ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Neuro vigilance of *Syzygium Cumini* plant phytochemicals

Ashok Vardhan N[1], Senthil Kumar S*[2], Vijay Raghavan R[2]

[1]Department of Biochemistry, Saveetha Dental College, Saveetha Institute Medical and Technical Sciences, Saveetha University, Chennai, India
[2]Department of Research and Development, Saveetha Institute of Medical and Technical Sciences, Thandalam, Chennai – 602105, Tamil Nadu, India

Article History:

Received on: 09.03.2018
Revised on: 13.05.2018
Accepted on: 17.05.2018

Keywords:

Syzigium cumini,
Neuroprotection
Alzheimers
CNS problems

ABSTRACT

According to WHO international and national status, Central Nervous System (CNS) problems (neurological disorders: Alzheimers, dementia, epilepsy, multiple sclerosis, neuroinfections, neurological disorders associated with malnutrition, pain associated with neurological disorders, Parkinson's disease, stroke and traumatic brain injuries) are getting worse day by day because of lifestyle, environmental imbalance and genetic problems. In 2015 WHO reported that the prevalence of CNS problems is 27.8 in 1000 and 3 people in every 100 are facing any of these CNS problems. However, unfortunately, chemically synthesized drugs used to control these problems in patients poses side effects, and therefore we need natural neuroprotective agents to avoid such complications. *Syzygium cumini* is herbal, a medicinal plant with reported medicinal properties in various traditional and modern medicines. Plant phytochemicals from stem bark, leaves, flowers, fruits and seeds of *Syzygium cumini* were using to treat many diseases in modern medicine also. So far, it is used mostly to treat diabetes mellitus, pain, inflammation, ulcers, and diarrhea, and in the recent studies, it was proven that *Syzygium cumini* could be used as chemopreventive, radioprotective and antineoplastic. Although the therapeutic efficacy of SZ is studied well for many systemic diseases including diabetes, much needs to be explored on its role in neurological diseases. The phytochemicals present in different parts of SZ were showing evidence that it can show neuroprotection effectively. Those phytochemicals which were already studied as neuroprotection in them, a fine number of those phytochemicals are present in *Syzygium cumini*. It is intimating us that Syzygium cumini can be used as an effective neuroprotective natural medicine. In this review, we elaborated there may be a possibility of potentially effective treatment with different phytochemical that has the neuroprotective effect in one plant.

* Corresponding Author

Name: Dr. S. Senthil Kumar
Phone: +91-8778469065
Email: senbio@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v9i3.1572

Production and Hosted by

IJRPS | https://ijrps.com

INTRODUCTION

Classification of Syzygium Cumini: Kingdom: Plantae, Division: Angiosperms, Sub Division: Eudicots, Order: Myrtales, Family: Myrtaceae, Genus: Syzygium, Species: Cumini.

Syzygium cumini (SC) well known as Eugenia jambolana, is a species native from tropical Asia and well adapted in so many countries. It is also known as Blak plum, Brahaspati, Gambu, Indian blackberry, Jam Kol, Jambool, Jambu, Jambul, Jamun, Java plum, Kalajam, Malabar plum, Naval, Nerale Beeja, Neredu, Njaval, Pomposia, Portuguese Plum.

A web link datasheet http://www.cabi.org/isc/datasheet/52426 has the general and tropical distribution, history ecology and general uses of SC worldwide. In the ancient as well as modern medicine, the usage of Syzygium cumini is witnessed in treatments as antidiabetic, antibacterial, antiviral, anti-inflammatory as well as antitoxic, chemoprotective, radioprotective, antineoplastic and so many other diseases (Shrikant Baslingappa Swami et al., 2012). There is strong literature that supports SC containing different phytochemicals those are alkaloids, essential oils, flavonoids, glycosides, lipids, polyphenols and terpenoids (Azra Kamal, 2014). Many of those are having an effective neuroprotective function.

Medicinal properties

Syzygium cumini containing more than 43 different phytochemicals (Shrikant Baslingappa Swami et al., 2012) have been reported based on different extractions like water, ethanol, methanol and chloroform. These phytochemicals are used as the main course in the treatment of different disorders. Based on the phytochemicals presence in different parts those parts are procured and isolated or crude purified extract of those phytochemicals was given in the treatment procedure from ancient days to till now. Widely used as a 11b-hsd-inhibitor, 5-lipoxygenase-inhibitor, acaricide, aldosereductase-inhibitor, allelopathic, androgenic, anthelmintic, antiadenomic, antiaging, antiallergic, antianalgesic, antibacterial antibronchitic, anticancer (cervix), anticancer/tumour, anticatarrh, antidiabetes, antiedemic, antifatigue, antifeedant, antigingivitic, antigonadotrophic, antihistaminic, antihyperlipoproteinaemic, antiinflammatory, antilaryngitic, antilymphocytic, antimalarial, antimutagenic, antineoplastic, anti-ophidic, antioxidant, antiinsomniac, antiperiodontic, antipharyngitic, antiplasmodial, antiprostatitic, antiradicular, antiseptic, antistaphylococcic, antithyreotropic, aphrodisiac, apoptotic, artemicide, candidicide, candidicide, chemopreventive, choleretic, contraceptive, convulsant, copper-chelator, cox-2inhibitor, cyclooxygenase-inhibitor, cytotoxic, depressant, diaphoretic, edemagenic, estrogenic, fibrocystic disease, gabanergic, gonadotrophic, gram(-)icide, hepatoprotective, hepatotonic, herbicide, hypnotic, hypocholesterolemic, hypoglycaemic effect, hypotensive, hypothermic, icam-1-inhibitor, immunostimulant, inos-inhibitorinsectifuge, iodothyronine-deiodinase-inhibitor, lipoxygenase-inhibitor, mao-inhibitor, mutagenic, myorelaxant, nematicide, noinhibitor, perfumery, progesteronigenic, protisticide, sedative, serotoninergic, spermicide, teratologic, thyrotropic, transdermal, ulcerogenic etc., (Muniappan Ayyanar et al., 2012, S Ramya et al., 2012) each and every phytochemical has its own activity in the above listed medicinal properties those were already explored and reported in different studies.

