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REVIEW

Polyphenol Ellagic Acid-Targeting To Brain: A Hidden Treasure

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ABSTRACT

Alzheimer's disease is a severe neurodegenerative disorder that gradually results in loss of memory and impairment of cognitive functions in the elderly.Thedeposition of amyloid plaques is the primary event that leads to an oxidative and inflammatory reactions, neurofibrillary tangle formation, and ultimately neuronal death. The most prominent losses occur with cholinergic neurons that plays an important role in the formation of memory and cognitive functions. Insulin receptor numbers also altered, thusglucosemetabolism is defected in AD. Polyphenol ellagic acid (EA) possesses anti-oxidant, anti-inflammatory, anti-carcinogenic, anti-diabetic and cardioprotection activities.Activities of EA that are linked with protection of neuronal abnormalities like anti-depressant, anti-anxiety, anti-nociception. Ellagic acid inhibits β-secretase enzymatic activities, thus prevents the main pathologic hallmark of AD. There are varieties of herbal extracts and phytochemicals formulations extensively used to provide symptomatic relief to AD patients. Together these results our hypothesis that EA may prevent the neuronal dysfunctions as well as further work is also required to examine the pharmacological properties of EA in the protection of specially neurodegenerative disorder like AD. Here, we discuss how we can use the knowledge to improve treatment strategies of EA in AD and to explore the various signaling pathways involved in the progression of neuronal death.

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INTRODUCTION

Alzheimer's disease is a severe neurodegenerativedisease that gradually results in loss of memory andimpairment of cognitive functions in the elderly[1]. According to Alzheimer's Association, Alzheimer's disease (AD) is affecting an estimated 5.2 million Americans in 2014, including 5.0 million over age 65[2]. AD include extracellular amyloid deposition in senile plaques and intra-neuronal neurofibrillary tangles of hyperphosphorylated microtubule-associated tau protein[3-6]. The extracellular deposition of amyloid plaques is a major event that progress an inflammatory reaction, intracellular neurofibrillary tangle formation, and ultimately cause neuronal death[7,8]. The neuronal loss produces insufficiencies in several neurotransmitter systems[8]. However, the most prominent losses occur with cholinergic neurons in the basal forebrain, which project into the hippocampus and neocortex, the brain structures that play an important role in memory and cognitive function[9,10]. The loss of cholinergic neurons results in up to 90% reduction in the activity of an enzyme, choline acetyltranferase (ChAT), needed for the synthesis of the neurotransmitter acetylcholine[11].

Treatment strategies have focused on boosting acetylcholine, by the development of cholinesterase inhibitors. Acetylcholinesterase (AChE) inhibitors work by reversibly bindingto the choline binding subsite of acetylcholinesterase, thus preventing degradation of acetylcholine[12]. Themechanisms of neuronal cell loss in AD have not yet beenfully elucidated, but increased oxidative stressandinflammationare considered important mediators of neuronal damage in AD[13]. The brains of individuals with AD had increasedlevels of lipid peroxidation products such as 4-hydroxynonenalor 2-propenal, and enhanced lipid peroxidationwas also detected in the cerebrospinal fluid and plasma ofindividuals with AD[14,15]. In addition, oxidativedamage to membrane proteins, cellular mitochondrial and nuclear DNA isalso an important event in AD pathology[1].

The first neurotransmitter defect discovered in AD involved acetylcholine[16] (Francis *et al*, 1999). As cholinergic function isrequiredfor short-term memory, the cholinergic deficitin AD was also believed to be responsiblefor much of the short-term memory deficit[16,17]. Clinical drug trials in patients with AD have focused on drugs that augmentlevels of acetylcholine in the brain to compensatefor the loss ofcholinergic function[18]. These drugs have included acetylcholine precursors, muscarinic agonists, nicotinic agonists, andacetylcholinesterase inhibitors[9]. Herbal drugs are alsopre-clinically as well as clinically tested and shown to be very effective as Galantamine[19,20], Ginkgo biloba[21,22], Bacopa monnieri (brahmi)[23,24], Celastrus paniculatus[25,26], Curcumin[27-29], coffee[30-32] and Lavender essential oil[33].

Many naturally occurring compounds have been proposed as potential therapies to slow or prevent the progression of AD, mostly by acting as antioxidants[34], but also with some direct anti-amyloid actions[35]. Recent studies have suggested the positive effects of dietary antioxidants as an aid in potentially reducing somatic cell and neuronal damage by free radicals[36]. The beneficial health effects of plant-derived products have been largely attributed to polyphenolic compounds, as well as vitamins, minerals and dietary fibers[37]. Polyphenols occur as products of the plant secondary metabolism in response to biotic and abiotic stress[38,39]. Polyphenols are the main compounds of green tea and there are a class of polyphenolic flavonoids known as catechins (the most abundant component) which comprise of (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG) and (−)-epicatechin (EC) respectively. Green tea polyphenols may play a protective effect on cultured rat primary prefrontal cortical neurons against Aβ-induced cytotoxicity and AKT is involved in the green tea polyphenols-induced protective effects[40]. Epigallocatechin-3-gallate protects neuronal cells by disrupting amyloid-β fibril formation; bioactive polyphenols which disrupt fibril aggregation may confer additional neuroprotection when compared against antioxidant activity alone[35]. Grape seed polyphenol extract (GSPE) has a significant potential for therapeutic development by neutralizing phosphoepitopes and disrupting fibrillary conformation leading to disintegration of paired helical filaments (PHFs)[41]. LMN diet rich in polyphenols, dry fruits and cocoa, was able to decrease behavioral deterioration caused by aging and Tg2576 genotype and to delay the Aβ plaque formation. These results corroborate the increasing importance of polyphenols as human dietary supplements in amelioration of the cognitive impairment during aging and neurological disorders such as AD[42]. At present, there is mounting evidence that alterations in dietary intake could be beneficial for preventing and treating oxidative disorders and neurodegenerative illnesses such as AD, which could offer an alternative or supplementary therapy.

Natural polyphenols have pleiotropic activity including antioxidant properties. Particularly, natural polyphenols significantly attenuated cognitive impairments and amyloid-beta burden. Natural polyphenolic compounds exhibit their antioxidant effect by quenching free radical species and/or promoting endogenous antioxidant capacity. Thus, the antioxidant properties certainly contribute to their neuroprotective effects[43].

Ellagic acid (EA), is a powerful non-flavonoid polyphenol compound with various pharmacological actions and said to be a degraded product of certain plant tannins[44] (Table 1). Ester bonds hydrolysis of ellagitannins with acids or bases produce hexa-hydroxydiphenic acid (HHDP), which rearranges spontaneously to produce ellagic acid[45]. EA is present in fruit, food and beverages but berries are potential dietary source of quercetin or ellagic acid. High concentration of ellagic acid is found in cloudberry (60mg/100g), blackberry (42.4mg/100g), strawberry (19.8/100g) red raspberry (17.9mg/100g), cranberry (12mg/100g), boysenberry (30mg/kg), marion blackberry (32mg/kg), evergreen blackberry (21mg/kg)[45-47], while, blueberry (0.9mg/100g), walnut (590μg/g) and pecans (330μg/g) have low concentration of ellagic acid[48,49]. It is also found in seeds of red raspberry (8.7mg/kg) and black raspberry (6.7 mg/kg)[45]. Juice of red muscadine grapes and fresh arils of pomegranate also contains ellagic acid in concentration of 10.2 mg/100g and 15.3 mg/L respectively[48,50]. Various extracts are also rich in ellagic acid as hot water extract of guava contains 36.68 mg/g and muscadine grape cultivas extract contains 49.7 mg/kg while, ethanolic extract of longan seeds have 1.6mg/g of ellagic acid in concentration[45,51]. Ellagic acid is present either in free form or as conjugate of sulphate ester, glucuronide, and glutathione[45,52]. Ellagic acid being a weak acid gets ionized at physiological pH, form poorly soluble complexes with calcium and magnesium ions in the intestine and bind to intestinal epithelium, thereby it is poorly absorbed[52,53]. Cerda et al., (2005) showed the presence of metabolites of ellagic acid in bile and urine suggesting that its absorption take place in stomach[55]. Bioavailability of this phenolic components from plants is low due to its occurrence in glycosidic form[56] but bioavailability studies conducted by Aiyer *et al* (2008) revealed that ellagic acid availability is more as compare to chlorogenic acid which, may be due to its absorption in upper part of the gut, in the stomach and small intestine[57]. After being absorbed, EA is metabolized by phase II enzymes, such as glucuronosyl transferases and sulfotransferases[53]. Ellagic acid is released from ellagitannins in jejunum, and is metabolize to yield urolithin D. Chemically urolithin D is tetrahydroxydibenzopyran-6-one, more lipophilic and well absorbed than EA. Urolithin D is further metabolize to urolithin C (trihydroxydibenzopyran-6-one), urolithin A (dihydroxydibenzopyran-6-one) and urolithin B (monohydroxydibenzopyran-6-one) respectively. The removal of hydroxyl groups from metabolites increases the lipophilicity and thereby their absorption as compare to ellagic acid[52]. Thus the presence of urolithin plays an important role in absorption. Further, the presence of urolithin A, C, and D metabolites in bile show an active entro-hepatic circulation, this cause low clearance of metabolites. Only urolithin A shows its presence in feces[52]. The half life of ellagic acid is 8.4±1.8 hrs with 50% plasma protein binding[58]. Solubility studies conducted by Bala et al., (2005) demonstrated that Ellagic acid was soluble in various pharmaceutically acceptable solvents including triethanolamine, polyethylene glycol 400 and N-methyl pyrrollidone (NMP). Ellagic acid showed poor solublity in water (9.7μg/mL) and due to its acidic nature it is soluble in phosphate buffer while, highly soluble in methanol[59]. Ellagic acid is

Table 1 Ellagic Acid mediated various pharmacological activities.

