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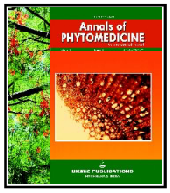

Review Article : Open Access

Flavonoids: An alternative pathway for the treatment of Alzheimer's disease

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Abstract

Alzheimer's is a non-curative disease that occurs in most of the geriatric patients worldwide. It is one of the top 10 diseases which lead to mortality. According to Indian statistics 2020, the average age for symptoms to occur in Alzheimer's is 66-68 years. Patients can survive up to 8 years after the symptoms of dementia. Women are predominant than men. As there is no permanent treatment for Alzheimer's, but medication and management strategies may temporarily improve. On the basis of clinical trials, it can be suggested that single herbs may offer complementary benefits to the approved drugs. Flavonoids are used prophylactically to treat Alzheimer's, as flavonoids are present in most of the fruits, vegetables, and other daily essential products like apple, berries, spinach, red cabbage, onion, dark chocolate, green tea, *etc*. Flavonoids are also used to treat early symptoms of Alzheimer's like learning and memory loss as flavonoids cross blood-brain barrier (BBB) and prevent tangles. Natural flavonoids mainly possess antioxidant and neuroprotective action which helps to restore damaged brain cells up to a certain extent. Myricetin, morin. rutin, quercetin, fisetin, ginkgo biloba extract, genistein, kaempferol, apigenin, anthocyanin, glycitein are some of the flavonoids used in prevention of Alzheimer's disease. In present study, we discuss different flavonoids to prevent and treat symptoms that are associated with Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is the neurodegenerative disorder and a most frequent basis of dementia which is more affected in elderly people and provokes alternation in the Cerebrospinal Nervous System (Francesca *et al*., 2010). Neuropsychiatric symptoms are the main features of Alzheimer's disease (Constantine *et al*., 2011). Few sources show that 50% of people above 80 years suffer from this kind of dementia (Elena *et al*., 2018). Alzheimer's disease is a continuous degradation of certain nerve cells that are responsible for memory and other important functions. The major cause for Alzheimer's disease is protein (amyloid) built up in the brain cell, which leads to formation of plaques (Perry *et al*., 1980). Presently, three genes responsible for rapid onset of Alzheimer's disease such as Amyloid Precursor Protein (APP), Presenilin-1(PSEN1), Presenilin-2 (PSEN2) (Uddin *et al*., 2019). It also occurs due to the generation of oxidative strain and free radicals (Roxana *et al*., 2018). Cholinesterase inhibitors and N-methyl D-aspartate (NMDA) antagonist is the current AD therapy. Contemporary researches suggest that some flavonoids are effective in treating Alzheimer's disease (Airlodi *et al*., 2018).

Flavonoid belongs to polyphenols shows outstanding therapeutic properties. Myricetin, morin, rutin, quercetin, fisetin, ginkgo biloba extract, glycitein, genistein, kaempferol, apigenin, anthocyanin, are few of the flavonoids used prophylactically in Alzheimer's disease (Carmona *et al*., 2020). Flavonoids show its neuroprotective action by inhibiting the development of reactive oxygen species and aggregation of beta-amyloid in PC 12 cells, certain flavonoids show anti-AD effects such as myricetin, latin, fisetin, catechins, quercetin, kaempferol and apigenin. Among that, quercetin shows a significant role in the neuroprotective activity (Judy *et al*., 2007).

1.1 History and present status of flavonoids

It has been centuries that the people have known that the plant possesses biological activity. In 1930, the discovery of vitamin P from orange was made. Later, it was known as rutin in 1938 which was flavonoids (Robert *et al*., 2001). At present, there are more than 4000 different types of flavonoids that are used for symptomatic treatment in most of the diseases due to their vast health benefit (Shashank *et al*., 2013).

1.2 Distribution of plant species and their taxonomy

There are about 1 million secondary metabolites that are obtained from plants, which play a vital role in defence mechanism in different diseases. It includes about 9000 compounds of flavonoids that are used in treating neurological disorders. Flavonoids are distributed in various ferns, mosses, liverworts, lycophytes, flowering and non-flowering plants; further flavonoids are subgrouped into flavones, flavonols, chalcones, anthocyanins and proantho cyanidans. Flavonoids are absent in hornworts (Keiko *et al*., 2019). Bioflavonoids are flavonoids with biological activity, which are stored in edible parts of plants mainly in vegetables and fruits. They impart colour to berries and citrus fruits. The different flavonoids used in AD are described in Table 1 along with geographical sources, taxonomy and their uses (Katarzyna *et al*., 2017).

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Table 1: Taxonomy of flavonoids

Source	Taxonomy				Flavonoid	Geographi-cal source	Uses
	Order	Family	Genus	Species			
Indian guava	Myrtales	Myrtaceae	Psidiuni	*P. guajava*	Monn	India	Antioxidant Neuroprotective
Grapes	Vitales	Vitaceae	Vitis	*V. vmifera*	Quercetin	China	Antiproliferative Chemo preventive
Strawberry	Rosales	Rosaceae	Fragana	*F virginiana*	Fisetin	Southern new England	Antioxidant Neuroprotective
Chamomile tea	Asterales	Asteraceae	Matricaria	*M. chamomilla*	Apigenin	Japan	Antiamyloidogenie Anxiolytic
Buckwheat	Caryophyllales	Polygonaceae	Fagopyrum	*F. esculentum*	Rutin	China	Antioxidant Fibril disagregating effect
Spinach	Caiyophyllaes	Amaranthaccae	Spinacia	*S. oleracca*	Kaempferol	Italy	Antioxidant Anticoagulant
Lupin	Fabales	Fabaceae	Lupinus	*L. abramsu*	Genistein	Australia	Cholinesterase Inhibitors Immuno-suppressant
Black currant	Saxifragales	Grossulariaceae	Ribes	*R. nigrum*	Anlhocvanin	Russia	Antineoplastic Anti-inflammatory
Ginkgo leaf	Ginkgoales	Ginkgoaceae	Ginkgo	*G. biloba*	Ginkgo biloba	China	Antipsychiatric Antiageing
Soybean	Fabales	Fabaceae	Glycine	*G. gracilis*	Glycitein	United States	Neuroprotective Anticoagulant