Phytochemicals present in Syzygium Cumini

Stem Bark: Betulinic Acid, Ellagic Acid, Ellagitannin, Friedelan-3-A-Ol, Friedelin, Gallic-Acid, Gallotannin, Kaempferol, Myricetin, β-Sitosterol, β-Sitosterol-D glucoside

Flowers: Ellagic Acid, Isoquercetin, Kaempferol, Myricetin, Oleanolic Acid, Quercetin

Leaves: Betulinic Acid, Crategolic (Maslinic) Acid, Flavonol Glycosides, Myricetin-3-O-4-Al rhamnopyranosides, Mycaminose, Myricetin, Myricitrin, N-Dotricontanol, N-Hentriacontane, N-Hepatcosane, N-Nonacosane, Noctacosanol, N-Triacontanol, Quercetin, β –Sitosterol

Fruit Pulp: Anthocyanins, Delphinidin, Malvidin-Diglucosides, Petunidin

Seeds: 1-Galloylglucose, 3-Galloylglucose, 3, 6-Hexahydroxy Diphenoylglucose, 4, 6 Hexahydroxyl diphenyl glucose, Corilagin, Ellagic-Acid, Gallic-Acid, Jambosine, Quercetin, B-Sitosterol

Essential oils: 1, 8-cineole, Eucarvone, Geranyl acetone, Muurolol, Myrtenol, Pinocarvone, α-cadinol, α-myrtenol, α-terpineol Some of the phytochemicals present more than one part:

Betulinic acid - Stem, Leaves
Ellagic acid - Seed, Stem, Flowers
Gallic acid - Stem, Seed
Kaempferol - Stem, Flowers
Myricetin - Stem, Flowers, Leaves
Quercitin - Flower, Seed, Leaves
β -Sitosterol - Seed, Stem, Leave

Neuroprotective properties

So far there is no work has been reported related to the neuroprotective functions exclusively by using SC plant, but it contains an adequate number of neuroprotective phytochemicals in it. These phytochemicals are used and reported as neuroprotective effective in several studies. There are 23 neuroprotective phytochemicals out of 43 phytochemicals present in SC plant, in our study we reporting glucose containing neuroprotective phytochemicals as glucose derivatives and isomers, derivatives under one column. All these phytochemicals are given along with their PubChem id to get further (3D structure, synonyms, chemical and physical properties) references in https://www.ncbi.nlm.nih.gov/pccompound

a) 1, 8-cineole
b) Anthocyanins
c) Beta-sitosterol
d) Betulinic acid

e) Corilagin
f) Ellagic acid, ellagitannin
g) Gallic acid, gallotanin
h) Glucose derivatives
i) Kaempferol
j) Malvidin di glucoside
k) Maslinic acid
l) Myricetin
m) Myricitrin
n) Oleanolic acid
o) Quercitin,
p) Iso quercitin
q) Rhamnopyranosides

a) 1, 8-cineol: 1, 8-cineole is a monoterpene in es- sential oils present in SC. Chemical formula: C12H20O3 molecular weight: 212.28 and PubChem id: 11218113. 1, 8 cineole structure-Figure 1. 1, 8-cineole affects the ischemic injury it has been reported that decreased oxygen-glucose deprivation/reoxygenation (OGD/R)-induced cortical cell injury, reduced n-methyl-d-aspartate (NMDA)-induced cell injury. 1, 8-cineole has significantly lowered the OGD/R- and NMDA-induced higher production of reactive oxygen species (ROS). The decrease in OGD/R-induced intracellular superoxide in 1, 8-cineole-treated cortical cells was associated with the upregulation of superoxide dismutase activity. In an assay of oxygen radical absorbance capacity, 1, 8-cineole showed direct ROS scavenging activity (Ryu S et al., 2014). In the study of microemulsion drug patches by using 1, 8 cineole as a molecule in the patch has a potential effect on Alzheimer disease (Shi J et al., 2012). These findings are promising the neuroprotective property of 1, 8-cineole.

b) Anthocyanins: Anthocyanins (ANC) are natural polyphenolic compounds widely distributed as pigments in fruits and vegetables. SC fruit is rich in ANC, Chemical formula: $C_{15}H_{11}O^{+}$ molecular weight: 207.24 and PubChem id: 145858, anthocyanin structure-Figure2. ANC pelargonidin was shown to alleviate motor deficits and nigral dopaminergic cell death in 6-OHDA-treated rats (Roghani M et al., 2010), ANC-mediated neuroprotection are likely relevant to *in vivo* protective effects, given that a number of ANC have been detected as intact glycosides in the brains of rats (Ho L et al., 2013, Janle EM et al., 2010, Talavera S et al., 2005, Wang J et al., 2013) and pigs (Milbury PE et al., 2010) fed diets supplemented with ANC-rich extracts. Anthocyanins display significant *anti-apoptotic* activity in neurons. Antioxidant properties of these nutraceuticals, particularly at the level of the mitochondria, appear to underlie their neuroprotective effects (Erika K. Ross et al., 2012). These are elaborating the individual effectiveness of ANC in neuroprotection.

c) Beta-sitosterol: Beta (β) sitosterol and β-Sitosterol D-glucoside are one of the plant sterol present in SC seed and stem bark β-Sitosterol Chemical formula: $C_{29}H_{50}O$, molecular weight: 414.70 and PubChem id: 222284, β-Sitosterol structure-Figure3. β-Sitosterol D-glucoside Chemical formula: $C_{35}H_{60}O_{6,}$ molecular weight: 576.84 and PubChem id: 70699531, β-Sitosterol D-glucoside structure-Figure 4. Beta-sitosterol individually may or may not have the neuroprotective capacity, but when both β-sitosterol and β-sitosterol D-glucoside (BSSG) are combined, they have the capacity of neurodegeneration and progression of neuron loss (Van Kampen JM et al., 2014). BSSG has the capacity of causing Parkinson Disease (PD) if it was given in daily diet for few days and it aggravates the PD symptoms on continuation of feeding BSSG (Jackalina M et al., 2015). It shows that the BSSG combinable can cause the neurodegenerative disorders.

d) Betulinic acid: Betulinic acid is a triterpene present in SC stem bark and leaves. Chemical formula: $C_{30}H_{48}O_{3,}$ molecular weight: 456.70 and PubChem id: 64971, Betulinic acid structure-Figure5. Betulinic acid reduces the oxidative stress and causes down-regulation of Nox2 in cerebral ischemia in mice showing the neuroprotective mechanism (Lu, Q et al., 2011). Activation of the mitochondrial pathway and induction of apoptosis in neuroblastoma and some other cells showed positive neuroprotection via mitochondrial mechanism activation by betulinic acid. (Fulda S et al., 1997, Jeremias I et al., 2004, Tan Y et al., 2003), betulinic acid in the treatment or prevention of anxiety got patented (Durst T et al., 2002). Betulinic acid has GABAA-receptor-related properties betulin competed with [3H]GABA for binding to the corresponding sites on the GABAA receptor, whereas betulinic acid and lupeol did not show any binding affinity (Muceniece R et al., 2008).

