neurodegenerative disorders

Due to their therapeutic properties flavonoids seem to be a unique class of therapeutic molecules. Different flavonoids like Rutin, Apigenin, Hesperidin, Kaempferol, Quercetin, Naringenin, Astilbin, Catechin, Epicatechin, epigallocatechin, epigallocatechin gallate act in neurodegenerative diseases to protect brain from the neurodegenerative disorders. These

Flavonoids present in various medicinal plants have an ability to suppress neuroinflammation and have potential to protect brain against neuronal injury and promote memory, learning and cognitive function.



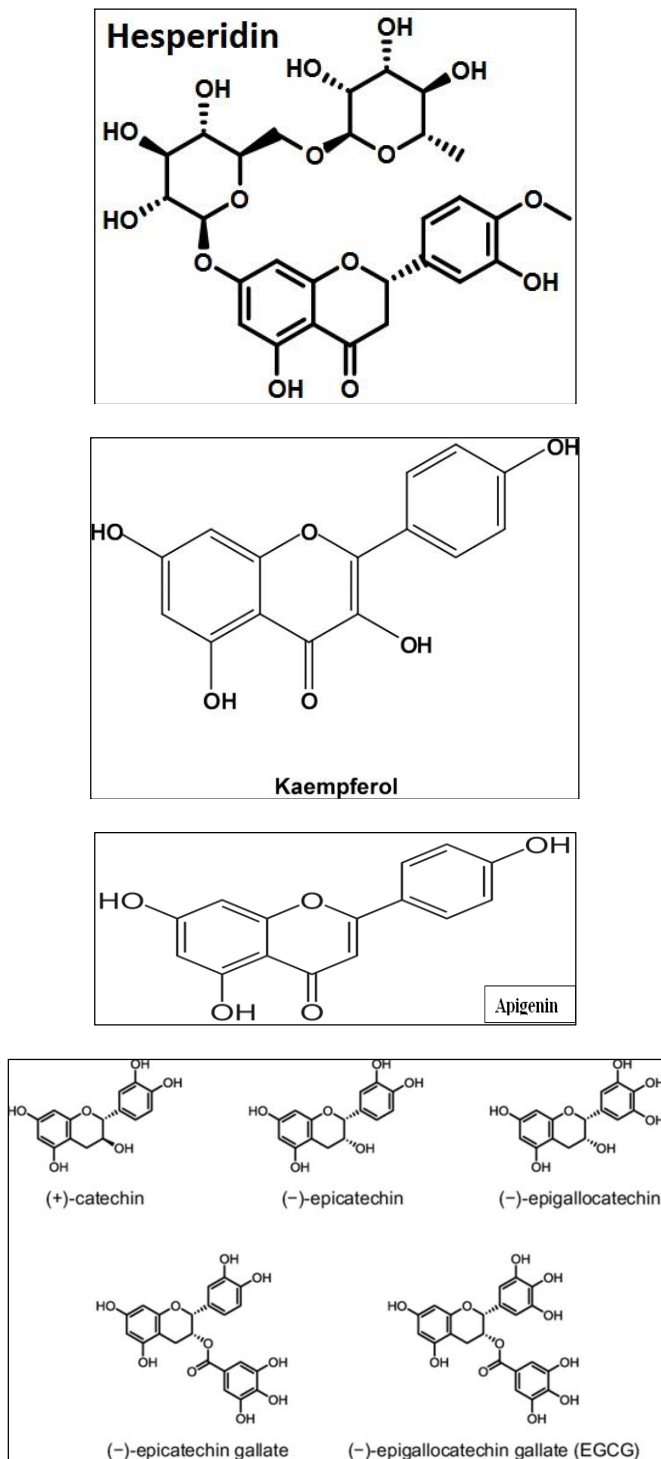


Fig 3: The Structure of Flavonoids, neuro-inflammatory, neurodegeneration, Rutin, Apigenin, Hesperidin, Kaempferol, Naringenin, Anthocyanins, Naringin, Baicalein, Catechin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate (EGCG).