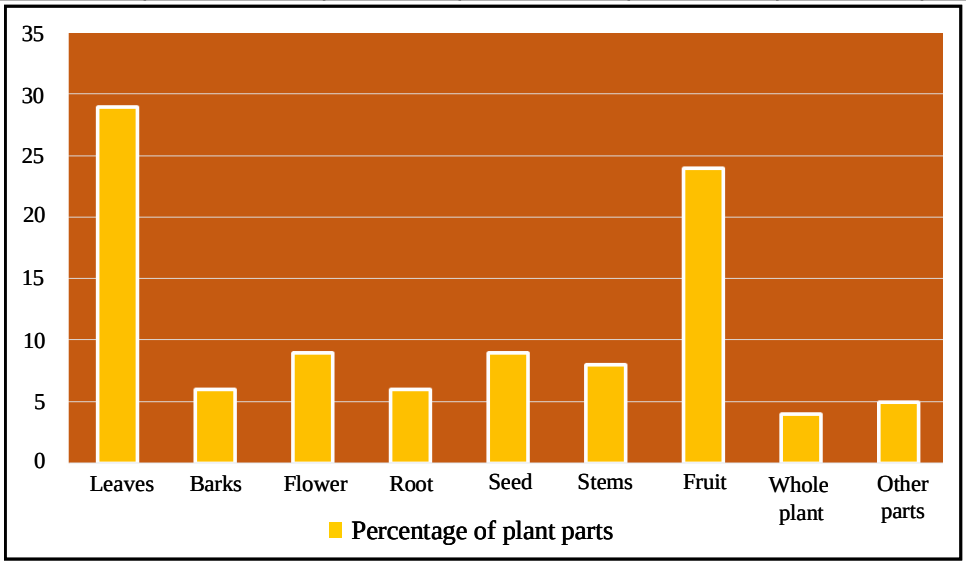

Figure 1: Percentage of plant parts used in Alzheimer's disease.

2. Methods

A search of scientific literature and data on recent developments of flavonoids for the treatment of various diseases by using various sources of information available in internet by reviewing scholarly reviews, research articles, magazines, newsletters, thesis, and conference proceedings through search engine such as Google Scholar, Science Direct, PubMed, Core, Embase, Medline, Medline Plus. PubChem, Scopus, *etc.*

3. Biosynthesis of flavonoids

P- coumaryl CoA are the substrate derived from phenyl propranoid pathway. It utilizes malonyl CoA (Figure 2) and produce naringenin chalcone with the help of chalcone synthase. On further, it undergoes cyclization giving naringenin a major component for producing

isoflavones (genistein, glycitein), flavones (apigenin, ginkgo biloba) and dihydroflavanol. Dihydroflavonol on reacting with flavonol synthase gives flavonols (morin, quercetin, fisetin, rutin and kaempferol) or on reacting with dihydroflavonol-4-reductase gives leucoanthocyanins. Anthocyanin is formed from leucoanthocyanins with an intermediate anthocyanidins.