e) Corilagin: Corilagin has a Chemical formula: $C_{27}H_{22}O_{18,}$ molecular weight: 634.45 and PubChem id: 73568, Corilagin structure-Figure6. Corilagin can protect cerebral ischemia by maintaining Super Oxide Dismutases (SODs) and brain-derived neurotrophic factor (BDNF) levels as well as decreasing glial activation, it is showing that the oral administration of corilagin effective in neuroprotection (Park, J.H et al., 2011). In Alzheimer's disease formation of amyloid β through the proteolytic process from β-secretase, in the oral administration of corilagin with other molecules, it has shown that blocking or binding with β-secretase to improve the Alzheimer's condition (Youn K et al., 2013).

f) Ellagic acid, ellagitannin: Ellagic acid Chemical formula: $C_{14}H_{6}O_{8,}$ molecular weight: 302.19 and

PubChem id: 52818515, Ellagic acid structure-Figure 7; Elagitanin Chemical formula: $C_{44}H_{32}O_{27,}$ molecular weight: 992.70 and PubChem id: 101601927- Figure 8**.** Ellagic acid(EA) and ellagitannin(ET) are natural polyphenols present in SC seed, stem and flowers. ETs are hydrolyzed to EA under physiological conditions *in vivo* and EA is then gradually metabolized by the intestinal microbiota to produce different types of urolithins (J.M. Landete, 2011) Total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), the treatment of ellagic acid significantly lowered malondialdehyde (MDA) and nitric oxide (NO) levels in diabetic induced rat model and it is showing that paraoxonase, catalase, TAS levels decrease in brain and sciatic nerve tissue showing the potential neuroprotective effect of ellagic acid (Ertugrul Uzar et al., 2012). Ellagic acid acts on pain misperception and cognitive deficiencies by recovering of pain misperception and memory, learning parameters by the natural antioxidant to combat noxious oxidative effects of 6-OHDA induced PD animal model (Dolatshahi M et al., 2015). Maternal dietary supplementation with pomegranate juice (which is very rich in ellagic acid) is neuroprotective for the neonatal brain (David J. Loren et al., 2005). Ellagic acid possesses potent neuroprotective effects through its free radical scavenging properties, iron chelation, activation of different cell signaling pathways, and mitigation of mitochondrial dysfunction and ellagic acid may invoke a spectrum of cell signaling pathways to attenuate or slow down the development of neurodegenerative disorders (Ahmed T et al., 2016).

g) Gallic acid, Gallotanin: Gallic acid chemical formula: $C_7H_6O_5$, molecular weight: 170.11 and PubChem id: 370, gallic acid structure-Figure 9; Gallotanin chemical formula: $C_{101}H_{60}O_{50}$, molecular weight: 2073.52 and PubChem id: 16133691, gallic acid structure-Figure 10. Gallic acid and gallotanins are polyphenols present in stem and seed of SC plant. Gallotanin is an hydrolysable tannin which turns in to gallic acid and glucose. Tannase acts on ester and depside linkages (acyl bond i.e. C-O) in hydrolysable tannins, mainly gallotannins. A typical reaction catalyzed by tannase is shown in Fig. 1.5 b wherein Tannic acid (I) was found to be hydrolysed to gallic acid and glucose through 2, 3, 4, 6 tetragalloyl glucose (III) and monogalloyl glucose (IV) (Lekha and Lonsane, 1997). Gallic acid treatment involving inhibition of nuclear factor kapp B (NF-κB) acetylation has shown potential decrease in cytokine production in microglia and Aβ-induced neurotoxic protection and selective inhibition of NF-κB acetylation by the histone acetyltransferase inhibitor. Gallic acid is promising as better therapeutic approach for Alzheimer disease (Kim MJ et al., 2011). P66shc protein expression and anisomycin-induced secretion of Aβ1-42 were significantly decreased and there is an improvement in SOD activity and acetylcholine secretions in SH-SY5Y cells by the treatment of gallic acid neuronal oxidative stress injury in AD patients can get better treatment by using gallic acid (Yun Wang et al., 2015).

h) Glucose derivatives: Compounds containing high amounts of glucose as well as metabolic glucose derivatives of other molecules are discussed below:

i. 1-Galloylglucose
ii. 3-Galloylglucose
iii. 3, 6-Hexahydroxy Diphenoylglucose
iv. 4, 6 Hexahydroxyl diphenyl glucose

In case of neuro disorders like Alzheimer's disease, hypometabolism of glucose leads to a loss of glucose transporters in neurons and endothelial cells of the blood-brain barrier (BBB). In a study by Niccoli et al. in Aβ toxicity in Drosophila, they proposed that increased neuronal uptake of glucose against Aβ toxicity and highlight Grp78 as a novel therapeutic target for the treatment of AD (Niccoli T et al., 2016). Oxygen and glucose deprivation (OGD) causes significant loss of mitochondrial complex-I activity, mitochondrial membrane potential collapse, ATP depletion and necrosis occurred in the OGD neurons, in such cases NADPH concentrations also decreases in neurons in that conditions glucose metabolism would supply NADPH, through the pentose–phosphate pathway, by reducing oxidative stress, mitochondrial damage and neurotoxicity during oxygen deprivation to neural cells (Angeles Almeida et al., 2002). Its strongly elaborating that in some CNS problems there is a need of glucose transportation and alternative pathways to overcome its complications.

i) Kaempferol: Chemical formula: $C_{15}H_{10}O_{6,}$ molecular weight: 286.23 and PubChem id: 5280863, Kaempferol structure-Figure11. Kaempferol has a protective effect on neurons by scavenging the free radicals and antioxidant capacity in MPTP induced PD model. It prevents the tyrosine hydroxylase positive neurons loss thereby showing anti PD potentials (Shen LI and Xiao-Ping P, 2011). In the progression of the AD, oxidative stress plays a detrimental role while treatment of kaempferol through its antioxidant capacity as well as its ability in ameliorating the breakdown in mitochondria and neuronal cell membrane. It showed improvement in Aβ-induced memory impairment in animal models and these properties support the neuroprotective capacity of Kaempferol (Jae Kyeom KIM et al., 2010).