Activity	Model	Dose of Ellagic acid	Mechanisms	Reference
Anti-inflammatory	0.1N HCl, induced acute lung injury in mice	10mg/kg (p.o.)	Inhibit COX-2, Reduce IL-6 and increase IL-10 levels	Favarin et al, 2013
	Trinitrobenzene, Sulfonic acid induced chronic colonic inflammation in rats	10 mg/kg (diet)	Decrease TNF-α, Inhibit COX-2 and iNOS, Block the activation of NF-κB pathway	Rosillo et al, 2012
	3% Carrageenan Paw edema in male Sprague Dawley rats	75 mg/kg (i.p.)	COX-2 inhibition	Corbett et al, 2010
	1,2-Dimethylhydrazine-induced rat colon carcinogenesis	60 mg/kg (p.o.)	Reduce the expressions of NF-κB, COX-2, iNOS, TNF-α and IL-6	Umesalma & Sudhandiran, 2010
	UV irradiation skin tissue of hairless mouse	Topical treatment 10 μmol/L	Inhibition of ICAM-1 expression of keratinocytes, Inhibition of production of IL-1β and IL-6, Retard the cutaneous gathering of macrophages.	Bae et al, 2009
Anti-oxidant activity	Isoniazid–Rifampicin induced liver damaged in rats	25 and 50 mg /kg / day (p.o.)	Reduction in elevated levels of SGPT, SGOT, SALP and bilurubin	Ambrose et al, 2013
	Carbon tetrachloride induced liver toxicity in mice	50 mg/kg/day and 100 mg/kg/day (p.o.)	Reduction in MDA levels, Prevent reduction of GSH, GSH-Px and CAT activities, Reduction in SGPT, SGOT, SALP and bilurubin	Girish & pradhan, 2012
	Oxidative Stress induced by aluminum in Spraque-dawley rats	12 mg/kg (p.o.)	Decrease NADP-H levels, Increase GSH, CAT and GSH-Px activities, Increase liver Vitamin E level	ÖZKAY et al.,2010
	Cyclosporine A-induced testicular and spermatozoal damages in rats	10 mg/kg/day (p.o.)	Reduction in MDA levels, Prevent reduction of GSH levels, GSH-Px and CAT activities	Türk et al, 2009
	Cisplatin-Induced oxidative stress in liver and heart tissue of rats	10 mg/kg/day (i.p.)	Decrease MDA levels, Prevent reduction of GSH, GSH-Px and CAT activities	Yüce et al, 2007
Anti-carcinogenic activity	Human bladder cancer cell lines T24.	33.7 μM	Increase mRNA and protein expression of Phospho-p38 MAPK, Decrease mRNA and protein expression of MEKK1 and Phospho-c-Jun, Caspase-3 activation, Increase PPAR-γ protein expression Decrease in the intracellular ROS and MDA levels Increase SOD activity	Qiu et al, 2013
	Pancreatic cancer cells xenografted in Balb C nude, Mice	40 mg/kg p.o.	Inhibits PI3K/Akt pathways, Caspase-3 activation, Inhibit angiogenesis	Zhao et al, 2013
	1,2-dimethyl hydrazine (DMH) mediated experimental colon carcinogenesis in wistar rats	60 mg/kg p.o.	Inactivate PI3K/Akt kinases, Increase the caspase-3 expression	Umesalma & Sudhandiran,2011
	DEN-induced hepatocellular carcinogenesis in wistar rats	30 mg/kg p.o.	Caspase-3 activation, Decrease lipid peroxidation, AST, ALT, ALP, LDH γ-GT and 5`NT levels Increase antioxidants level	Srigopalram et al, 2011
	Human Prostate carcinoma PC3 cells	10-100 mol/L	Induction of apoptosis	Malik et al, 2011
	Human Umbilical Vein Endothelial Cells (HUVEC)	1–100 μmol/L	Decrease ATP levels, Decrease active MMP-2 and MMP-9, Decrease VEGF expression	Losso et al, 2004
Cardio protection	Streptozotocin-induced diabetic rats	2% EA, ad libitum	Inhibit smooth muscle cell proliferation	Rani et al, 2013
	Isoproterenol induce myocardial infarction in rats	15 mg/kg	Anti lipid peroxidation property anti hyperlipidaemic activity through 3-hydroxy-3 methyl glutaryl CoA reductase inhibition	Kannan and Quine, 2012
Anti-diabeticactivity	STZ induced diabetes in rats	2% EA in diet	Inhibition of aldose reductase (ALR2)	Akileshwaria et al, 2013
	Streptozotocin induced Diabetes Mellitus in albino wistar rats	50 mg/kg and 100 mg/kg	Antihyperglycemic effects	Malini et al, 2011
	alpha-glucosidase and pancreatic lipase activity in-vitro	10 mg/mL	Inhibit alpha-glucosidase and pancreatic lipase	You et al, 2011
Coagulantactivity	In-vitro in circular dichroism	10^{-5} M	Inhibit Hageman factor	McMiliun et al, 1974
	Nor epinephrine induced Incidence of glomerular capillary Thrombi in female albino rabbits, female monkeys	0.24 mg./mL; 105 mL/hr	Inhibit Hageman factor	McKay et al, 1968
	Thrombin induced excessive bleeding from cut tail of rats	1mL of $2X\ 10^{-4}$ M /100g	Inhibit Hageman factor	Cliffton et al, 1965

soluble at physiological pH and it remain insoluble at pH less than 7, while at pH more than 7, ellagic acid chelates with divalent cations such as Zn^{2+}, Ca^{2+}, Fe^{2+}, Cd^{2+}, Cu^{2+} which, contributes in its anti-carcinogenic property[60].

Ellagic acid plays an essential role in explaining the sensory properties of fruits, food, beverages which exhibit this phytoconstituent. The major contribution of berries as antioxidant is due to ellagic acid[46]; antioxidant effects of pomegranate juice was due to ellagic acid[50] likewise, Gauva leaf extract exhibit antioxidant potential due to ellagic acid[51]. Favarin *et al*, (2013)[61] and Corbett *et al*, (2010)[62] evaluateanti-inflammatory potential of ellagic acid in animal models. Several *in vivo* and *in vitro* studies mention ellagic acid as anti-proliferative[60,63,64]. Further studies designed to found ellagic acid's cardiopreotective role prove that it is a novel therapeutic strategy to manage myocardial infarction and atherosclerosis[65,66] (Figure 1). The present review mainly summarize the signaling mechanisms involved in the pathogenesis of Alzheimer's and find out the better way to overcome that destructive neuronal changes in AD brain via ellagic acid treatment.

ELLAGIC ACID AND AMYLOID BETA (AB) PEPTIDE

Neuropathological hallmarks of AD are accumulation of extracellular ''senile plaques'' containing amyloid β-peptide (Aβ) fibrils and intracellular ''neurofibrillary tangles'' containing hyper-phosphorylated tau protein[67]. Neurologicalevents that contribute to AD progression include amyloid-beta (Aβ) aggregation, acetylcholine depletion, and oxidative stress[68].

Amyloid beta-protein (Aβ) is the major component of senile plaques and cerebrovascular amyloid deposits in individuals with Alzheimer's disease[1]. Aβ fibril formation is a multi-step process that is preceded by oligomerization and aggregation of monomeric Aβ, and it involves conformational change of the peptide from alpha-helical to beta-pleated sheet structure[69]. Recent evidences suggest that solubleoligomers of Aβ in the brain are neurotoxic and a major risk factor for the onset and progression of cognitive deterioration in AD[70]. Aβ is known to increase free radical production in neuronal cells[1].

Possible benefit of EAtreatment was demonstrated in Sprague-Dawley rats, infused with Aβ followed by control solution had significantly impaired spatial working and reference memory, where the EA treatments restored to normal condition. This study not only demonstrated detrimental effects of a single Aβ mixed peptide infusion, but also some beneficial effects of multiple EA treatments in reducing these Aβ-induced deficits. Further, Aβ-treatment decreased working and reference memory capabilities while EA treatment restored those capabilities. Also consistent with the hypotheses, the measure of ROS activity (MDA content via the TBARS assay) in the hippocampus was significantly increased in animals treated with Aβ and only control aCSF (Artificial cerebrospinal fluid) solution whenAβ-treated animals were infused with Ellagic Acid, they showed MDA levels that were significantly lower than the Aβ+aCSF group and comparable to the aCSF animals[68].