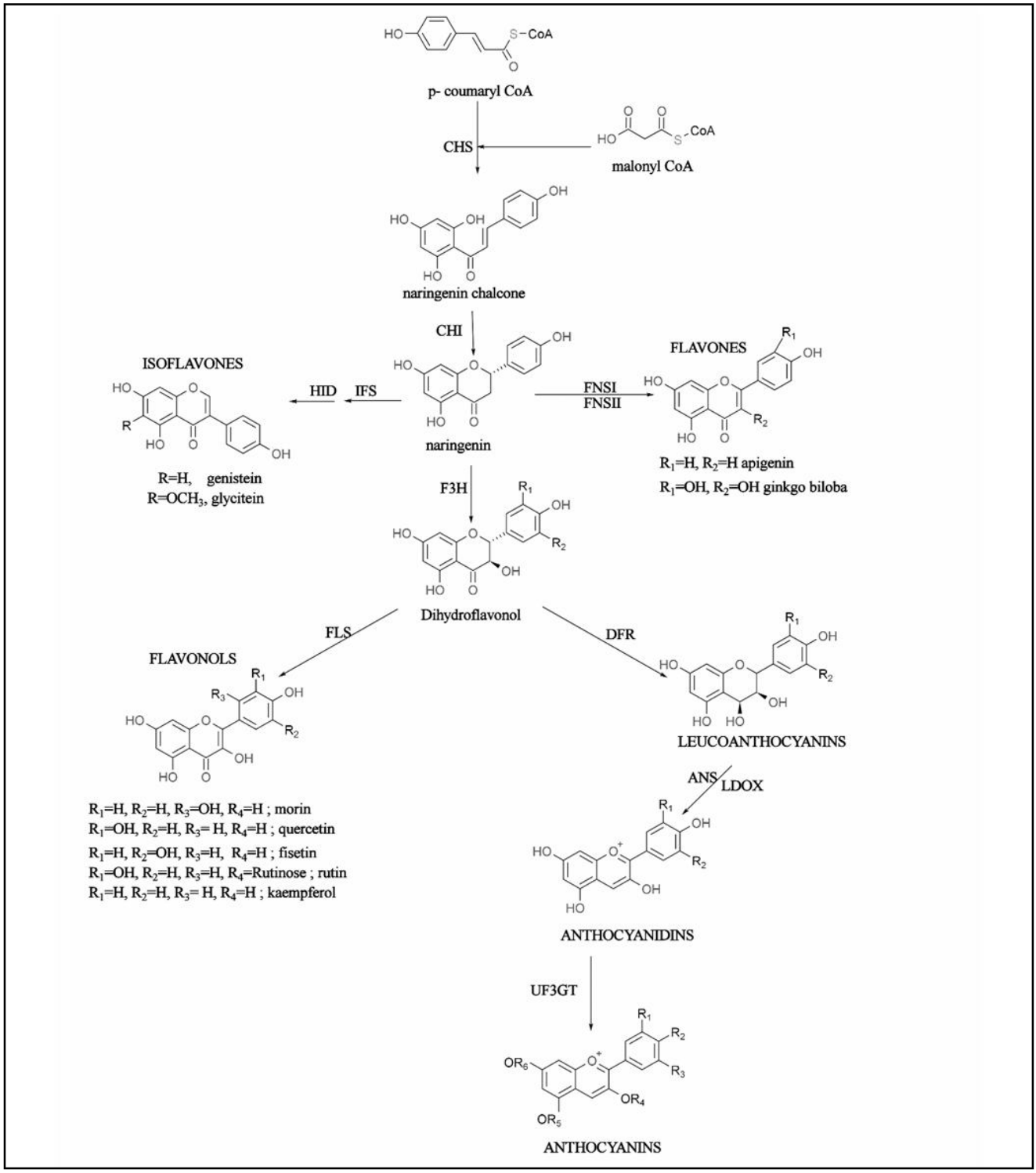

Figure 2: Biosynthesis of flavonoids ANS, anthocyanidin synthase; CHI, chalcone isomcrase; CHR, chalcone reductase; CHS, chajconc synthase; DFR, dihydroflavonol 4-rcductase, F2H, flavanone 2-hydroxylase,F3H, flavanone 3-hydroxylase; FLS, Davonol synthase; FNS, flavone synthase, HID, 2-hydroxyisoflavanone dehydratase; IFS, Isoflavone synthase; LDOX leucoanthocyanidin dioxygenase, UF3GT, UDP glucose flavonoid 3-O-glucosyltransferase.

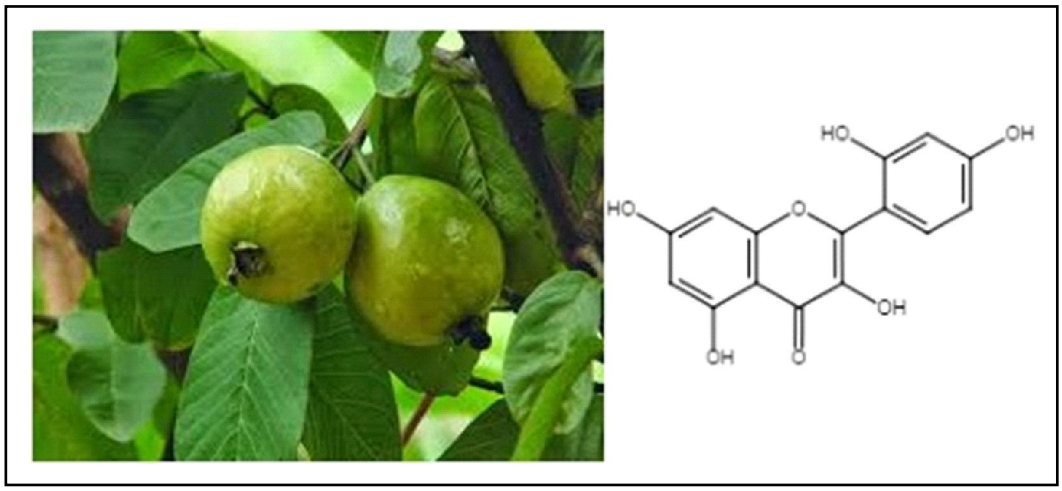

Figure 3: Morin is a main constituent of *Psidium guajava*.

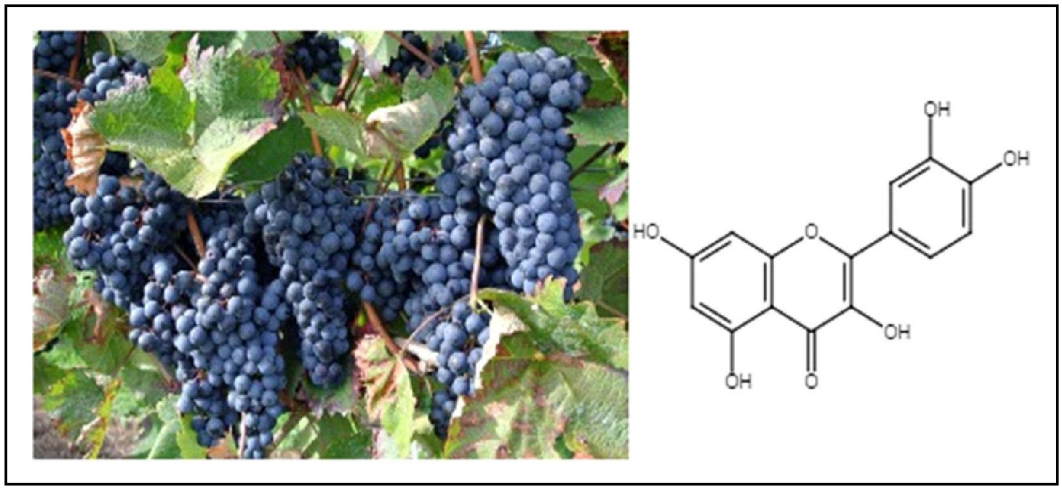

Figure 4: Quercetin is a major constituent of *Vitis vinifera*.

Figure 5: Fisetin is a main constituent of *Fragaria virginiana*.