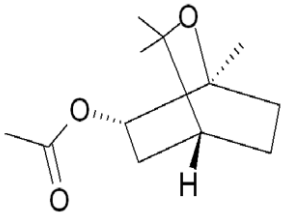

Figure 1: 1, 8-cineol

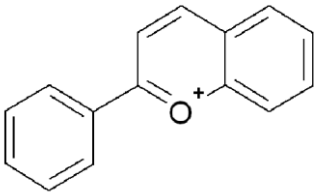

Figure 2: anthocyanin

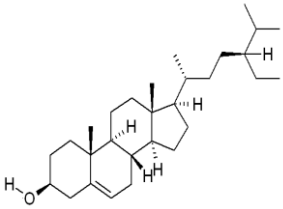

Figure 3: β-Sitosterol

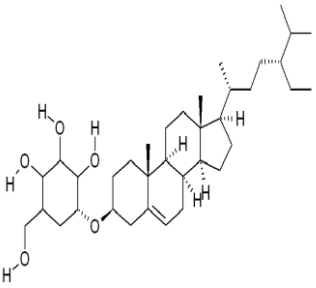

Figure 4: β-Sitosterol D-gluco-side

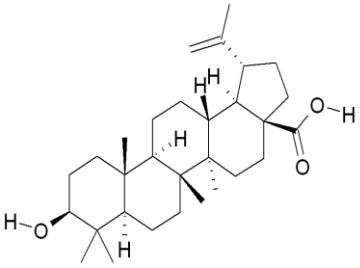

Figure 5: Betulinic acid

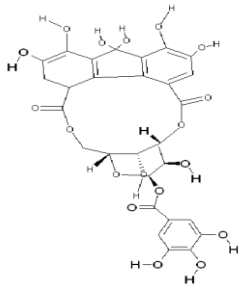

Figure 6: Corilagin

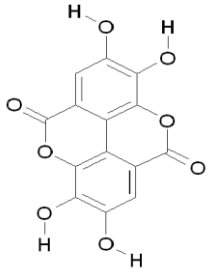

Figure 7: Ellagic acid

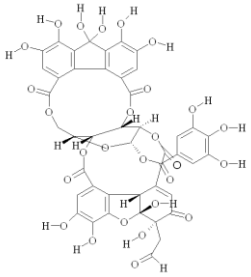

Figure 8: Ellagitannin

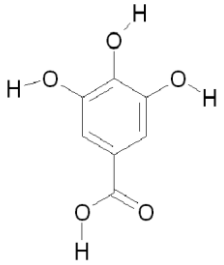

Figure 9: Gallic acid

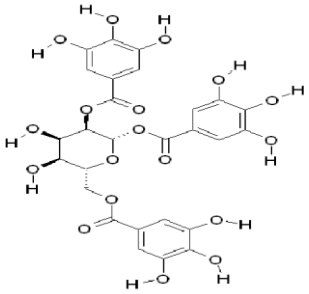

Figure 10: Gallotanin

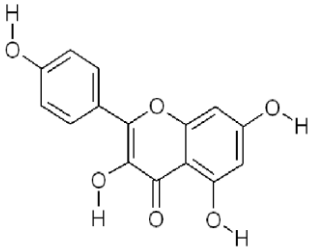

Figure 11: Kaempferol

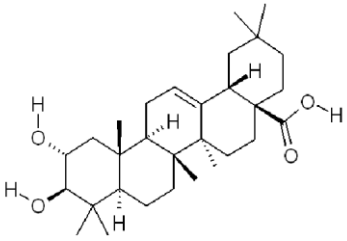

Figure 12: Maslinic acid

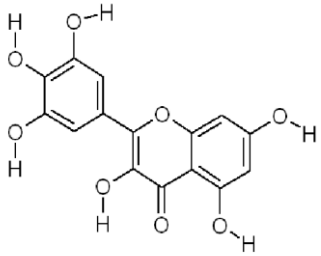

Figure 13: Myricetin

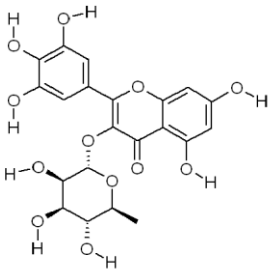

Figure 14: Myricitrin

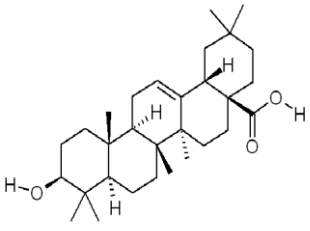

Figure 15: Oleanolic acid

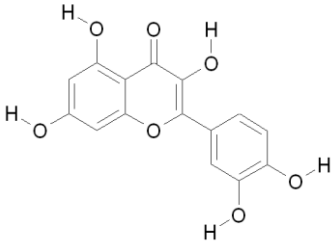

Figure 16: Quercitin

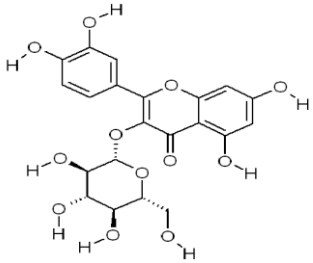

Figure 17: Iso Quercitin

j) Malvidin di glucoside: Chemical formula: $C_{29}H_{35}O_{17}^{+}$, molecular weight: 655.57 and PubChem id: 44256978. Malvidin is one of the anthocyanins very rich in wine. Wine polyphenolic compounds are well known for the antioxidant properties. Nozomu Matsunaga et al. in 2009 first reported, demonstrating that in the VMA (Vaccinium myrtillus (bilberry) anthocyanoside (VMA) and/or its main anthocyanidin constituents (cyanidin, delphinidin, and malvidin) can protect retinal ganglion cells (RGCs) against retinal damage in vitro and in vivo.) can protect the retina against NMDA-induced neurotoxicity in vivo. Furthermore, we found that VMA was effective against the SIN-1- induced elevation of ROS and lipid peroxidation in mouse forebrain homogenates. Taken together, the above findings indicate that the protective effects of VMA against NMDA-induced neurotoxicity may be partly mediated by an inhibition of NMDA-induced oxidative stress (36). Oxidative stress is involved in many forms of cellular and molecular deterioration. This damage can lead to cell death and various neurodegenerative disorders, such as Parkinson's or Alzheimer's diseases (Abdelkader Basli et al., 2012).