Pomegranate juice (PJ) consisted of polyphenols (phenolic acids and flavonoids). Phenolic acids included 115 ppm ellagic acid and 5ppm gallic acid. Flavonoids included 1880 ppm hydrolysable tannins (e.g., gallotannins, ellagitannins, punicalagin) and 369 ppm anthocyanins and their glycosides (e.g., cyanidin, delphinidin, pelargonidin). Tg2576/APPsw mice, commonly used as a model of Aβ deposition and associated AD-like pathology, were given pomegranate juice in their drinking water. PJ improved behavioral
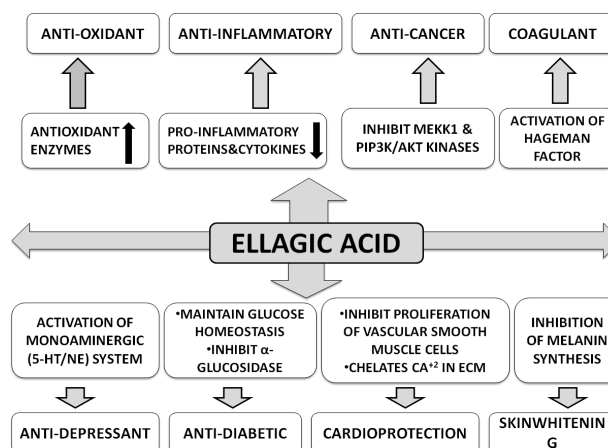

Figure 1 Pharmacological actions of EA.

performance of APPsw mice in the water maze. PJ decreased Aβ and amyloid levels in the hippocampus. When their learning behavior was assessed PJ-treated mice exhibited improvements on cued and spatial learning tasks as well as faster overall swim speeds. Additionally, plaque load (both Aβ and fibrillar Aβ/amyloid) and soluble Aβ42 were significantly reduced in the hippocampus[71].

In-vitro activity of human recombinant β-secretase (BACE1) was studied using a fluorogenic substrate based on the cleavage site for the enzyme in the Swedish mutation of amyloid precursor protein. Amyloid plaques are formed by overproduction and subsequent aggregation of the 40-42 amino acid peptide,β-amyloid (Aβ). β-amyloid is produced by cleavage of the membrane-anchored amyloid precursor protein (APP) by the β-site APP-cleaving enzyme (BACE1), also known as β-secretase, which is subsequently cleaved by γ-secretase to form either Aβ 40 or Aβ 42. The longer form of Aβ is implicated as causative in AD through association with early onset AD. *In vitro* studies have shown that Aβ42 aggregates into fibrils faster than Aβ40 and it is considered to be more toxic than Aβ40. Non-competitive inhibitors of BACE1 were identified from natural products, including polyphenolics: ellagic acid and punicalagin from pomegranate husk. Pomegranate husk inhibited BACE1 with an EC50 of 1.19 $\mu g.mL^{-1}$,which could be partly explained by the inhibitory activity of ellagic acid with an EC_{50} value of 0.85μg/mL (2.8μM). Ellagic acid is heterocyclic polyphenolics with extensive peripheral substitution by hydroxyl groups, which may account for inhibitory activity. Thus, Ellagic acid is a strong inhibitor[72].

EA prevented Aβ neurotoxicity by promoting Aβ aggregation into fibrils with significant oligomer loss. Thus EA could significantly reduce Aβ42-induced neurotoxicity toward SH-SY5Y cells[67].

Walnuts (Juglans regia L.) are an excellent source of α-linolenic acid (plant-based omega-3 fatty acid) and have a high content of antioxidants such as flavonoids, phenolic acid (ellagic acid), melatonin, gamma tocopherol and selenium. Walnutextract can counteract Aβ-induced oxidative stress and associated cell death[1]. EA inhibit β-secretase (BACE1) in vitro, thus inhibiting Aβ-fibrillation[73]. Therefore, ellagic acid can be a potential therapeutic treatment that inhibits amyloid beta-protein (Aβ), which is the major component of senile plaques and amyloid deposits in AD patients.

ELLAGIC ACID AND NEURO-OXIDATION

During respiration, mitochondria produce semi-reduced oxygen species, superoxide and hydrogen peroxide that cause the oxidative

stress[74]. Brain is susceptible to oxidative damage because of various reasons such as ease of peroxidation of brain membrane as it is enrich in peroxidizable fatty acids, high consumption of oxygen and glucose, and areas enriched in ferrous ascorbate/pro-oxidant in comparison to other body parts and anti oxidant capacity is lower than oxidant possibilities such as catalase activity, which is 10-20% of liver and heart[75]. H_2O_2 is generated by almost all sources of oxidative stress. DNA is damaged by H_2O_2 via fenton reaction in presence of oxygen and transition metal ions[76,77]. During neurodegenerative diseases, the various oxidative reactions involved that leads to neuronal cell death[78]. Some resources such as vitamins, lipoic acid, antioxidant enzymes and redox sensitive protein transcriptional factors,help to compensate oxidative stress in neuronal cells[79-83].

Polyphenols, the nutritional antioxidants can modulate this defence system[78]. Ellagic acid prevents oxidationin liver,heart, kidney testicular and spermatozoal damages associated with oxidation[84-89].

Terminalia Chebula contain polyphenols such as quercetin, gallic acid and ellagic acids[90]. *T. Chebula* extract has protective effectsagainst in-vitro experiment where oxygen-glucose deprivation followed by reoxygenation (OGD-R) ischemia and hydrogen peroxide (H_2O_2) induced cell death on PC12 cells. T. chebula extract showed the diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity and reduced H_2O_2-induced MDA production where DPPH radical scavenging activity of *T. chebula* is mostly related to the hydroxyl group in ellagic acid[91]. Moreover, Ellagitannins produces hexa-hydroxydiphenic acid (HHDP) on ester bonds hydrolysis with acids or bases, which rearranges spontaneously to produce Ellagic acid[45]. Ellagitannins showed remarkable neuroprotective activity via inhibition on the H_2O_2-induced oxidative damage in NG108-15 hybridoma cell line[92].

Diabetic neuropathy and encephalopathy are common life threatening complications of diabetes mellitus[93]. Ellagic acid exhibits neuro-protective effects against oxidative damage in streptozotocin-induced diabetic rats. Ellagic acid has the ability to reduce the oxidative damage to the diabetic rat sciatic and brain tissues. Malonaldehyde (MDA), total oxidant status (TOS), oxidative stress index (OSI), and nitric oxide (NO) levels in brain and sciatic tissues were found to be significantly reduced in the ellagic acid-treated diabetic group compared to the untreated diabetic group in these tissues[94]. Ellagic acid possesses non-enzymatic antioxidant activity such as scavenging free radicals, and enzymatic antioxidant activitysuch as increasing protein level of antioxidant enzymesSuperoxide Dismutase (SOD), Catalase (CAT),Glutathione and Glutathione Peroxidase(GSH-PX)[86].

The rat pheochromocytoma line PC12 provides a useful model system for investigating neuronal cell injury.Tert-Butyl hydroperoxide(t-BHP) may act through formation of peroxynitrate (ONOO-) and hydrogen peroxide (H_2O_2) through hydroxyl radicals, their effects in PC12 cells are cytotoxicity via lipid peroxidation and free radical generation[95]. EA has strong free radical scavenging and protective activities towards oxidative damage through t-BHP and $FeSO_4$ in PC12 cell culture of neuronal origin. $FeSO_4$, suspected to produce superoxide radicals, induced comparable changes in viability and GSH content and enhanced lipid peroxidation as measured by MDA production and ROS production. ROS formation and enhanced lipid peroxidation are not the direct cause of cell death in PC12 cells, while loss of GSH much better correlates with cytotoxicity, where EA significantly restored the antioxidant defense modulation. EA can also chelate metal ions and prevent iron- and copper- catalysed formation of ROS[96].

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a persistent environmental contaminant that has been found to produce adverse effects in brain. TCDD caused significant increases in superoxide anion production in cerebral cortex and hippocampus[97]. EA provided protection against TCDD-induced superoxide anion production in brain tissues. Ellagic acidresults in significant reduction in the production of superoxide anion in cerebral cortex and hippocampus when administered simultaneously with TCDD, as compared with corresponding regions of the TCDD-treated animals. EA administered in combination with TCDD, the compounds resulted in significant reductions in TBARS production in cerebral cortex and hippocampus, as compared with the corresponding regions in the TCDD-treated group. EA result in significant reductions in TCDD-induced DNA single-strand breaks in cerebral cortex and hippocampus[98]. On the basis of above review, Ellagic acid can be a capable therapeutic treatment in AD patients, where various oxidative reactions involved that leads to neuronal cell death.

ELLAGIC ACID AND NEUROINFLAMMATION

Alzheimer disease (AD) brain is characterized by extracellular plaques of amyloid β (Aβ) peptide with reactive microglia[99]. Cognitive impairment in neurodegenerative diseases such as Alzheimer's disease may be partly due to long-term exposure and increased susceptibility to inflammatory insults[100]. The association between inflammation and AD manifests itself through (1) the presence of activated microglia surrounding senile plaques and (2) higher levels of inflammatory mediators in the brains of AD patients versus age-matched controls[5,101,102].