4.1 Rutin

Rutin is one of the active constituents in tea leaves, apples and many more. Number of pharmacological effects of rutin, also known as vitamin P or rutoside, has been explored and it has also been observed for its nutraceutical effects. Apart from promoting neural crest cell survival, thyroid uptake and preventing neuro-inflammation it acts as sedative, anticonvulsant, anti-Alzheimer, Stroke, analgesic and anti-arthritis, showing anti-diabetic and anti-hypercholesterolemic effects. Different effects are observed in other systems of body like: hypertension, blood coagulation, antiplatelet aggregatory effects, cardioprotective effects in cardiovascular

system, antiulcer effects in gastrointestinal system, antiosteoporotic and antiosteopenic effect in bones, antiasthmatic activity and other associated effects in respiratory system, Diuretic effect in excretory system, anticataract and ophthalmic effect and retino-protective activity, in Eye, Sunscreen effects, In atopic dermatitis, effect on sperm quality and male reproductive organs in reproductive system, body strength, prevention of, splenocyte and Anti fatigue activity in immune system It has various other protective functions like anticancer effects, chemotherapeutic activity, antibacterial activity, antifungal activity, antimycobacterial activity, larvicidal activity, antimalarial activity, antiretroviral activity, antiviral activity, organ protective effects, neuroprotective activity protective effect on lung tissue, apoptosis, hepatoprotective activity, nephroprotective activity, protective effect on blood vasculature, wound healing activity, radio modulatory effects. It also participates in pharmacokinetics and drug interaction (Ganeshpurkar and Saluja 2017).

4.2 Apigenin

Remarkable anti-inflammatory, antioxidant and anti-carcinogenic properties have been reported in apigenin. There has been significant progress in studying its biological effects at cellular and molecular levels. Studies show the cancer chemopreventive effects of apigenin in an organ-specificity format, evaluating its limitations and its considerable potential for development as a cancer chemopreventive agent (Patel *et al.* 2007) [47].

4.3 Hesperidin

Hesperidin shows significant 702nti-inflammatory, analgesic, antifungal, antiviral, and anticancer properties (Gaur *et al.* 2010) [21]. Contribution to the intracellular antioxidant defense system and reduction in neuronal death are some of its remarkable benefits. It has also been reported to act as a powerful agent against superoxide, singlet oxygen and hydroxyl radicals (Galleano *et al.* 2010) [22]. It also has a pharmacological profile as a sedative and sleep-inducing compound in the central nervous system (CNS) (Marder *et al.* 2003) [42]. In diverse cases of neuronal insults such as ischemia, oxidative-induced damage, Dopamine-induced neurotoxicity it exhibits neuro-protective property and functions as anti-amyloidogenic in Alzheimer's disease (Obregon *et al.* 2006) [45].

4.4 Kaempferol

Plants and other foods such as apples, broccoli, onions and red wine naturally contain the flavonoid, quercetin (3, 3', 4', 5, 7-pentahydroxyflavone), which exhibits antiapoptotic, antioxidant, pharmacological and cardioprotective properties (Li *et al.* 2017). Their neuroprotective action is thought to be associated to the prevention of neurodegenerative disorders like Parkinson's disease and Alzheimer's disease (Spagnuolo *et al.* 2017) [71].

4.5 Naringenin

A flavonoid derived from milk thistle of the species *Silybum marianum* is Silibinin, (2R, 3R)-3, 5, 7-trihydroxy-2-[(2R, 3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2, 3-dihydro-1, 4-benzodioxin-6-yl]-2, 3-dihydro-4H -chromen-4-one (Švagera *et al.* 2003) [68]. Effects of silibinin on the inflammatory process, oxidative stress, autophagy (Wang *et al.* 2016) [85] and effect of silibinin treatment on locomotor activity, learning, and spatial memory was recently