k) Maslinic acid: Maslinic acid is a natural phytoalexin it is a pentacyclic triterpene present SC leaves. Chemical formula: $C_{30}H_{48}O_4$, molecular weight: 472.69 and PubChem id: 73659, maslinic acid structure-Figure12. Maslinic acid has an anti-inflammatory effect on astrocytes which are containing NADPH releasing capacity in OGD conditions to maintain mitochondria from damage and it shows faithful effects on improvement of inflammation-related CNS problems (Huang, L et al., 2011). High expression of GLAST and GLT-1 caused the extracellular glutamate load and neuron damage, while in the treatment of maslinic acid controlled the glutamate load by the release of LDH and increased the neuron integration and morphology (Qian, Y et al., 2011). Treatment of maslinic acid has shown the release of LDH and decrease in induced nitric oxide synthase iNOS enzyme to protect the CNS, its strongly recommending that maslinic acid can be used as a nutraceutical (Glòria Lozano-Mena et al., 2014).

l) Myricetin: Myricetin is a naturally occurring flavonoid present in stem flowers and leaves of SC plant. Chemical formula: $C_{15}H_{10}O_8$, molecular weight: 318.23 and PubChem id: 5281672, myricetin structure-Figure13. Intracellular Ca2+ overload via the N-methyl-D-aspartate receptor (NMDAR), reactive oxygen species (ROS) generation and caspase-3 activation occurs in Glutamate excitotoxicity, when its exposed to treatment of myricetin it phosphorylates the NMDR first and foremost and decreases the Ca2+ overload, decreases the ROS production and finally binds to the capase3 to protect the glutamate-induced ischemia and AD (Shimmyo Y et al., 2008). Myricetin has cytoprotective capacity in vitro experimental conditions in models of predominantly apoptotic death such as that induced by medium concentrations (200 M) of H2O2 added to PC12 cells in culture (Dajas F et al., 2003). Blockage of Cav2.2 (N-type) and Cav2.1 (P/Q-type) channels except for the intracellular Ca2+ release by the myricetin shows the effect on release in 4-AP-evoked glutamate. These results suggest that myricetin inhibits glutamate release from cerebrocortical synaptosomes by attenuating voltage-dependent Ca2+ entry and rescue the cerebrocortical nerve terminals to protect from acute and chronic brain disorders (Yi Chang et al., 2015).

m) Myricitrin: Chemical formula: $C_{21}H_{20}O_{12}$, molecular weight: 464.37 and PubChem id: 5281673, myricitrin structure-Figure14. KIM HD et al. in 2016 reported in their studies they found no significant neuroprotective effect of 30 mg/kg myricitrin on 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in the substantia nigra (SN) of mice. However, myricitrin treatment with 60 mg/kg protected DA neurons against 6-OHDA-induced neurotoxicity. Moreover, myricitrin treatment preserved TH enzyme activity and mTORC1 activation in nigral DA neurons in the SN of 6-OHDA-treated mice, and its treatment suppressed an increase in tumour necrosis factor-α expression in activated microglia. These results suggest that myricitrin may have neuroprotective properties linked to mTORC1 activation, preservation of TH enzyme activity, and anti-neuroinflammation for preventing DA neuronal degeneration in vivo. It concludes higher doses treatment of myricitrin causes the mammalian target of rapamycin complex 1 (mTORC1) activation, anti-inflammatory and antioxidant properties and maintains of TH enzyme activity, nigral dopaminergic neurons in the substantial nigra of 6-OHDA-treated mice and it decreases the tumor necrosis factor- α (TNF- α) expression in microglia showing the neuroprotective capacity myricitrin (Kim HD et al., 2016).

n) Oleanolic acid: Chemical formula: $C_{30}H_{48}O_3$, molecular weight: 456.7 and PubChem id: 10494, oleanolic acid structure-Figure15. Synthetic triterpenoid analogs of oleanolic acid, such as methyl-2-cyano-3, 12-dioxooleana-1, 9-dien-28-oate (CDDO-Me, RTA 402) have potent neuroprotective functions reported in LPS-, TNF- or fibrillar amyloid beta 1–42 (Aβ1–42) peptide-induced increases in reactive microglia and inflammatory gene expression without an overall effect on cell viability. CDDO-Me can inhibit the microglial-derived cytokines production and not TNF-dependent pro-apoptotic pathways, CDDO-Me enhanced

phagocytic activity of BV2 cells in a stimulus-specific manner but inhibited generation of reactive oxygen species (ROS) in mixed neuron/glia basal forebrain cultures and dopaminergic cells (Thi A Tran et al., 2008). Nrf2/ARE (NFE2 related factor 2/antioxidant response element) signalling program and nucleus formation were estimated by using the synthetic triterpenoid analogs of oleanolic acid in amyotrophic lateral sclerosis (Arie Neymotin et al., 2011). Nrf2 for retinal ganglion cells in ischemia-reperfusion for the retinal neuroprotective effect estimation by using CDDO (Zhenhua Xu et al., 2015).

o) Quercitin: Chemical formula: $C_{15}H_{10}O_{7,}$ molecular weight: 302.23 and PubChem id: 5280343, quercitin structure-Figure16**.** 6-OHD induce the PD in an animal model by degrading dopamine and antioxidant enzymes in the striatum. Treatment of quercetin for 2 weeks shows a significant decrease in oxidative stress and dopaminergic protection against 6-OHD induced PD in an animal model (Nagaraja Haleagrahara et al., 2011). Treatment of quercetin along with polyunsaturated fatty acids containing fish oils against rotenone-induced PD model showed effective recovery in behavioural, dopamine levels in the striatum and mitochondrial damage and therefore combination treatment approach using quercitin has much neuroprotective effect (K. M. Denny Joseph et al., 2015). The reduced dose of quercetin (25mg/kg bwt) against MPTP induced PD, reserpine and haloperidol-induced catalepsy models of neurodegeneration have shown beneficial neuroprotective effect. There is a significant decrease in reserpine-induced high frequencies of chewing movements by the quercetin and an increase in behavioural parameters like actophotometer (PAM). Increased glutathione and decreased lipid peroxidation observed in MPTP model in quercetin treatment. The anti-inflammatory and anti-oxidant property of quercitin tested so far implicates it is potential to be used in the treatment of CNS problems (Suryakanta Pany et al., 2014).