Oxidative damage due to the ROS/RNS play the vital role to initiate a wide range of intracellular stress signaling processes that culminate in excessive cytokine such as inducible COX-2 and iNOS and adhesion molecule as intracellular adhesion molecule (ICAM)-1 and E- andP-selectins upregulation[91,103]. Neuroinflammatory processes have been shown to have a fundamental role in the pathogenesis of neurodegenerative disorders like Alzheimer's disease (AD)[104].

Ellagicacid inhibits upregulation of COX-2 and reduces IL-6 and increase IL-10 levels in 0.1N HCl induced acute lung injury in mice modelvia its anti-inflammatory mechanism[61]. Ellagic acid decrease TNF-α, inhibit COX-2 & iNOS and block the activation of NF-κB pathway in trinitrobenzene sulfonic acid induced chronic colonic inflammation in rats[105]. Ellagic acid also reduce the expressions of NF-κB, COX-2, iNOS, TNF-α and IL-6 in 1,2-Dimethylhydrazine-induced rat colon carcinogenesis[106]. Moreover ellagic acid inhibits TNF-α induced endothelial activation and expression of ICAM-1 and VCAM-1 adhesion molecules in Human aorta endothelial cells (HAEC)[107].

The activation of the primary microglia is one of the major reasons of cellular inflammation in ischemic condition. Terminalia chebula extract reduced LPS induced cell death and inhibited the production of NO by BV2 cellsin Lipopolysaccharide activated microglia cells (BV2 cell) and reduce cellular inflammation[91].

Pomegranates extract feeding improved behavioral performance in APP/PS1 mice, which correlated with decreased microgliosis, nuclear factor of activated T-cell c2 (NFATc2) activity, and brain TNF-α concentration. Thus pomegranate extract suppressed nuclear factor of activated T-cell c2 (NFATc2) expression, attenuated brain cytokine concentrations and decreased Aβ plaque load in the amyloid precursor protein/presenilin 1 (APP/PS1) mice and decreased microgliosis in the APP/PS1 mice.Pomegranate extract

component, ellagic acid attenuated microglial proinflammatory cytokine release in-vitro as ability to inhibit NFAT activity and cytokine secretion in-vitrocell culture of C57BL/6 mouse brains microglia. Possible mechanism for these may as ellagic acid, is absorbed and able to enter the brain to inhibit microglial activation via attenuation of, particularly, NFAT activity or ellagic acid can be directly taken up into cells or may be these large polyphenol molecules may also act extra-cellularly to exert their anti-inflammatory action[99].

Blueberry poly-phenols, such as ellagic acid reduced activation of the inflammatory marker (OX-6), expression of the inflammatory cytokines IL-1β and TNF-α, the transcription factor NF-κB and increased expression in the neuroprotective trophic factor IGF-1 in centrally administered kainic acid inflammatory rat model where as ellagic acid significantly reduced the impairment in their spatial learning and memory abilities[48,100]. Shukitt-Hale *et al*, (2008) suggested that possible mechanism of action of the blueberry polyphenols like ellagic acid could be reduction of the deleterious effects of an inflammatory stimulus by altering the expression of genes associated with inflammation, protecting the brain and/or reducing its susceptibility to insults[100].

ELLAGIC ACID AND ACETYLCHOLINESTERASE INHIBITION

Cholinergic dysfunction in neurodegenerative diseases can be the result of reduction in Ach synthesis due to reduced choline acetyltransferase (ChAT) or choline uptake, cholinergic neuronal and axonal abnormalities, and degeneration of cholinergic neurons[108,109]. Acetyl cholinesterase inhibitors have been extensively used for the symptomatic treatment of Alzheimer's disease[110-112].

Walnut extract and EA, one of its constituents, have been shown to inhibit the action of two sites on AChE that are involved in Aβ aggregation and acetylcholine catabolism[68]. In vitro studies found that IC50 value of AchE inhibitory activity of ellagic acid was 13.79 μg/mL(45.63μM)[113]. EC$_{25}$ value of Ellagic acid, from Cochlospermum angolensis Welw extracts was found to be 2362.6 mg/ml (hydromethanolic extract) and 2235.5mg/mL (boiling water extract), for AChE inhibitory assays[114]. Moreover by using brain tissue showed a marked decrease in brain AChE activity in the presence of EA[68,114]. These results show the therapeutic efficacy of EA in AD patients.

ELLAGIC ACID AND INSULIN

AD causes alteration in insulin receptor numbers[115]. Recent studies suggested that glucose metabolism is defected during AD[116-118]. GLUT4 translocation from an intracellular pool to the cell surface is the primary factor responsible for insulin induced glucose uptake in adipocytes and skeletal muscles. This process can be studied in vitro by employing a chimeric GLUT4 construct with an epitope at an extracellular domain so that the extent of the epitope externalization directly matches with the amount of GLUT4 present on the plasma membrane[119]. Due to presence of ellagic acid (EA) as an active component present in the methanol extract prepared from the leaves of *Terminalia Arjuna* stimulate glucose transport in 3T3-L1 adipocytes and C2C12 myotubes.

AMPK activation is known to stimulate glucose transport in adipocytes and muscles in an insulin independent manner. EA also stimulated GLUT4 translocation occurs in an AMPK dependent manner and involves extracellular signal-regulated kinase 1/2

(ERK1/2) and atypical protein kinase C ζ/λ (αPKC ζ/λ) activation[120]. Protein phosphorylation studies with EA suggest that its stimulatory effect on GLUT4 translocation is achieved through stimulating AMPK ERK- αPKC pathway. Glucose transport stimulated by EA was inhibited by treatment with AMPK inhibitor Compound C and MEK inhibitor PD98059. Application of compound C also inhibits ERK1/2 phosphorylation to a similar extent, suggesting that AMPK lies upstream to ERK in the EA signaling pathway[121].

Resistin, a peptidesignaling molecule, is secreted by adipocytes and induced during adipogenesis (the differentiation of preadipocytes to adipocytes). Resistin neutralization enhance insulin-stimulated glucose uptake in adipocytes. Resistin is thus a hormone that potentially links obesity to diabetes[122]. Therefore, reducing circulating resistin levels would be very beneficial for ameliorating obesity-induced insulin resistance. The consumption of pomegranate juice and ellagic acid, a main component of pomegranate, reduced serum resistin levels in ovariectomized mice, the animal model having elevated serum resistin levels[123]. Type 2 diabetes is potentially preventable by suppressing elevated serum resistin levels[124,125].

In a study, pomegranate fruit extract (PFE) is fed to ovariectomized mice as an animal model with high resistin levels to investigate the effects of pomegranate on resistin in vivo. Moreover, investigation of mechanism of the action of PFE usingdifferentiated murine 3T3-L1 adipocytes revealed PFE, particularly EA, significantly suppress resistin secretion by 3T3-L1 adipocytes without altering the mRNA expression of resistin. Therefore, EA is a unique component derived from food material that can regulate resistin by a novel mechanism[123].

Ellagic acid also present in aqueous Jamun seed (*Syzigium Cumini*) extract (JSEt) as well as in alcoholic JSEt[126]. Oral administration of an aqueous Jamun seed extract (JSEt) caused a significant decrease in lipids, thiobarbituric acid reactive substances (TBARS) and an increase in catalase and superoxide dismutase in the brain of alloxan induced diabetic rats[127]. Furthermore, EA can be a promisingtherapeutic diet in AD patients where insulin resistance occurs, due to imbalance of glucose transportation for other insulin dependent activation.

ELLAGIC ACID AND DEPRESSION

Depression is a common, debilitating, life-threatening illness with a high incidence. Numerous antidepressant compounds presumably act via different mechanisms involving the serotonergic, noradrenergic and dopaminergic systems[128].

The serotonergic (5-HT4) receptor may play a role in memory and learning and 5-HT4 receptor activation has been suggested to modulate acetylcholine release and to reduce amyloid-β (Aβ) accumulation[129]. GABA-mediated inhibitory transmission can be strongly modulated by 5-HT: such modulation, in parallel with 5-HT-glutamate interactions, has been observed in structures involved in learning and memory, sensory processing, nociception and motor control[130].

In vitro antidepressant potential of ellagic acid was found in MAO-A inhibition assay[114]. Further, ellagic acid produce anti-immobility effect in anti-depressant models mediated through monoaminergic system (serotonergic and noradrenergic systems)[131]. Pretreatment with prazosin (an alpha-adrenoceptor antagonist) and p-CPA (serotonin synthesis inhibitor) reverse the anti depressive effect of ellagic acid where ellagic acid interacts with α-adrenoceptors and serotonergic receptors to produce anti depressive effect[128].

Emblica officinalis (EO) fruits mainly contain tannins and vitamin C like substances in abundance and their chemical constituents include gallic acid, ellagic acid, emblicanin A, emblicanin B, punigluconin and flavanoids[132]. The aqueous extract of the EO fruits contain 30.0% tannins and 10.0% Gallic acid[133].