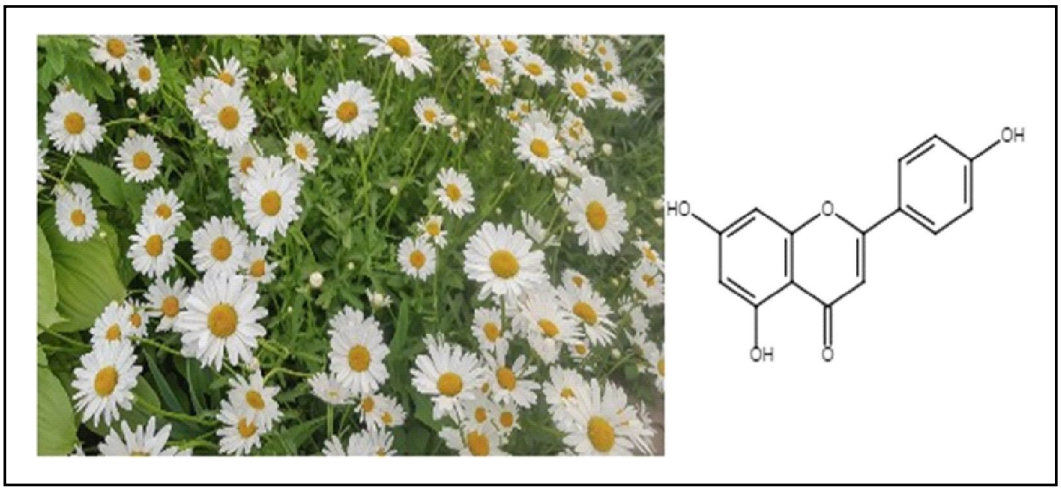

Figure 6: Apigenin is a major constituent of *Matricaria chamomilla*.

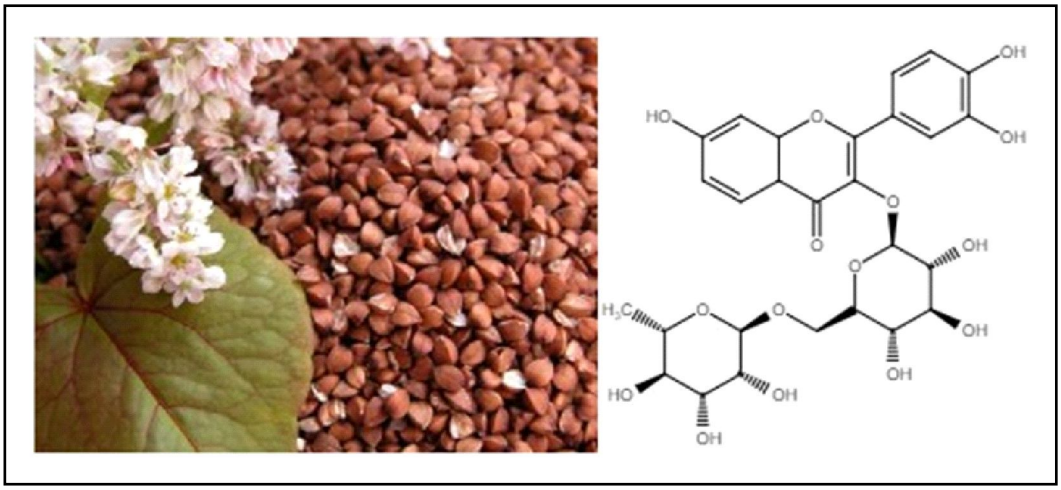

Figure 7: Rutin is a major constituent of *Fagopyrum esculentum*.

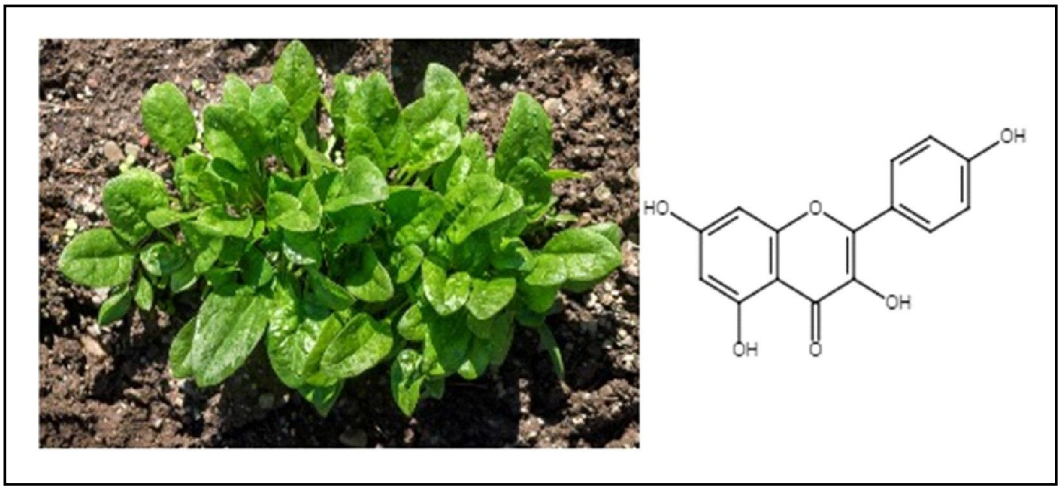

Figure 8: Kaempferol is a major constituent of *Spinacia oleracea*.

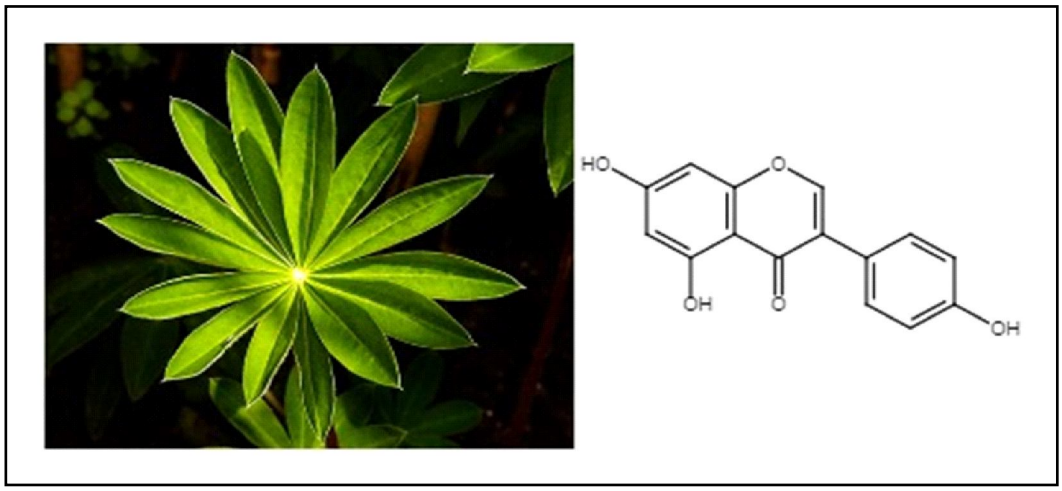

Figure 9: Genistein is a major source of *Lupinus abramsii*.