investigated by Song. In addition to the concentration of the proinflammatory cytokines IL-1 β , IL-4, and the levels of the antioxidant enzyme (GSH) and malondialdehyde (MDA), a lipid peroxidation marker, which occurs in response to excess free radicals the NF- κ B (nuclear factor kappa B), a regulator of the immune response released in different situations among these oxidative stress, cyclooxygenase-2 (COX-2), i-NOS (nitric oxide synthase) are products of glial cells contributing to an inflammatory response in the brain. P-53, a tumor suppressor agent, is a critical component of the acute stress cell response, and p-p53 is its phosphorylated component. Memory damage and spatial learning caused by the treatment of A β 25-35 is seen to be reversed by silibinin, also improvement in ability to recognize new objects, memory flexibility and decrease in anxiety-like behavior has been observed. Apart from suppressing the expression of p-p53 and p-53 and inflammatory response, silibinin has the ability to improve oxidative stress levels in the hippocampus. Along with neuroprotective potential, silibinin especially acts on inflammatory response, components of oxidative stress, and neuronal death (Song *et al.* 2017) [67].

4.6 Anthocyanins

Widely found in fruits, flowers, grains, and vegetables are polyphenolic flavonoids Anthocyanins (Wang *et al.* 2016) [85]. Along with memory and cognition improvement it shows anti-inflammatory, antioxidant and anti-apoptosis properties (Winter *et al.* 2017) [84]. A basic flavylum core (2-phenylbenzopyryl cation) consisting of two aromatic rings joined by a three-carbon unit and condensed by an oxygen is the characteristic of anthocyanins. The anthocyanin molecule consists of two or three portions, an aglycone (anthocyanidin), a group of sugars, and often a group of organic acids (Smeriglio *et al.* 2016) [72]. Role of flavonoids in cognition and memory has been characterized with a neuroprotective factor in the dementias by several evidences. The ability of anthocyanin particles and (ethylene glycol) gold nanoparticles (PEG-AuNPs) (polyphenolic flavonoid anthocyanins for conjugation to PEG-AuNPs) to improve memory loss and synaptic deficit and neurodegeneration in genetically modified mice (A β 1-42 mouse model of AD) has been observed by (Alim *et al.* 2016) [1].

The behavioral assessment showed that the latency times of the required to reach the hidden platform in were shorter, so number of platform crossings and time spent in the target quadrant during the probe test in mice treated with anthocyanins and anthocyanin-loaded PEG-AuNPs was increased. Furthermore, anthocyanins and anthocyanin-loaded PEG-AuNPs increased the spontaneous alteration behavior. The levels of A β (β -amyloid protein), BACE-1 (a beta-secretase, a key enzyme in the formation of the β -amyloid protein), and APP (protein precursor anti-amyloid) were found to be reduced in Anthocyanin-loaded PEGAuNPs suggestive of potential action of this flavonoids on the production of beta-amyloid protein. The administration of free anthocyanins and anthocyaninloaded PEG-AuNPs mitigated the effect of A β 1-42 and increased the expression levels of synaptophysin, PSD95, and SNAP23; these molecules are related to the synapse process between the neurons. Anthocyanins and anthocyaninloaded PEG-AuNPs increased the phosphorylation of GluR1 at Ser 845 and increased the expression level of p-CREB (Ser133), which can improve the memory process. The administration of free anthocyanins and anthocyaninloaded PEG-AuNPs increased phosphorylation and elevated the levels of p-PI3K and p-Aktat Ser 473,

increased the level of p-GSK3 β at Ser9, and reduced the level of p-tau at Ser413 and Ser404, which consequently may reduce the level of formation of fibrillar components. Reduction of the ratio of Bax/Bcl2 and Cyt c was observed, but anthocyanin-loaded PEG-AuNPs were more effective than free anthocyanin. Reduced caspase-9, cleaved caspase-3, and PARP-1 levels in the hippocampus was also observed, and these results demonstrate the Neuroprotective action of this flavonoid. The A β 1-42-induced-degenerated neuronal cells in the hippocampus and cortex were reduced and number of surviving neurons increased (Alim *et al.* 2016) [1]. A β 1-42-induced AD mouse model was also investigated to study the therapeutic efficacy of anthocyanins alone and anthocyanin-loaded PEG-AuNPs. Transfer of anthocyanin-loaded PEG-AuNPs across the blood-brain barrier and accumulation in the A β -injected mice was observed. Furthermore reduced β -amyloid and BACE-1 expressions and prevention of tau hyperphosphorylation GSK-3 β /CDK5 pathway, by anthocyanin-loaded PEG-AuNPs was observed, reduced A β 1-42-induced microglia and astrocyte cell activation was also seen (Kim *et al.* 2017) [41]. Another report showed inhibition of activated astrocytes and various inflammatory markers including p-NF- κ B, inducible nitric oxide synthase (iNOS), and tumor necrosis factor-alpha (TNF- α) by anthocyanins in the hippocampus and cortex regions of D-gal-treated rats. Anthocyanins are able to inhibit the cascade of myeloid beta-protein production and to decrease synaptogenesis and neuronal death also microglial activation in areas important to the process of memory as hippocampus and cortex is induced by them (Rehman *et al.* 2017) [53].