The development of immobility when rodents were suspended by their tail during TST (tail suspension test) and placed in an inescapable cylinder of water during FST (forced swim test) reflects the cessation of their persistent escape-directed behavior. EO reliably decreases the duration of immobility in animals during these tests. This decrease in duration of immobility is considered to have a good predictive value of ellagic acid in the evaluation of potential antidepressant agents[133].

The ethanolic extract of stem barks of Lafoensia pacari (PEtExt), which contains Ellagic acid as major compoundalso possesses antidepressant-like effect[134,135].

Fruits of *T. Bellirica* contain about 17% tannin and sitoterol, gallic acid ellagic acid, ethyl gallate, galloyl glucose and chebulagic acid. The effect of aqueous and ethanolic extracts of Terminalia bellirica was tested on depression in mice using FST and TST. Both aqueous and ethanolic extract reversed reserpine induced extension of immobility period of mice in FST and TST and elicited a significant antidepressant like effect in mice by interaction with adrenergic, dopaminergic and serotonirgic systems[136].

In addition to cholinergic deficits, deficiencies in central GABAergic neural transmission may also play a critical role in some of the clinical manifestations of AD[137]. Some studies evident for the dysregulation of genes related to the glutamatergic and GABAergic transmitter systems in depression individuals. As the ratio of excitatory-inhibitory neurotransmitter levels disturb, cytotoxic damage to neurons and glia occurs. Significantly reduced numbers of neuroglia is reported in major depressive disorder[138]. GABA concentrations are lower in cerebrospinal fluid and plasma in unipolar depressed patients[139]. In a study ellagic acid also produces anti anxiety-like effect which was antagonized by a non-competitive GABAA receptor antagonist and a benzodiazepine site antagonist which shows modulation of GABAergic system by EA[140].

Receptorfor advanced glycation endproducts (RAGE), is a tentative cell membrane receptor for Aβ, binds to Aβ with high affinity[141]. GABA increases the formation of soluble RAGE and decreases the levels of full-length RAGE, therefore lowering Aβ uptakeby RAGE[142,143]. These findings suggest that GABA receptor modulation can be a potential treatment for AD. Moreover, ellagic acid can modulate deficiencies in central GABAergic neural transmission.

ELLAGIC ACID AND NOCICEPTION

Ellagicacid shows central and peripheral anti-nociceptive effect. Possible mechanisms of anti-nociception activity of ellagic acid are involvement of opioidergic system and L-arginine–NO– cGMP–ATP sensitive K+ channels pathwayin tail flick test and in writhing test Central nervous system may be the primary site for EA to exert its analgesic effect and also the activation of opioid receptors and/or an increment of endogenous opioids might be involved in the antinociceptive effect of EA[144]. Ellagic acid has also antinociceptive properties via cyclooxygenase (COX) inhibition. Ellagic acid with ketorolac significantly shows antinociceptive activity in inflammatory

pain induced by carrageenan[145]. Moreover, EA can be a nascent therapeutic herbal where excessive cytokine such as inducible COX-2 is up regulated as in neuroinflammation in AD patients.

FUTURE PROSPECTIVE OF ELLAGIC ACID IN AD BRAIN

The deposition of amyloid plaques is the primary event of AD that further starts the other neuronal dysfunctions like inflammatory reaction, neurofibrillary tangle formation, and ultimately neuronal death[7,8]. The neuronal loss produces insufficiencies in several neurotransmitter systems[8]. Amyloid beta-protein (Aβ) is the major component of senile plaques and cerebrovascular amyloid deposits in individuals with Alzheimer's disease[1]. During neurodegenerative diseases, the various oxidative reactions involved that leads to neuronal cell death[78]. The presence of activated microglia surrounding senile plaques and higher levels of inflammatory mediators are manifestations of AD[5,102]. Ellagic acid, is a polyphenol, inhibit the amyloid deposition and effective tool as an anti-oxidantand anti-inflammatory. However, the most prominent losses occur with cholinergic neurons in the basal forebrain, which play an important role in memory and cognitive function[9,10] (Table 2) (Figure 2). Ellagic acid also plays its role as it inhibits the acetyl cholinesterase enzyme thus it can minimize the effect of deficiency of acetylcholine. Furthermore, EA can be a promising therapeutic diet in AD patients where insulin resistance occurs, due to imbalance of glucose transportation and other insulin dependent activation. Because there are no effective neuroprotective therapies that delay the progression of the AD, symptomatic treatment remains the cornerstone of medical management. Need of today's is diets or drugs that modify age-related degenerative disease and provide a strong symptomatic relief to AD patients. There is major requirement to determine therapeutic potential for EA in cases of AD with suitable biochemical markers. Drug and methodological manipulations should be explored in future investigations.

CONFLICT OF INTERESTS

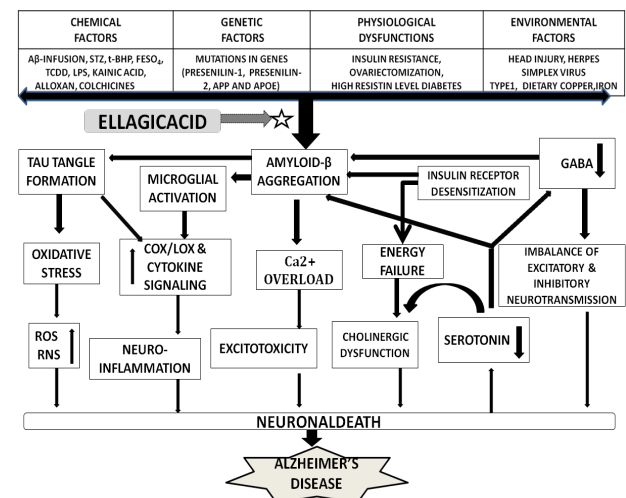The authors have no conflicts of interest to declare.

Figure 2 Neuroprotective action of EA via modulating various signaling pathways involved in the progression of Alzheimer's disease.

Table 2 EA targeting brain dysfunctions.

Pharmacological Activity	Model	Mechanism	Reference
Effect on Amyloid beta	Amyloid Beta Peptide-Induced Oxidative Stress in PC12 Cells	Antioxidant activity	Muthaiyah et al., 2011
	Human recombinant β-secretase (BACE1) in Swedish mutation of amyloid precursor protein	Inhibition of BACE1	Sheean et al., 2011
	Infusion of amyloid-beta (Aβ) peptide fragments in adult rats	Antioxidant activity	Wilson et al., 2010
	Aβ42-induced neurotoxicity in SH-SY5Y cells	Promote Aβ fibrillization, Reduces Aβ42 cytotoxicity in SH-SY5Y cells	Feng et al., 2009
	Tg2576/APPsw mice	Improved behavioral performance	Hartman et al., 2006
Inhibition of Neuro-oxidation	OGD-R Induced PC12 Cell Death	Anti-oxidant activity	Gaire et al., 2013
	H2O2-induced oxidative damage in NG108-15 hybridoma cell line	Anti-oxidant activity	Tan et al., 2011
	Streptozotocin-induced diabetic rats	Anti-oxidant activity	Uzar et al., 2011
	Tert-Butylhydroperoxide induces cytotoxicity PC12 cells	Anti-oxidant activity	Pavlica & Gebhardt, 2005
	TCDD-Induced Oxidative Stress in rats	Anti-oxidant activity	Hassoun et al., 2004
Inhibition of Neuroinflammation	LPS Induced Microglia Activation	Anti- inflammatory	Gaire et al., 2013
	APP/PS1 mice	Anti- inflammatory activity decreased Aβ plaque load	Rojanathammanee et al., 2013
	Kainic acid inflammatory rat	Anti- inflammatory Improve spatial learning and memory abilities	Shukitt-Hale et al., 2008
AchE inhibition	In-vitro	Inhibit sites of AChE; Aβ aggregation and acetylcholine catabolism	Wilson et al., 2010
	Rat brain	Decrease in brain AChE	Wilson et al.,2010
Effect on Insulin	In-vitro	Stimulate glucose transport	Poulose et al., 2011
	Ovariectomized mice	Suppress resistin secretion	Makino-Wakagi et al., 2012
	Alloxan induced diabetic rats	Antioxidant	Stanely M. Princeet al., 2003
Antidepressant activity	In-vitro	MAO-A inhibition	Ferreres et al., 2013
	Anti anxiety-like effect	modulation of GABAergic system	Girish et al., 2013
	Anti-immobility effect in Swissalbino mice,	Activation of monoaminergic system	Girish et al., 2012
	In-vitro GABA modulation	decreases the levels of full-length RAGE	Sun et al., 2012.
	Acute immobilization-induced stressed mice	Activation of monoaminergic system	Dhingra and Chhillar, 2012
	Anti-immobility effect in swiss Albino mice	reduced the duration of immobility	Pemminati et al., 2010
	Acute immobilization-induced stressed mice	Activation of monoaminergic system	Dhingra and Valecha,2007
Nociception action	Acetic acid-induced abdominal writhing test and tail flick test in Wistar rats	Cyclooxygenase (COX) inhibition	Mansouri et al., 2013
	Inflammatory pain induced by carrageenan	Cyclooxygenase (COX) inhibition	Gainok et al., 2011

REFERENCES

1. Muthaiyah B, Essa MM, Chauhan V, Chauhan A. Protective Effects of Walnut Extract Against Amyloid Beta Peptide-Induced Cell Death and Oxidative Stress in PC12 Cells. Neurochem Res. 2011; 36(11): 2096–2103.doi: 10.1007/s11064-011-0533-z.