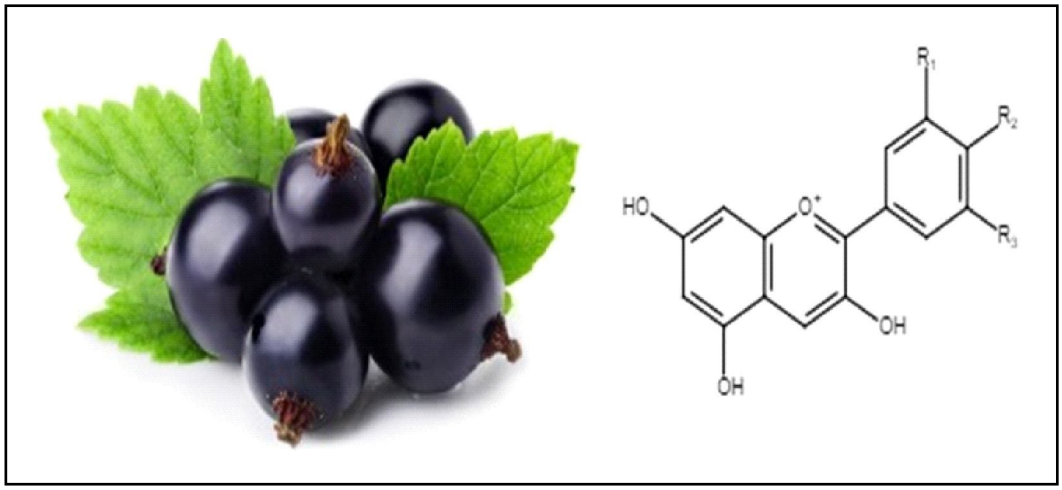

Figure 10: Anthocyanin is a major source of *Ribes nigrum*.

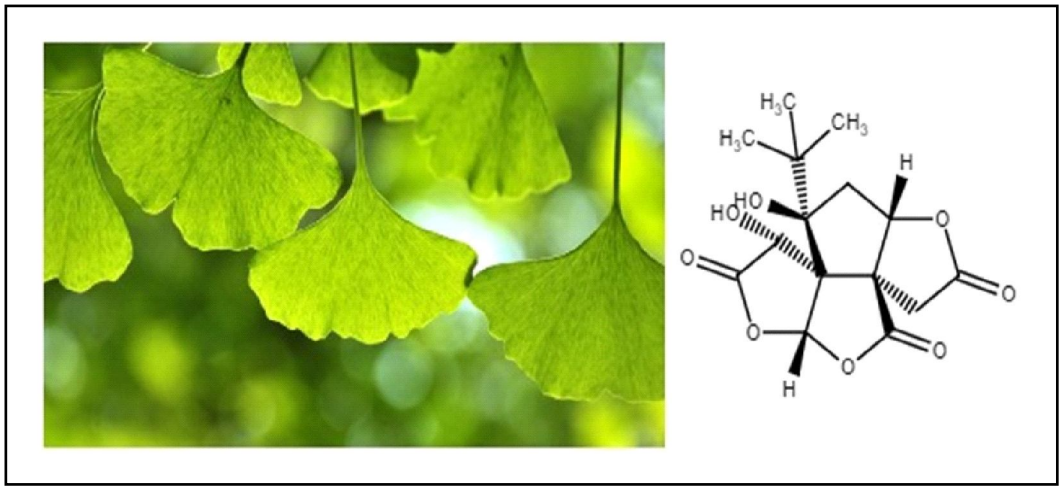

Figure 11: *Ginkgo biloba* is a major source of *Ginkgo biloba*.