p) Iso Quercitin: Chemical formula: $C_{21}H_{20}O_{12,}$ molecular weight: 464.37 and PubChem id: 5280804, iso-quercitin structure-Figure17. Ischemia model of oxygen-glucose deprivation followed by reperfusion (OGD/R) were examined for the neuroprotective effects of iso quercitin on rat cortical neuron cells, by inhibiting protein expression of toll-like receptor 4 (TLR4), nuclear factor-kappa B (NF-κB), and mRNA expression of TNF-α and IL-6, down-regulation of extracellular-regulated kinase (ERK), Jun kinase (JNK) and p38, and arresting the caspase-3 activity through its anti-inflammatory and anti-apoptosis pathways to protect the neuronal cells (Cai-Ping Wang et al., 2013). Along with the above finding inclusion of p38 mitogen-activated protein kinase (MAPK), cAMP-responsive element-binding protein (CREB), Bax, Bcl-2 and interleukin-1β (IL-1β) were studied in rat hippocampus neurons for the ischemic stroke and other neuro disorders can be treated with iso quercitin potentially (Wang C et al., 2016).

q) Rhamnopyranosides: Rhamnopyranosides are derivatives of rhamnose which is a naturally occurring de-oxy sugar phenylpropanoid ester of rhamnose, buergerisides A1, B1, B2 and C1 were used to estimate the effective neuropotential benefits along with some other polyphenols against glutamate-induced neurotoxicity in cortical cell cultures of the rat. In these, rhamnose along with the other polyphenols has shown a better neuroprotective effect against glutamate-induced neurodegeneration (Kim SR et al., 2000).

CONCLUSION

In this review article tried to show the availability of very important plant phytochemical constituents (corilagin, ellagic acid, gallic acid, quercetin, kaempferol, oleanolic acid, anthocyanins and 1, 8 cineole) in SC which neuroprotective functions have been already tested for neuroprotective potentials in neurological disorders like AD, PD, sclerosis and ischemia. The role of SC plant phytochemicals in anti-oxidant, anti-inflammatory and apoptosis properties will be beneficial for eliciting neuroprotective functions in disease conditions. Our aim in this review is to discuss and focus exclusively on only phytochemicals that can play a crucial role against neurological problems. Based on considerable proof of evidence, the SC plant can be used as a better therapeutic approach in CNS related problems.

Acknowledgements: The authors thankful to Director, Saveetha Dental College and Hospital and Saveetha Medical College and Hospital, for the encouragement and motivation.

REFERENCES

Abdelkader Basil, Stephanie Soulet, Nassima Chaher, Jean-Michel M´erillon, Mohamed Chibane, Jean-PierreMonti, and Tristan Richard "Wine Polyphenols: Potential Agents in Neuroprotection"- Oxidative Medicine and Cellular Longevity Volume 2012, Article ID 805762; doi:10.1155/2012/805762

Ahmed T, Setzer WN, Nabavi SF, Orhan IE, Braidy N, Sobarzo-Sanchez E, Nabavi SM "Insights Into Effects of Ellagic Acid on the Nervous System: A Mini Review"- Curr Pharm Des. 2016;22(10):1350-60.

Andres-Lacueva C, Shukitt-Hale B, Galli RL, Jauregui O, Lamuela-Raventos RM, Joseph JA. Anthocyanins in aged blueberry-fed rats are found centrally and may enhance memory. Nutr Neurosci. 2005; 8:111–20. [PubMed: 16053243]

Angeles Almeida, Marı´a Delgado-Esteban, Juan P. Bolan˜os and Jose´ M. Medina "Oxygen and glucose deprivation induces mitochondrial dysfunction and oxidative stress in neurons but not in astrocytes in primary culture"- Journal of Neurochemistry, 2002, 81, 207–217

Arie Neymotin, Noel Y. Calingasan, Elizabeth Wille, Nima Naseri, Susanne Petri, Maria Damiano, Karen T. Liby, Renee Risingsong, Michael Sporn, M. Flint Beal1, and Mahmoud Kiaei "Neuroprotective effect of Nrf2/ARE Activators, CDDO-ethyl amide and CDDO-trifluoroethylamide in a Mouse Model of Amyotrophic Lateral Sclerosis"- Free Radic Biol Med. 2011 July 1; 51(1): 88–96. doi:10.1016/j.freeradbiomed.2011.03.027

Azra Kamal "PHYTOCHEMICAL SCREENING OF SYZYGIUM CUMINI SEEDS"-Indian Journal Of Plant Sciences ISSN: 2319–3824; http://www.cibtech.org/jps.htm 2014 Vol. 3 (4) October-December, pp 1-4/Kamal

Cai-Ping Wang, Jian-Long Li, Lu-Zhong Zhang, Xiao-Chuan Zhang, Shu Yu, Xin-Miao Liang, Fei Ding, Zhi-Wei Wang "Isoquercetin protects cortical neurons from oxygen-glucose deprivation–reperfusion-induced injury via suppression of TLR4–NF-κB signal pathway"- Neurochemistry International volume 63, Issue 8, December 2013, Pages 741–749

Dajas F, Rivera-Megret F, Blasina F, Arredondo F, Abin-Carriquiry JA, Costa G, Echeverry C, Lafon L, Heizen H, Ferreira M, Morquio A" Neuroprotection by flavonoids"- Braz J Med Biol Res. 2003 Dec;36(12):1613-20

David J. Loren, Navindra P. Seeram, Risa N. Schulman, And David M. Holtzman "Maternal Dietary Supplementation with Pomegranate Juice Is Neuroprotective in an Animal Model of Neonatal Hypoxic-Ischemic Brain Injury"- Pediatr Res 57: 858–864, 2005; DOI: 10.1203/01.PDR. 0000157722.07810.15

Dolatshahi M, Farbood Y, Sarkaki A, Mansouri SMT, Khodadadi A. Ellagic acid improves hyperalgesia and cognitive deficiency in 6hydroxidopamine induced rat model of Parkinson's disease. Iran J Basic Med Sci 2015; 18:38-46.

Durst T, Merali Z, Arnason JT, Sanchez-Vindas EP, Poveda AL. (2002). Anxiolytic Marcgraviaceae compositions were containing betulinic acid, betulinic acid derivates, and methods. WO/2002/091858.