2. Alzheimer's Association. Alzheimer's Disease Facts and Figures, Alzheimers Dement. 2014; 10(2):16

3. Anderson DC. Alzheimer's Disease Biomarkers: More Than Molecular Diagnostics. Drug Dev Res. 2013; 74: 92–111. DOI: 10.1002/ddr.21073

4. Blennow K, Zetterberg H, Fagan AM. Fluid biomarkers in Alzheimer disease. Cold Spring Harb Perspect Med. 2012; 2(9): a006221. doi: 10.1101/cshperspect.a006221.

5. Metcalfe MJ, Figueiredo-Pereira ME. Relationship between Tau Pathology and Neuroinflammation in Alzheimer's disease. Mt Sinai J Med. 2010; 77(1):50-58.doi:10.1002/msj.20163

6. Zheng H, Koo EH. The amyloid precursor protein: beyond amyloid. Mol Neurodegener. 2006;1:5.doi:10.1186/1750-1326-1-5. http://creativecommons.org/licenses/by/2.0

7. Luo BY, Xu ZB, Chen Z, Chen F, Tang M. Investigation on apoptosis of neuronal cells induced by Amyloid beta-Protein. JZUS. 2004; 5(8):989-994.

8. Capone R, Quiroz FG, Prangkio P, Saluja I, Sauer AM, Bautista MR, Turner RS. Amyloid-beta-induced ion flux in artificial lipid bilayers and neuronal cells: resolving a controversy. Neurotox Res. 2009; 16(1):1-13. doi: 10.1007/s12640-009-9033-1.

9. Akhondzadeh S, Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2006; 21(2):113-118. doi: 10.1177/153331750602100211

10. Suh YH, Checler F. Amyloid Precursor Protein, Presenilins, and α-synuclein: Molecular Pathogenesis and Pharmacological Applications in Alzheimer Disease. Pharmacol Rev. 2002; 54(3):469-525.

11. Sramek JJ, Zarotsky V, Cutler NR. Review of Drug Development and Therapeutic Role of Cholinesterase Inhibitors in Alzheimer'sDisease. Drug Dev Res. 2002; 56:347-353. doi: 10.1002/ddr.10087.

12. Kihara T, Shimohama S. Alzheimer's disease and acetylcholine receptors. Acta Neurobiol Exp. 2004; 64: 99-105.

13. Galasko D, Montine TJ. Biomarkers of oxidative damage and inflammation in Alzheimer's disease. Biomark Med. 2010; 4(1):27-36. doi:10.2217/bmm.09.89.

14. Montine TJ, Neely MD, Quinn JF, Beal MF, Markesbery WR, Roberts LJ, Morrow JD. Lipid Peroxidation in Aging Brain and Alzheimer's disease. Free Radic Bio Med. 2002;33(5):620-626.

15. Arlt S, Beisiegel U, Kontush A. Lipid peroxidation in neurodegeneration: new insights into Alzheimer's disease. Curr Opin Lipidol. 2002; 13(3):289-294.

16. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosur Psych. 1999; 66(2):137-147.

17. Drachman DA, Leavitt J. Human Memory and the Cholinergic System A Relationship to Aging? Arch Neurol. 1974; 30(2):113-121. doi:10.1001/archneur.1974.00490320001001.

18. Akhondzadeh S, Noroozian M. Alzheimer's disease: pathophysiology and pharmacotherapy. IDrugs. 2002; 5(11):1062-1069.

19. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Ef-

fects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. J Neurol Neurosur Psychiat. 2001; 71(5):589-595.

20. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurol. 2000; 54(12):2261-2268.

21. Kanowski S, Hoerr R. Ginkgo biloba extract EGb 761 in dementia: intent-to-treat analyses of a 24-week, multi-center, double-blind,placebo-controlled, randomized trial. Pharmacopsychiatry. 2003; 36(6):297-303.

22. Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA. 1997; 278(16):1327-1332.

23. Goswami S, Saoji A, Kumar N, Thawani V, Tiwari M, Thawani M. Effect of Bacopa monnieri on Cognitive functions in Alzheimer's disease patients. Int J Collab Res Internal Med Public Health. 2011; 3(4):285-292.

24. Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of Bacopa monnieri in Alzheimer's disease model. J Ethnopharmacol. 2010; 127(1):26-31. doi:10.1016/j.jep.2009.09.056

25. Kumar MHV, Gupta YK. Antioxidant property of Celastrus paniculatus Willd.:a possible mechanism in enhancing cognition. Phytomedicine. 2002; 9: 302–311.doi:10.4061/2009/972178.

26. Gattu M, Boss KL, Terry Jr AV, Buccafusco JJ. Reversal of Scopolamine-Induced Deficits in Navigational Memory Performance by the Seed Oil of Celastrus paniculatus.Pharmacol Biochem Behav. 1997; 57(4):793-799.

27. Cole GM, Teter B, Frautschy SA. Neuroprotective Effects Of Curcumin.Adv Exp Med Bio. 2007; 595: 197–212.

28. Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL. A potential role of the curry spice curcumin in Alzheimer's disease. Curr Alzheimer Res. 2005; 2(2):131-136.

29. Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. J Alzheimers Dis. 2004; 6(4):367-377.

30. Jang YJ, Kim J, Shim J, Kim CY, Jang JH, Lee KW, Lee HJ. Decaffeinated coffee prevents scopolamine-induced memory impairment in rats. Behav Brain Res. 2013; 245:113-119. doi: 10.1016/j.bbr.2013.02.003.

31. Arendash GW, Cao C. Caffeine and coffee as therapeutics against Alzheimer's disease. J Alzheimers Dis. 2010;20 Suppl 1:S117-S126.Doi: 10.3233/JAD-2010-091249

32. Chen X, Ghribi O. Geiger JD. Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's disease. J Alzheimers Dis. 2010; 20 Suppl 1:S127-S141. doi: 10.3233/JAD-2010-1376

33. Hancianu M, Cioanca O, Mihasan M, Hritcu L. Neuroprotective effects of inhaled lavender oil on scopolamine-induced dementia via anti-oxidative activities in rats. Phytomedicine. 2013; 20:446-52.

34. Staehelin HB. Neuronal protection by bioactive nutrients. Int J Vitam Nutr Res. 2008; 78:282-5.

35. Harvey Harvey BS, Musgrave IF, Ohlsson KS, Fransson A, Smid SD. The green tea polyphenol (-)-epigallocatechin-3-gallate inhibits amyloid-b evoked fibril formation and neuronal cell death in vitro. Food Chemistry. 2011; 129:1729-36. doi:10.1016/j.foodchem.2011.06.040.

36. Thomas P, Wang YJ, Zhong JH, Kosaraju S, O'Callaghan NJ, Zhou XF, Fenech M. Grape seed polyphenols and curcumin reduce genomic instability events in a transgenic mouse model for Alzheimer's disease. Mutat Res. 2009; 661:25-34. doi: 10.1016/j.mrfmmm.2008.10.016.

37. Anhe FF, Desjardins Y, Pilon G, Dudonne S, Genovese M, Lajolo FM, Marette A. Polyphenols and type 2 diabetes: A prospective review. PharmaNutrition. 2013; 1:105-14.

38. Cushnie TP, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. Int J Antimicrob Agents. 2011;38(2):99-107. doi: 10.1016/j.ijantimicag.2011.02.014.

39. Cesoniene L, Jasutiene I, Sarkinas A. Phenolics and anthocyanins in berries of European cranberry and their antimicrobial activity. Medicina (Kaunas). 2009; 45 (12):992-999.

40. Qin XY, Cheng Y, Yu LC. Potential protection of green tea polyphenols against intracellular amyloid beta-induced toxicity on primary cultured prefrontal cortical neurons of rats. Neurosci Lett. 2012;513 (2):170-173. http://dx.doi.org/10.1016/j.fct.2013.06.025

41. Ksiezak-Reding H, Ho L, Santa-Maria I, Diaz-Ruiz C, Wang J, Pasinetti GM. Ultrastructural alterations of Alzheimer's disease paired helical filaments by grape seed-derived polyphenols. Neurobiol Aging. 2012; 33:1427-39.

42. Fernández-Fernández L, Comes G, Bolea I, Valente T, Ruiz J, Murtra P et al. LMN diet, rich in polyphenols and polyunsaturated fatty acids, improves mouse cognitive decline associated with aging and Alzheimer's disease. Behav Brain Res. 2012; 228:261-71.

43. Choi DY, Lee YJ, Hong JT, Lee HJ. Antioxidant properties of natural polyphenols and their therapeutic potentials for Alzheimer's disease. Brain Res Bull. 2012; 87:144-53. doi: 10.1016/j.brainresbull.2011.11.014.