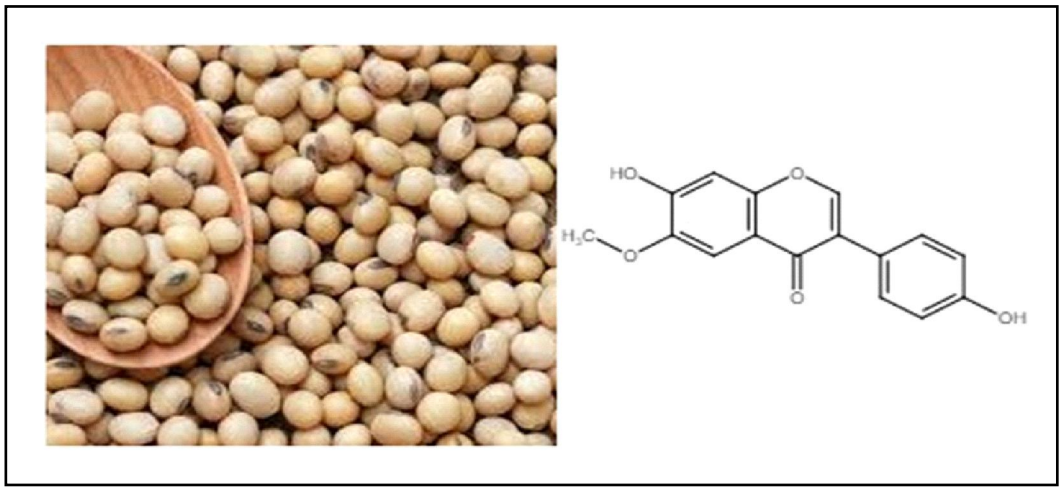

Figure 12: Glycitein is a major source of *Glycine gracili.*

4. Flavanoids used against Alzheimer's diseases

4.1 Morin

Morin is yellow color plant-derived natural flavonoids (Moraceae). Almond, fig, and Indian guava contain a high quantity of morin (Choudhury *et al*., 2017). It exhibits antioxidant, antineoplastic, cardioprotective, antiproliferative, antiamyloidogenic, fibril destabilization, anti-inflammatory, and neuroprotective (Choudhury *et al*., 2017; Simunkova *et al*., 2019; Qadeer *et al*., 2014; Elena *et al*., 2018). Morin can easily cross the blood-brain barrier (BBB) which aids in the restoration of reminiscence and cerebral functions (a major symptom of AD) (Justin *et al*., 2010). It gets metabolized and finally gets absorbed in the gut as aglycone moiety (Choudhury *et al*., 2017). The compulsive characteristic of AD is the poisonous buildup of aggregated Aβ through peptide linkage, which is the resultant of misfolding B hairpin monomer (Gargari *et al*., 2018). Morin inhibits β-secretase and γ-secretase that helps in the prevention of further plaque development in nerve cells (Michal *et al*., 2005; Etis *et al*., 2012). In *in vivo*, morin inhibits GSK-3B, is the major enzyme for determining AD, thereby decreasing the brain levels of phosphorylated Tau (p Tau) (Justin *et al*., 2010; Yu *et al*., 2018). Morin acts on p Tau accumulation but does not affect the motor function. Morin has a superior tendency to form H bonds with the accumulated Aβ at the terminal clusters of the fibrils, that leads to destabilization of Aβ aggregate (Justin *et al*., 2010; Simunkova *et al*., 2019). The antioxidant effect of morin is increased by Cr (III)-morin complex (Qadeer *et al*., 2014). Mitochondrial dysfunction and redox homeostasis are the primary cause of AD, this can be reinstated by the consumption of morin (Elena *et al*., 2018). As an aqueous solubility, morin hydrate has 18 µg/ml, where the desired activity is not achieved. Hence, the oral route of micellar is preferred (Sharma *et al*., 2017). Flavonoids have a greater affinity for metals, the complex formed causes damage to DNA. The more the interaction of flavonoids and metals, the more the antioxidant effect. The complexes include Cd (II) with morin, Zn (II), and Mn (II) with quercetin and other metal-flavonoid complexes which cause programmed cell death (Simunkova *et al*., 2019).

4.2 Quercetin

Quercetin is a flavonol derived from Latin name quercetum which means oak forest. It is mostly present in the citrus fruits, leafy vegetables, tomatoes, honey, nuts, onions, *etc*. (Anand *et al*., 2016; Li *et al*., 2016). *Ginkgo biloba*, hypericum perforatum, and *Sambucus canadensis* are the medicinal botanicals where quercetin is found. Higher concentration of quercetin is found in red onions whereas leaves of green and black tea contain lower concentration of quercetin (Li *et al*., 2016). It is a yellow colour bioflavonoid which acts as antiproliferative, chemopreventive, antioxidant, anti-tumour, antiallergy, anticancer, antiviral, anti-inflammatory, anti-ulcer, antihypertensive and immunomodulatory (Anand *et al*., 2016; Khan *et al*., 2020; Olajide *et al*., 2020; Chen *et al*., 2014). Quercetin in combination with ascorbic acid protects brain cell from oxidative damage, thereby preventing Alzheimer's disease (Geetha *et al*., 2005). Quercetin crosses BBB same as when compared to rutin. The absorption of quercetin is about 3-17%. It has high metabolism and rapid elimination (Li *et al*., 2016). Quercetin interferes lipid peroxidation, platelet aggregation and capillary permeability. These are the properties that are useful in reduction of plasma lipid level (Xinjun *et al*., 2020). Metabolism of quercetin takes place in small intestine, colon, liver and kidney (Li *et al*., 2016). Quercetin inhibits Tau phosphorylation and Aβ aggregation that are the main hall mark of AD (Khan *et al*., 2020). It also guards neuronal cell by decreasing neuroinflammation and oxidative strain (Olajide *et al*., 2020). Quercetin has toxic effects such as mutagenicity, pro-oxidant activity, mitochondrial toxicity and it inhibits the enzymes involved hormone metabolism (Chen *et al*., 2014).

4.3 Fisetin

Fisetin is a flavonol derivative extracted from vegetables and fruits of about 2-160 µg/g concentration. Strawberries, apple, persimmon have high concentration whereas cucumber, onion and grapes have a low concentration of fisetin belonging to Anacardiaceae and Fabaceae family (Naghma *et al*., 2013). They exhibit antioxidant, neuroprotective, anti-inflammatory, anticarcinogenic, antiallergy, antiviral, anti-immunomodulatory, antiangiogenic, antifungal and antiageing properties (Rashid *et al*., 2019). Fisetin inhibits Aβ protein formation. It helps in promoting cognitive functions and memory

in AD (Shifeng *et al*., 2021). Fisetin crosses BBB when administered orally, and it improves synaptic functions in Hippocampus (Wen-bin *et al*., 2018). Fisetin lowers oxidative damage induced by hemeoxygenase-1 (HO-1) and ultraviolet radiation. It inhibits extracellular signal regulated kinase (ERK) which promotes intellectual function in AD (Maher *et al*., 2020; Wang *et al*., 2018). Amyloid-β aggregation, beta strand formation and Tau production are inhibited by fisetin (Wen-bin *et al*., 2018). Glutathione is a main antioxidant that is produced in liver, this activity is improved by fisetin. Hepatotoxicity is comparatively less than other flavonoids in fisetin as it enhances protective action in liver. 5-HT and nor-adrenaline levels are increased in brain by fisetin, these act against AD (Meghana *et al*., 2016; Manorma *et al*., 2018). Fisetin is rapidly transformed into sulphate in liver (Meghana *et al*., 2016).