Erika K. Ross, Natalie A. Kelsey, Daniel A. Linseman "Anthocyanins: Janus Nutraceuticals Displaying Chemotherapeutic and Neuroprotective Properties"- Natural compounds as inducers of cell death pp 491-513; DOI10.1007/978-94-007-4575-9_21 Print ISBN- 978-94-007-4574-2 Online ISBN-978-94-007-4575-9

Ertugrul Uzarmailto:ertuzar@yahoo.com, Harun Alp, Mehmet Ugur Cevik, Ugur Fırat, Osman Evliyaoglu, Adnan Tufek, Yasar Altun "Ellagic acid attenuates oxidative stress on the brain and sciatic nerve and improves histopathology of the brain in streptozotocin-induced diabetic rats"- Neurological Sciences June 2012, Volume 33, Issue 3, pp 567-574

Fulda S, Friesen C, Los M, Scaffidi C, Mier W, Benedict M, Nunez G, Krammer PH, Peter ME, Debatin KM. (1997). Betulinic acid triggers CD95 (APO-1/Fas)-and p53-independent apoptosis via activation of caspases in neuroectodermal tumours. Cancer Research 57, 49564964.

Glòria Lozano-Mena *, Marta Sánchez-González, M. Emília Juan and Joana M. Planas "Maslinic Acid, a Natural Phytoalexin-Type Triterpene from Olives — A Promising Nutraceutical?"- Molecules 2014, 19, 11538-11559; doi:10.3390/molecules190811538; www.mdpi.com/journal/molecules

Ho L, Ferruzzi MG, Janle EM, Wang J, Gong B, Chen TY, Lobo J, Cooper B, Wu QL, Talcott ST, Percival SS, Simon JE, Pasinetti GM. Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease. Faseb J. 2013; 27:769– 81. [PubMed: 23097297]

Huang, L.; Guan, T.; Qian, Y.; Huang, M.; Tang, X.; Li, Y.; Sun, H. "Anti-inflammatory effects of maslinic acid, a natural triterpene, in cultured cortical astrocytes via suppression of nuclear factor-kappa B"- Eur. J. Pharmacol. 2011, 672, 169–174

J.M. Landete "Ellagitannins, ellagic acid and their derived metabolites: A review about the source, metabolism, functions and health"- Food Research International Volume 44, Issue 5, June 2011, Pages 1150–1160.

Jackalina M. VanKampen, David C. Baranowski, Harold A. Robertson, Christopher A. Shaw, Denis G. Kay "TheProgressiveBSSGRatModelof Parkinson's: Recapitulating MultipleKey Features of the Human Disease"- PLoSONE10(10): e0139694; doi:10.1371/ journal.pone.0139694

Jae Kyeom Kim, Soo Jung CHOI, Hong Yon CHO, Han-Joon HWANG, Young-Jun Kim, Seung Taik LIM, Chang-Ju Kim, Hye Kyung Kim, Sabrina PETERSON & Dong-Hoon SHIN (2010) Protective Effects of Kaempferol (3, 4′, 5, 7-tetrahydroxyflavone) against Amyloid Beta Peptide (Aβ)-Induced Neurotoxicity in ICR Mice, Bioscience, Biotechnology, and Biochemistry, 74:2, 397-401, DOI: 10.1271/bbb.90585; http://dx.doi.org/10.1271/bbb.90585

Janle EM, Lila MA, Grannan M, Wood L, Higgins A, Yousef GG, Rogers RB, Kim H, Jackson GS, Ho L, Weaver CM. Pharmacokinetics and tissue distribution of 14C-labeled grape polyphenols in the periphery and the central nervous system following oral administration. J Med Food. 2010; 13:926–33. [PubMed: 20673061]

Jeremias I, Steiner HH, Benner A, Debatin KM, Herold-Mende C. (2004). Cell death induction by betulinic acid, ceramide, and TRAIL in primary glioblastoma multiforme cells. Acta Neurochirurgica (Wien) 146, 721-729.

K. M. Denny Joseph, Muralidhara "Combined Oral Supplementation of Fish Oil and Quercetin Enhances Neuroprotection in a Chronic Rotenone Rat Model: Relevance to Parkinson's disease"- Neurochemical Research 2015, Volume 40, Issue 5, pp 894-905

Kim HD, Jeong KH, Jung UJ, Kim SR "Myricitrin Ameliorates 6-Hydroxydopamine-Induced Dopaminergic Neuronal Loss in the Substantia Nigra of Mouse Brain"- J Med Food. 2016 Apr;19(4):374-82. doi: 10.1089/jmf.2015.3581

Kim MJ, Seong AR, Yoo JY, Jin CH, Lee YH, Kim YJ, Lee J, Jun WJ, Yoon HG "Gallic acid, a histone acetyltransferase inhibitor, suppresses β-amyloid neurotoxicity by inhibiting microglial-mediated neuroinflammation"- Mol Nutr Food Res. 2011 Dec;55(12):1798-808. doi: 10.1002/mnfr.201100262.

Kim SR, Kim YC "Neuroprotective phenylpropanoid esters of rhamnose isolated from roots of Scrophularia buergeriana"- Phytochemistry. 2000 Jun;54(5):503-9

Lu, Q.; Xia, N.; Xu, H.; Guo, L.; Wenzel, P.; Daiber, A.; Munzel, T.; Forstermann, U.; Li, H. Betulinic acid protects against cerebral ischemia-reperfusion injury in mice by reducing oxidative and nitrosative stress. Nitric Oxide 2011, 24, 132–138

Milbury PE, Kalt W. Xenobiotic metabolism and berry flavonoid transport across the blood-brain barrier. J Agric Food Chem. 2010; 58:3950–6. [PubMed: 20128604]

Muceniece R, Saleniece K, Rumaks J, Krigere L, Dzirkale Z, Mezhapuke R, Zharkova O, Klusa V. (2008). Betulin binds to γ-aminobutyric acid receptors and exerts anticonvulsant action in mice. Pharmacology, Biochemistry and Behavior 90, 712-716.