44. Sepúlveda L, Ascacio A, Rodríguez-Herrera R. Aguilera-Carbó A. Aguilar CN. Ellagic acid: Biological properties and biotechnological development for production processes. African J Biotech. 2011; 10(22):4518-4523.http://www.academicjournals.org/AJB

45. Landete JM. Ellagitannins, ellagic acid and their derived metabolites: A review about source metabolism, functions and health. Food Res Int. 2011; 44:1150–60. doi:10.1016/j.foodres.2011.04.027.

46. Hakkinen S, Heinonen M, Karenlampi S, Mykkanen H, Ruuskanen J, Torronen R. Screening of selected favonoids and phenolic acids in 19 berries. Food Res Int. 1999; 32: 345-53.

47. Thiem B. Rubus chamaemorus L.-a boreal plant rich in biologically active metabolites: a review. Biol. Lett. 2003; 40:3-13

48. Mertens-Talcott SU, Talcott ST, Percival SS. Low concentrations of quercetin and ellagic acid synergistically influence proliferation, cytotoxicity and apoptosis in MOLT-4 human leukemia cells. J. Nutr. 2003; 133:2669-74.

49. Daniel EM, Krupnick AS, Heur YH, Blinzler JA, Nims RW, Stone GD. Extraction, stability, and quantitation of ellagic acid in various fruits and nuts. J Food Compost Anal. 1989; 2:338-49

50. Gil MI, Tomas-Barberan FA, Hess-Pierce B, Holcroft DM, Kader AA. Antioxidant Activity of Pomegranate Juice and Its Relationship with Phenolic Composition and Processing. J Agric Food Chem. 2000; 48:4581-9

51. Nantitanon W, Yotsawimonwat S, Okonogi S. Factors influencing antioxidant activities and total phenolic content of guava leaf extract. LWT - Food Sci Technol. 2010; 43:1095-103.

52. Espín JC, González-Barrio R, Cerdá B, López-Bote C, Rey AI, Tomás-Barberán FA. Iberian pig as a model to clarify obscure points in the bioavailability and metabolism of ellagitannins in humans. J Agric Food Chem. 2007; 55:10476-85.

53. Seeram NP, Lee R, Heber D. Bioavailahility of ellagic acid in human plasma after consumption of ellagitannins from pomegranate (Punica granatnm L.) juice. Clin Chim Acta. 2004; 348:63-8.

54. Lei F, Xing DM, Xiang L, Zhao YN, Wang W, Zhang LJ et al. Pharmacokinetic study of ellagic acid in rat after oral administration of pomegranate leaf extract. J Chromatogr B Analyt Technol Biomed Life Sci. 2003; 796:189-94.

55. Cerdá B, Periago P, Espín JC, Tomás-Barbera FA. Identification of urolithin A as a metabolite produced by human colon microflora from ellagic acid and related compounds. J Agric Food Chem. 2005; 53:5571-6.

56. Jimenez-Garcia SN, Guevara-Gonzalez RG, Miranda-Lopez R, Feregrino-Perez AA, Torres-Pacheco I, Vazquez-Cruz MA. Functional properties and quality characteristics of bioactive

compounds in berries: Biochemistry, biotechnology, and genomics. Food Res Int. 2013; 54:1195-1207.http://dx.doi.org/10.1016/j.foodres.2012.11.004

57. Aiyer HS, Srinivasan C, Gupta RC. Dietary berries and ellagic acid diminish estrogen-mediated mammary tumorigenesis □ ACI rats Nutr Cancer. 2008; 60:227-34.

58. Hamad, A.W.R., W.M. Al-Momani, S. Janakat and S.A Oran. 2009. Bioavailability of Ellagic Acid After Single Dose Administration Using HPLC. Pakistan Journal Of Nutrition, 8 (10): 1661-1664

59. Bala I, Bhardwaj V, Hariharan S, Kumar MN. Analytical methods for assay of ellagic acid and its solubility studies. J Pharmaceut And Biomed Ana. 2006; 40(1):206-210.

60. Losso JN, Bansodea RR, Trappey A, Bawadi HA, Truax R. In vitro anti-proliferative activities of Ellagic acid. J Nutr Biochem. 2004; 15:672-8. doi:10.1016/j.jnutbio.2004.06.004.

61. Cornélio Favarin D, Martins Teixeira M, Lemos de Andrade E, de Freitas Alves C, Lazo Chica JE, Artério Sorgi C et al. Anti-Inflammatory Effects of Ellagic Acid on Acute Lung Injury Induced by Acid in Mice. Mediators Inflamm. 2013; 2013:164202. doi:10.1155/2013/164202.

62. Corbett S, Daniel J, Drayton R, Field M, Steinhardt R, Garrett N. Evaluation of the anti-inflammatory effects of Ellagic acid. J Perianesth Nurs. 2010; 25:214-20. doi: 10.1016/j.jopan.2010.05.011.

63. Zhao M, Tang SN, Marsh JL, Shankar S, Srivastava RK. Ellagic acid inhibits human pancreatic cancer growth in Balb c nude mice. Cancer Lett. 2013; 337:210-7. doi:10.1523/JNEUROSCI.2860-04.2004

64. Srigopalram S, Ilavenil S, Jayraaj IA. Apoptosis associated inhibition of DEN-induced hepatocellular carcinogenesis by ellagic acid in experimental rats. Biomedicine & Preventive Nutrition. 2012; 2:1-8. doi:10.1016/j.bionut.2011.12.003.

65. Kannan MM, Quine SD. Ellagic acid inhibits cardiac arrhythmias, hypertrophy and hyperlipidaemia during myocardial infarction in rats. Metabolism. 2013; 62:52-61. http://dx.doi.org/10.1016/j.metabol.2012.06.003

66. Yu YM, Chang WC, Wu CH, Chiang SY. Reduction of oxidative stress and apoptosis in hyperlipidemic rabbits by ellagic acid. J Nutr Biochem. 2005; 16:675-81. doi:10.1016/j.jnutbio.2005.03.013

67. Feng Y, Yang SG, Du XT, Zhang X, Sun XX, Zhao M et al. Ellagic acid promotes Aβ42 fibrillization and inhibits Aβ42-induced neurotoxicity. Biochem Biophys Res Commun. 2009; 390:1250-4. doi:10.1016/j.bbrc.2009.10.130

68. Wilson Wilson GN, Mickley GA, Matera KM. The efficacy of ellagic acid in attenuating neurophysiological and cognitive-behavioral symptoms associated with infusion of amyloid-beta (Aβ) peptide fragments in adult rats. The Baldwin-Wallace College Journal of Research and Creative Studies, Spring 2010; 3:15-30.

69. Dasilva KA, Shaw JE, McLaurin J. Amyloid-β fibrillogenesis: Structural insight and therapeutic intervention. Exp Neurol. 2010; 223(2):311-321. doi: 10.1016/j.expneurol.2009.08.032.

70. Sakono M, Zako T. Amyloid oligomers: formation and toxicity of Aβ oligomers.FEBS Journal. 2010; 277:1348–1358.doi:10.1111/j.1742-4658.2010.07568.x

71. Hartman RE, Shah A, Fagan AM, Schwetye KE, Parsadanian M, Schulman RN et al. Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiol Dis. 2006; 24:506-15. doi:10.1016/j.nbd.2006.08.006.

72. Sheean P, Rout MK, Head RJ, Bennett LE. Modulation of in vitro activity of zymogenic and mature recombinant human β-secretase by dietary plants. FEBS J. 2012; 279:1291-1305.doi:10.1111/j.1742-4658.2012.08524.x.

73. Kwak HM, Jeon SY, Sohng BH, Kim JG, Lee JM, Lee KB et al. Beta-secretase (BACE1) inhibitors from pomegranate (Punica granatum) husk. Arch Pharm Res. 2005; 28:1328-32.

74. Kirkinezos IG, Moraes CT. Reactive oxygen species and mito-

75. chondrial diseases. Annual Rev Cell Dev Bio. 2001; 12:449-457. doi:10.1006/scdb.2001.0282.

75. Floyd RA. Antioxidants, oxidative stress and degenerative neurological disorders.Proc Soc Exp Biol Med. 1999; 222(3):236-245.

76. Yen GC, Hung YL, Hsieh CL. Protective effect of extracts of Mesona procumbens Hemsl. on DNA damage in human lymphocytes exposed to hydrogen peroxide and UV irradiation. Food Chem Toxicol. 2000; 38(9):747-754.

77. Halliwell B, Clement MV, Ramalingam J, Long LH. Hydrogen Peroxide. Ubiquitous in Cell Culture and In vivo? International Union of Biochemistry and Molecular Biology Life. 2000; 50(4-5):251-257.

78. Fortalezas S, Tavares L, Pimpão R, Tyagi M, Pontes V, Alves PM et al. Antioxidant Properties and Neuroprotective Capacity of Strawberry Tree Fruit (Arbutus unedo). Nutrients. 2010; 2:214-29. doi:10.3390/nu2020214

79. Singh U, Devaraj S, Jialal I. Vitamin E, oxidative stress, and inflammation. Annu Rev Nutr. 2005; 25:151-74.

80. Maritim AC, Sanders RA, Watkins JB. Effects of alpha-lipoic acid on biomarkers of oxidative stress in streptozotocin-induced diabetic rats. J Nutr Biochem. 2003; 14:288-94. doi:10.1016/S0955-2863(03)00036-6.