4.7 Naringin

Grape fruit and other citrus fruits contains a 703lavonoids Naringin (4', 5, 7-trihydroxyflavanone 7- rhamnoglucoside), belonging to a family of C6-C3-C6 polyphenol compounds which possesses anti-inflammatory antioxidative benefits (Qin *et al.* 2016) [49]. *In vitro* and *in vivo* studies of naringin were done using Preclinical models of diabetes mellitus, atherosclerosis, osteoporosis, cardiovascular disorders, neurodegenerative disorders and rheumatological disorders (Bharti *et al.* 2014) [5]. Neuroprotective effect of naringin was demonstrated by modulation of endogenous biomarkers and downregulation of free radical and cytokines, including tumor necrosis factor- α (TNF- α) in streptozotocin-induced painful diabetic neuropathy (Kandhare *et al.* 2012) [32]. The effect of naringin against deltamethrin-induced neurotoxicity in male Wistar rats the treatment lead to a significant revival of the oxidative status, confirming the protective effect of naringin. Behavioral analysis of the effect of naringin on memory deficit in a pharmacological model (donepezil and scopolamine) in animals has demonstrated a significant difference in the locomotor activity and confirmed that naringin has no confounding influence on locomotion on improving the potential for episodic memory, in the familiarization trial no preference or discrimination toward any of the objects used. The 703 lavonoids reversed the time induced episodic memory deficit increase in novel object exploration time compared with familiar object and improvement in recognition and discriminative indices. Therefore, naringin reversed the scopolamine-induced short-term episodic memory deficits and improved discrimination and recognition (Ramalingayya *et al.* 2016) [55]. The preventive effect of autophagy and neuroinflammation of naringin was investigated in a model of animal excitotoxicity by treatment with kainic acid (KA), a potent agonist of

excitatory amino acids, especially glutamate. KA becomes a neurotoxin leading to neuronal death due to excitotoxicity. Significant decrease in the frequency of chronic spontaneous seizures in KA-treated mice compared with KA alone suggested the beneficial properties of naringin as an antiepileptic agent. Furthermore, loss of hippocampal neurons in the KA-treated CA1 region was attenuated by treatment with naringin indicating autophagic stress reducing property of naringin which might otherwise be involved in neuronal cell death. Additionally, increase in TNF- α within Iba1-positive microglia in the KA-treated hippocampus characteristic of diseases such as Parkinson's and Alzheimer's due to attenuation by naringin treatment was reported (Jeong *et al.* 2015) [30].