Muniappan Ayyanar, Pandurangan Subash-Babu "Syzygium cumini (L.) Skeels: A review of its phytochemical constituents and traditional uses"- Asian Pac J Trop Biomed 2012; 2(3): 240-246; www.elsevier.com/locate/apjtb 10.1016/S2221-1691(12)60050-1

Nagaraja Haleagrahara, Cheng Jun Siew, Nilesh Kumar Mitra, Mangala Kumari "Neuroprotective effect of bioflavonoid quercetin in 6-hydroxydopamine-induced oxidative stress biomarkers in the rat striatum"- Neurosci Lett. 2011 Aug 15;500(2):139-43. doi: 10.1016/j. neulet. 2011. 06.021

Niccoli T, Cabecinha M, Tillmann A, Kerr F, Wong CT, Cardenas D, Vincent AJ, Bettedi L, Li L, Grönke S, Dols J, Partridge L "Increased Glucose Transport into Neurons Rescues Aβ Toxicity in Drosophila"- Curr Biol. 2016 Aug 9. pii: S0960-9822(16)30768-0. doi: 10.1016/j. Cub. 2016. 07. 017

Park, J.H., Joo, H.S., Yoo, K. et al. Neurochem Res (2011) 36:2043 doi:10.1007/s11064-011-0528-9

Qian, Y.; Guan, T.; Tang, X.; Huang, L.; Huang, M.; Li, Y.; Sun, H.; Yu, R.; Zhang, F. "Astrocytic glutamate transporter-dependent neuroprotection against glutamate toxicity: An in vitro study of maslinic acid"- Eur. J. Pharmacol. 2011, 651, 59–65

Roghani M, Niknam A, Jalali-Nadoushan MR, Kiasalari Z, Khalili M, Baluchnejadmojarad T. Oral pelargonidin exerts dose-dependent neuroprotection in the 6-hydroxydopamine rat model of hemiparkinsonism. Brain Res Bull. 2010; 82:279–83. [PubMed: 20558255]

Ryu S, Park H, Seol GH, Choi IY "1, 8-Cineole ameliorates oxygen-glucose deprivation/reoxygenation-induced ischaemic injury by reducing oxidative stress in rat cortical neuron/glia"- J Pharm Pharmacol 2014 Dec; 66(12):1818-26; doi: 10.1111/ jphp.12295

S Ramya, K Neethirajan, and R Jayakumararaj "Profile of bioactive compounds in Syzygium cumini – a review"- Journal of Pharmacy Research 2012, 5(8), 4548-4553; www.jpronline.info

Shen LI and Xiao-Ping P "Neuroprotective Effect of Kaempferol against a 1-Methyl-4-phenyl-1, 2, 3, 6tetrahydropyridine-Induced Mouse Model of

Parkinson's Disease"- Biol. Pharm.Bull. 34(8) 1291-1296, 2011

Shi J, Cong W, Wang Y, Liu Q, Luo G "Microemulsion-based patch for transdermal delivery of huperzine A and ligustrazine phosphate in the treatment of Alzheimer's disease"- Drug Dev Ind Pharm. 2012 Jun;38(6):752-61; doi: 10.3109 /03639045.2011.625031

Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H "Three distinct neuroprotective functions of myricetin against glutamate-induced neuronal cell death: involvement of direct inhibition of caspase-3"- J Neurosci Res. 2008 Jun;86(8):1836-45. doi: 10.1002/jnr.21629

Shrikant Baslingappa Swami, Nayan Singh J. Thakor, Meghatai M. Patil, Parag M. Haldankar "Jamun (Syzygium cumini (L.)): A Review of Its Food and Medicinal Uses"-Food and Nutrition Sciences, 2012, 3, 1100-1117; http://dx.doi.org/ 10.4236/fns.2012.38146

Suryakanta Pany, Abhishek Pal, Pratap Kumar Sahu "Neuroprotective Effect of Quercetin In Neurotoxicity Induced Rats: Role of Neuroinflammation in Neurodegeneration"- Asian J Pharm Clin Res, Vol 7, Issue 4, 2014, 152-156

Talavera S, Felgines C, Texier O, Besson C, Gil-Izquierdo A, Lamaison JL, Remesy C. Anthocyanin metabolism in rats and their distribution to digestive area, kidney, and brain. J Agric Food Chem. 2005; 53:3902–8. [PubMed: 15884815]

Tan Y, Yu R, Pezzuto JM. (2003). Betulinic acid-induced programmed cell death in human melanoma cells involves mitogen-activated protein kinase activation. Clinical Cancer Research 9, 2866-2875.

Thi A Tran, Melissa K McCoy, Michael B Sporn and Malú G Tansey "The synthetic triterpenoid CDDO-methyl ester modulates microglial activities, inhibits TNF production and provides dopaminergic neuroprotection"- Journal of Neuroinflammation 2008, 5:1;doi:10.1186/1742-2094-5-14; http://www.jneuroinflammation.com/ content/ 5/1/14

Van Kampen JM, Baranowski DB, Shaw CA, Kay DG "Panax ginseng is neuroprotective in a novel progressive model of Parkinson's disease"- Exp Gerontol. 2014 Feb; 50:95-105. doi: 10.1016/ j. exger.2013.11.012.

Wang J, Tang C, Ferruzzi MG, Gong B, Song BJ, Janle EM, Chen TY, Cooper B, Varghese M, Cheng A, Freire D, Bilski A, Roman J, Nguyen T, Ho L, Talcott ST, Simon JE, Wu Q, Pasinetti GM. Role of standardized grape polyphenol preparation as a novel treatment to improve synaptic plasticity through attenuation of features of metabolic syndrome in a mouse model. Mol Nutr Food Res. 2013

Wang, C., Shi, Y., Tang, M. et al. Mol Neurobiol (2016);doi:10.1007/s12035-016-9806-5

Yi Chang, Chia-Ying Chang, Su-Jane Wang, and Shu-Kuei Huang "Myricetin Inhibits the Release of Glutamate in Rat Cerebrocortical Nerve Terminals"- Journal of Medicinal Food J Med Food 18 (5) 2015, 516–523; DOI: 10.1089/ jmf. 2014. 3219

Youn K, Jun M "In vitro BACE1 inhibitory activity of geraniin and corilagin from Geranium thunbergii"- Planta Med. 2013 Aug;79(12):1038-42. doi: 10.1055/s-0032-1328769

Yun Wang, Te Liu, Weidong Pan, Huiying Chi, Jiulin Chen, Zhihua Yu, Chuan Chen "Small molecule compounds alleviate anisomycin-induced oxidative stress injury in SH-SY5Y cells via downregulation of p66shc and Aβ1-42 expression" - Experimental and Therapeutic Medicine 11: 593-600, 2016; DOI: 10.3892/etm.2015.2921

Zhenhua Xu, Hongkwan Cho, Matthew Hartsock, Katherine L. Mitchell, Junsong Gong, Lijuan Wu, Yanhong Wei, Shuang Wang, Rajesh K. Thimmulappa, Michael B. Sporn, Shyam Biswal, Derek S. Welsbie, and Elia J. Duh "Neuroprotective role of Nrf2 for retinal ganglion cells in ischemia-reperfusion"- J Neurochem. 2015 April ; 133(2): 233–241. doi:10.1111/jnc.13064