4.4 Apigenin

Apigenin is a flavone derived flavonoid which is found in higher concentration in chamomile tea. Parsley, malabar spinach, dried oregano, celery varieties, artichoke and coriander are the other sources of apigenin. Naturally, apigenin is found in glycosylated form (Minqian *et al*., 2019; Balez *et al*., 2016). Apigenin exhibits properties such as antiamyloidogenic, antioxidant, anxiolytic, anti-inflammatory, anticarcinogenic, neuroprotective effect, super oxide anion scavenging effect, antiviral, antibacterial, antiparasitic and antifungal (Minqian *et al*., 2019; Venigalla *et al*., 2015; Zhao *et al*., 2013). Apigenin is poorly soluble, to enhance its solubility, it is converted to salt form like potassium salts. The salt form of apigenin helps in crossing blood-brain barrier. Apigenin improves memory, decrease Aβ plague and oxidative strain that are associated to AD. Excited calcium ions are blocked by apigenin in brain cells; these improves neuron signalling which helps in betterment of AD (Balez *et al*., 2016). Due to decrease in metabolic rate, there is decrease in absorption and excretion of apigenin takes place through bile and urine (Angeline *et al*., 2005). In mice, 90 days oral dose (40 mg/kg/day) of apigenin improved perception and cognitive functions in AD. Usually, apigenin is non-toxic, even in higher doses, it produces muscle relaxant and sedative action (Balez *et al*., 2016; Zhao *et al*., 2013).

4.5 Rutin

Rutin is sometimes known as sophorin. Rutin is a natural flavonoid, that belongs to flavonol group. Its name originates from the plant *Ruta graveolens*. It is extracted from plants mainly onions, tea, broccoli, apples, *etc*. (Isha *et al*., 2015; Adaze *et al*., 2018). It exhibits antioxidant, neuroprotective, anti-inflammatory, antiangiogenic, antiallergic, antiviral, antidiabetic, antineoplastic, fibril disaggregating effect, antiamyloidogenic activities (Adaze *et al*., 2018; Bang *et al*., 2015; Mostafa *et al*., 2019). The main drawback of rutin is its poor solubility, so the conversion of rutin to its salt form (sodium rutin) improves its solubility to cross the BBB (blood-brain barrier) and improves bioavailability. Salts of rutin enhance microglial cells in the brain, which clears Aβ plaques and reduces Alzheimer's disease (Rui-yuan *et al*., 2019). Rutin reduces the ischaemic neural apoptosis by lipid peroxidation and p53 expression with an increase in endogenous antioxidant defence enzyme, this thereby reduces neuroinflammation in Alzheimer's disease (Mahendra *et al*., 2020). Rutin has higher binding energy with protein when compared with other flavonoids (Raju *et al*., 2018). Cognitive dysfunction is mainly due to reduced blood flow to the brain in Alzheimer's disease, this is altered by rutin. Rutin undergoes phase-2 metabolism in the liver. It is available in tablets and capsules, about 4000 mg/day is safe. Rutin is non-toxic up to 5000 mg/kg therapeutically rutin is not widely used because of its poor absorption, high metabolism, and rapid excretion (Annoni *et al*., 1986).

4.6 Kaempferol

Kaempferol is also called as kaempferide. Its name originates from German naturalist Engelbert Kaempfer. It is flavonol derivative found in plants, vegetable and fruits like tea, sprouts, citrus fruits, grape, cabbage, strawberry, *etc*., medicinal plants like *Ginkgo biloba*, Equisetum species, *etc*. It occurs mostly in glycoside form. Kaempferol is a yellow crystalline powder, that is soluble in organic solvents. It exhibits anti-inflammatory, antioxidant, anti-cancer, neuroprotective, antidiabetic, antihistaminic, analgesic, immunomodulatory, anxiolytic, antiestrogenic, antiosteoporotic, antimicrobial (Rashid *et al*., 2019; Ren *et al*., 2019). Kaempferol has low absorption, poor bioavailability and metabolism takes place in intestine and liver by phase-1 oxidation and phase-2 glucuronidation. Nanotechnology improves absorption and bioavailability of kaempferol, excretion is usually high and occurs through bile (Barve *et al*., 2009; Ren *et al*., 2019). Kaempferol progresses intellectual functions related with AD by activating intracellular signalling pathway of memory when 10 mg/kg/day is administered for 21 days (Kouhestani *et al*., 2018). Various concentration of kaempferol attenuates apoptotic cells percentage and regulates gene expression and proteins (Chen *et al*., 2013; Zhang *et al*., 2021). Pathogenesis of AD is delayed owing to kaempferol and other natural antioxidants (Ren *et al*., 2019). The increased levels of copper in AD are complexed with kaempferol as it possesses pro-oxidant property to form Cu-kaempferol complex that protects brain from free radicals and restores brain function (Simunkova *et al*., 2021). Kaempferol has low toxicity, but on drug-drug interaction, or on herbal interactions its toxicity increases and therapeutic effect decreases (Chan *et al*., 2013).

4.7 Genistein

Genistein is an isoflavone derived from leguminous family (especially from soybean, fava bean, tofu, lupin and kudzu) (Li *et al*., 2017; NCBI, 2021). Naringenin produces genistein in plants, which exhibits antitumour, antioxidant, antimigration, metabolism regulation, neuroprotective, anti-inflammatory, antiangiogenic, immunosuppressive, antiacetylcholinesterase, antimicrobial, metal chelating (Li *et al*., 2017; Uddin *et al*., 2019; Hong *et al*., 2019; Baiping*et al*., 2018). Aβ formation is inhibited by genistein through activation of PKC (protein kinase C) signalling pathway (Uddin *et al*., 2019). Genistein helps in protection against Tau hyper phosphorylation, ER stress, apoptosis and maintains apolipo-protein E and GSK 3B (glycogen synthase kinase 3 beta) levels. Manganese superoxide dismutase decreases the formation of plague and NFTs by eliminating superoxide free radical that improves cognitive functions associated in AD (Duan *et al*., 2021). Genistein increases cognitive functions in Alzheimer's disease (Uddin *et al*., 2019). Genistein acts as an antioxidant which helps in deterrence of AD by inhibiting pro-oxygenic agents, neuronal necrosis, and influx of intracellular calcium (Duan *et al*., 2021). Genistein when given orally has poor bioavailability, glycosidic form is partially absorbed and aglycosidic form is well absorbed (Uddin *et al*., 2019). Genistein

effectively crosses BBB and neurological status was enhanced (Kloska *et al*., 2012). Genistein is a potent nontoxic drug at smaller doses used widely in treatment of AD (Hong *et al*., 2019).