4.8 Baicalein

A flavonoid originally isolated from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora* is Baicalein (5, 6, 7-trihydroxyflavone) (Makino *et al.* 2008) [78], having antioxidant, anti-inflammatory properties Neuroprotective properties against Parkinson's disease (Li *et al.* 2005) [35]. Observed attenuation of the motor deficits after baicalein treatment along with increase in striatal neurotransmitters: DA (dopamine), DOPAC (3, 4-dihydroxyphenylacetic acid), and HVA (homovanillic acid). Increase in number of TH positive neurons and decreased amount of α -syn in enteric nervous system was observed during analysis of fluorescence intensity by microscopy. Decrease of α -syn oligomers, not monomers, was seen in ileum, thoracic spinal cord, and midbrain; baicalein had no effect on α -syn mRNA expression, indicating its preventive action against the progression of α -syn accumulation in Parkinson's disease, by inhibiting the formation of α -syn oligomers (Hu *et al.* 2016) [48]. Rotenone-induced PD rats were used for investigating the therapeutic effects of baicalein and exploring whether the Neuroprotective potential practices by baicalein were through intervening in mitochondrial function and mitobiogenesis. Results showed that the motor dysfunction was partially ameliorated by baicalein and TH+ cells in the substance nigra (SN) increased in number. Neurons in SN were also against rotenone induced apoptosis. The dysfunction of mitochondrial complex I in the ventral midbrain that was damaged by rotenone was ameliorated by baicalein. Furthermore, the protein levels of PGC-1 α (a regulator of mitochondrial mitobiogenesis), NRF-1 (transcription factor that regulates the expression of antioxidant proteins), and TFAM (mitochondrial transcription factor) in the ventral midbrain, increased after the administration of baicalein suggestive of improvement in the brain's response to oxidative stress and consequent neuronal loss observed in Parkinson's disease (Zhang *et al.* 2017) [86]. Through a model of pharmacological parkinsonism in animals (MPTP administration), observed that in low doses, baicalein improves motor ability and prevented the loss of dopaminergic neurons caused by MPTP. Animal with pretreated baicalein Parkinson's disease showed reduced microglial activation and astrocyte activation. This study reveals the importance of astrocyte activation for the occurrence of the neurodegenerative process. Studies show involvement of baicalein in reducing MPP (a toxic molecule that interferes with oxidative phosphorylation in mitochondria) that is capable of inducing the activation of NF- κ B, ERK (protein kinase intracellular signaling), and JNK (c-jun N-terminal kinase) in the astrocyte leading to a mechanism of neuroinflammation considered as a potent inducer of Parkinson's disease (Lee *et al.* 2014) [37].

Associating with its neuroprotective action especially on mitochondrial activity and activation of glial cells both of which are known to increase the risk of neurodegenerative diseases baicalein turns out to be very effective against Parkinson's disease.

4.9 Catechin

For a long time, Clinical use of Chinese herbal medicines to treat Alzheimer's disease has shown significant effectiveness (Su *et al.* 2014) [87]. Catechins (flavan-3-ols) belong to the group of polyphenols. (-)-Epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC) are the major polyphenols in green tea (Gaur and A. Kumar 2010) [21]. (Esselen *et al.* 2014) [16] Fruits like gooseberries, kiwi, blueberries, apple and strawberries constitute catechin. Several molecular processes involved in angiogenesis, extracellular matrix degradation, the regulation of cell death, and multidrug resistance in cancers and related disorders are affected by catechin. Beneficial effects of catechin is mainly due to its antioxidant property apart from which it shows antihypertensive, anti-inflammatory, antiproliferative, antithrombotic, and anti-hyperlipidemic activity (Anand *et al.* 2014) [2].

5. Conclusion

On the basis of the above study it can be concluded that Indian medicinal plant are traditionally used as a medicine in Ayurveda, Numerous Indian plants are reported that have been used to treat cognitive disorders. In neurodegeneration natural products play essential role in prevention and therapy of various neurodegenerative diseases, and neuronal dysfunctions. Natural products like polyphenolic and alkaloids compounds from plants they have ability to delay neurodegeneration, it improve memory, cognitive functions also. Flavonoids present in various medicinal plants have potential to protect brain against neuronal injury. They have an ability to suppress neuroinflammation, and the potential to promote memory, learning and cognitive function. Thus flavonoids are strong candidates of being an important precursor molecule in the development of new generation of brain enhancing drugs. ROS (Reactive oxygen Species) goes beyond the limit which can be stabilized by the action of antioxidants is called oxidative stress called Neurodegeneration. Neurodegeneration caused Alzheimer disease, Parkinson disease, Autism and Migrain. Flavonoids, Rutin, Apigenin, Hesperidin, Kaempferol, Naringenin, Anthocyanins, Naringin, Baicalein, Catechin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate (EGCG) shows Neuroprotective functions.

6. Acknowledgement

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