4.8 Anthocyanin

Anthocyanin is a flavonol derived pigment which imparts colour to the plant (flowers, fruits and vegetables) (Jessie *et al*., 2014). Anthocyanin is water soluble and more than 600 types of anthocyanin are identified (Tarun *et al*., 2020). These are responsible for the colours; for instance blue, purple and red (Khoo *et al*., 2017). The main source of anthocyanin is such as berries, grapes, tubers, red cabbage and black current. It exhibits antioxidant, scavengers of ROS, anti-inflammatory, anticancer, immuno protective, antimutagenic, antimicrobial, antidiabetic, antineuro-degerative and reduces alopecia, obesity, dementia, and cardiovascular diseases (Marques *et al*., 2018; Tarun *et al*., 2020; Afzal *et al*., 2019; Jessie *et al*., 2014). Oxidative stress of brain cells causes mitochondrial dysfunction, Aβ toxicity and apoptosis. These are prevented by anthocyanin as it crosses BBB and helps in treating AD (Afzal *et al*., 2019). Neural sphingomyelin specific phospholipase C activity is modified by anthocyanin that enhances intellectual function in AD. Anthocyanins with hydroxyl groups (phenols) competitively binds with amino acids in amyloid fibril forming protein and disrupts Aβ aggregation by preventing AD (Miho *et al*., 2015). Anthocyanins have poor absorption and metabolism when these are given in oral route, it exhibits low toxicity (Pan *et al*., 2018). Anthocyanins find interest in food, nutraceutical, cosmetic and traditional medicine preparations for its water solubility property of pigments (Marques *et al*., 2018).

4.9 *Ginkgo biloba*

Ginkgo biloba (family: Ginkgoaceae) is the ancient trees (also known as maidenhair tree) which is a traditional medicine herb in Chinese system. The active constituents are obtained from leaf portion and it contains flavone, glycosides, diterpene lactones, bi-flavones, *etc*. (Bradly *et al*., 2000; Suresh *et al*., 2006; Li *et al*., 2017). The active constituents are extracted and concentrated using acetone water, it also removes toxic substance such as ginkgolic acid (Bradly *et al*., 2000). It exhibits antiapoptosis, neuroprotective, anti-inflammatory, mitochondrial protection, antidepressant, anti-amnestic, antioxidant, CNS stimulant (Suresh *et al*., 2006; Li *et al*., 2017; Shi *et al*., 2010). *Ginkgo biloba* enhances neurotransmission, neuroplasticity and protects toxic amyloid beta proteins (Bader *et al*., 2018). Hydrogen peroxide and amyloid beta peptide causes oxidative damage in brain cells. This is reversed by *Ginkgo biloba* by suppressing the activation of astrocytes and microglia (Zhang *et al*., 2018). Oral administration of ginkgo biloba is greatly metabolised by microorganisms present in GIT, thus decreasing the bioavailability of drugs, bioavailability is increased by individually binding the extract to phosphatidylcholine (Suresh *et al*., 2006). Usually, *Ginkgo biloba* does not cross BBB in normal physiological conditions but in case of ageing and AD, it crosses BBB effectively and restores cognitive functions (Shi *et al*., 2010). 120 mg/day ginkgo biloba improves dementia in AD and greater dose does not cause any toxicity and effect (Solomon *et al*., 2002).

4.10 Glycitein

Glycitein is a minor isoflavone (major being genistein and daidzein) obtained from the mycelia of fungus cordyceps (Bethesda *et al*., 2004). It is present 5-10% of total isoflavones in soybeans and a major constituent in soy germ ranging up to 50% (Hinkaruk *et al*., 2012). Glycitein exhibits antioxidant, neuroprotective, estrogenic activity, hypocholesterolaemia, and prevention of cell proliferation and DNA synthesis (Gutierrez *et al*., 2005). Glycitein protects neuronal cells from apoptosis induced by Aβ aggregation and prevents AD (Morelli *et al*., 2019). It delays the Aβ induced paralysis and also discard the hydroxyl free radicals (Gutierrez *et al*., 2005). Glycitein is the only isoflavone which alters the ROS and decreases the Aβ toxicity and helps in protecting from AD. These are absorbed at the jejunum and colon of the intestine (Gutierrez *et al*., 2005; Hinkaruk *et al*., 2012). The bioavailability of the glycitein in the body is very low compared to other isoflavones (Hinkaruk *et al*., 2012). Glycetein has a lower toxicity in normal cells but has higher effect on cancer cells (Zang *et al*., 2019).

5. Future aspects

The demand for the use of flavonoid has increased in past one decade. Integrative techniques are required for the use of flavonoid more widely in clinical use (Kay *et al*., 2010). Although, at present only 1 g/day is consumed through naturally available vegetables and fruits. This dose can be increased by improving the study of structure of flavonoids *in vivo* by inducing oxidative damage (Panche *et al*., 2016).

6. Conclusion

In many fields, traditional medicine knowledge offers intrusting leads for pharmacological research. In this review, we have compiled data on a large number of flavonoids used as traditional medicine against AD. Many of these species have also displayed activity in bioassay matching their traditional use. Based on this observation, future extensive investigations on those particular species can be targeted to identify the compounds responsible for the observed bioactivities as well as to unravel their MOA. It was observed that natural flavonoids had shown a better effect in most the dementia including AD. We hope that findings compiled in these review will contribute to the successful usage of ethnomedical knowledge of medicinal plants and their bioactive nature.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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