81. Sies H. Physiological society symposium: impaired endothelial and smooth muscle cell function in oxidative stress. Oxidative stress: oxidants and antioxidants. Exp physiol. 1997; 82:291-5.

82. Sen HK, Packer L. Antioxidant and redox regulation of gene transcription.The FASEB Journal, 1996; 10:709-720.

83. Chow CK. Vitamin E and Oxidative Stress. Free Rad BioMed. 1991;1:215-232.

84. Özkaya A, Celik S, Yüce A Şahin Z Yilmaz O. The effects of Ellagic acid on some biochemical parameters in the liver of rats against oxidative stress induced by aluminum. Kafkas Univ Vet Fak DerG. 2010; 16: 263-8.

85. Türk G, Sönmez M, Çeribaş AO, Yüce A, Ateşşahin A. Attenuation of cyclosporine A-induced testicular and spermatozoal damages associated with oxidative stress by ellagic acid. Int Immunopharmacol. 2010; 10:177-82. doi:10.1016/j.intimp.2009.10.013

86. Chao PC, Hsu CC, Yin MC. Anti-inflammatory and anti-coagulatory activities of caffeic acid and ellagic acid in cardiac tissue of diabetic mice. Nutri Metabol (Lond). 2009; 14;6:33. doi: 10.1186/1743-7075-6-33.

87. Yüce A, Ateşşahin A, Ceribaşi AO, Aksakal M. Ellagic acid prevents cisplatin-induced oxidative stress in liver and heart tissue of rats. Basic Clin Pharmacol Toxicol. 2007; 101:345-9. doi: 10.1111/j.1742-7843.2007.00129.x

88. Ateşşahín A, Ceríbaşi AO, Yuce A, Bulmus O, Cikim G. Role of Ellagic acid against cisplatin-induced nephrotoxicity and oxidative stress in rats. Basic Clin Pharmacol Toxicol. 2007; 100:121-6. doi: 10.1111/j.1742-7843.2006.00015.x

89. Singh K, Khanna AK, Chander R. Hepatoprotective activity of ellagic acid against carbon tetrachloride induced hepatotoxicity in rats. Indian J Exp Biol. 1999; 37:1025-6.

90. Sarabhai S, Sharma P, Capalash N. Ellagic acid derivatives from Terminalia chebula Retz. downregulate the expression of quorum sensing genes to attenuate pseudomonas aeruginosa PAO1 virulence. PLoS One. 2013; 8:e53441.doi:10.1371/journal.pone.0053441.

91. Gaire BP, Jamarkattel-Pandit N, Lee D, Song J, Kim JY, Park J et al. Terminalia chebula extract protects OGD-R induced PC12 cell death and inhibits LPS induced microglia activation. Molecules. 2013; 18:3529-42. doi:10.3390/molecules18033529.

92. Tan HP, Wong DZ, Ling SK, Chuah CH, Kadir HA. Neuroprotective activity of galloylated cyanogenic glucosides and hydrolysable tannins isolated from leaves of Phyllagathis rotundifolia. Fitoterapia. 2012; 83:223-9. doi:10.1016/j.fitote.2011.10.019.

93. Manschot SM, Biessels GJ, Rutten GE, Kessels RP. Gispen WH, Kappelle LJ, Utrecht Diabetic Encephalopathy Study Group. Pe-

ripheral and central neurologic complications in type 2 diabetes mellitus: No association in individual patients. J Neurol Sci. 2008; 264(1-2):157-162.doi:10.1016/j.jns.2007.08.011.

94. Uzar E, Alp H, Cevik MU, Fırat U, Evliyaoglu O, Tufek A et al. Ellagic acid attenuates oxidative stress on brain and sciatic nerve and improves histopathology of brain in streptozotocin-induced diabetic rats. Neurol Sci. 2012; 33:567-74. doi: 10.1007/s10072-011-0775-1.

95. Palomba L, Sestili P, Cantoni O. Tert-Butylhydroperoxide induces peroxynitrite-dependent mitochondrial permeability transition leading PC12 cells to necrosis. J Neurosci Res. 2001; 65:387-95.

96. Pavlica S, Gebhardt R. Protective effects of ellagic and chlorogenic acids against oxidative stress in PC12 cells. Free Radic Res. 2005; 39:1377-90. doi: 10.1080/09670260500197660.

97. Unkila M, Pohjanvirta R, Tuomisto J. Biochemical effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds on the central nervous system. Int J Biochem Cell Biol. 1995; 27:443-55.

98. Hassoun EA, Vodhanel J, Abushaban A. The modulatory effects of ellagic acid and vitamin E succinate on TCDD-induced oxidative stress in different brain regions of rats after subchronic exposure. J Biochem Mol Toxicol. 2004; 18:196-203.

99. Rojanathammanee L, Puig KL, Combs CK. Pomegranate polyphenols and extract inhibit nuclear factor of activated t-cell activity and microglial activation in vitro and in a transgenic mouse model of Alzheimer disease. J Nutr. 2013; 143:597-605. doi:10.3945/jn.112.169516.http://jn.nutrition.org/content/suppl/2013/04/11/jn.112.169516.DCSupplemental.html

100. Shukitt-Hale B, Lau FC, Carey AN, Galli RL, Spangler EL, Ingram DK et al. Blueberry polyphenols attenuate kainic acid induced decrements in cognition and alter inflammatory gene expression in rat hippocampus. Nutr Neurosci. 2008; 11:172-82. doi 10.1179/147683008X301487.

101. Mehan S, Meena H, Sharma D, Sankhla R. JNK: stress-activated protein kinase therapeutic strategies and involvement in Alzheimer's and various neurodegenerative abnormalities. J Mol Neurosci. 2011; 43:376-90.

102. Sastre M, Walter J, Gentleman SM. Interactions between APP secretases and inflammatory mediators. J Neuroinflam. 2008; 5:25. doi:10.1186/1742-2094-5-25. http://www.jneuroinflammation.com/content/5/1/25.

103. Lipton P. Ischemic Cell Death in Brain Neurons. Physiol Rev.1999; 79(4):1431-1568.

104. Olajide O, Fiebich B. Anti-neuroinflammatory and Anti-amyloidogenic Properties of Punicalagin in LPS Activated Rat Primary Microglia. Proceedings of the British Pharmacological Society at http://www.pA2online/abstracts/Vol10Issue4abst137P.pdf

105. Rosillo MA, Sánchez-Hidalgo M, Cárdeno A, Aparicio-Soto M, Sánchez-Fidalgo S, Villegas I et al. Dietary supplementation of an ellagic acid-enriched pomegranate extract attenuates chronic colonic inflammation in rats. Pharmacol Res. 2012; 66:235-42. http://dx.doi.org/10.1016/j.phrs.2012.05.006

106. Umesalma S, Sudhandiran G. Ellagic acid prevents rat colon carcinogenesis induced by 1, 2 dimethyl hydrazine through inhibition of AKT-phosphoinositide-3 kinase pathway. Eur J Pharmacol. 2011; 660:249-58.

107. Papoutsi Z, Kassi E, Chinou I, Halabalaki M, Skaltsounis LA, Moutsatsou P. Walnut extract (Juglans regia L.) and its component ellagic acid exhibit anti-inflammatory activity in human aorta endothelial cells and osteoblastic activity in the cell line KS483 Z. Br J Nutr. 2008; 99:715-22. doi: 10.1017/S0007114507837421.

108. Fisher A. Cholinergic treatments with emphasis on m1 muscarinic agonists as potential disease-modifying agents for Alzheimer's disease. Neurotherapeutics. 2008; 5:433-42.

109. Yan Z, Feng J. Alzheimer's Disease: Interactions between Cholinergic Functions and beta-amyloid. Curr Alzheimer Res. 2004; 1:241-8.

110. Grutzendler J, Morris JC. Cholinesterase inhibitors for Alzheimer's disease. Drugs. 2001; 61(1): 41-52.

111. Giacobini E. Cholinesterase Inhibitors Stabilize Alzheimer's Disease. Annals of the New York Academy of Sciences. The Molecular Basis of Dementia. 2000;920:321–327.

112. Nordberg A, Svensson AL. Cholinesterase Inhibitors in the Treatment of Alzheimer's disease.Drug Safety. 1998; 19(6):465-480.

113. Nag G, De B. Acetylcholinesterase inhibitory activity of Terminalia Chebula, Terminalia Bellerica and Emblica Officinalis and some phenolic compounds. Int J Pharm Pharm Sci. 2011; 3:121-4.

114. Ferreres F, Grosso C, Gil-Izquierdo A, Valentão P, Andrade PB. Ellagic Acid and derivatives from Cochlospermum angolensis Welw. Extracts: HPLC–DAD–ESI/MSn profiling, quantification and in vitro anti-depressant, anti-cholinesterase and anti-oxidant activities. Phytochem Anal. 2013; 24:534-40. doi: 10.1002/pca.2429.

115. Frölich L. Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Laufer S, Muschner D, Thalheimer A, Türk A. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease.J Neural Trans. 1998; 105(4-5):423-438.

116. Deshmukh R, Sharma V, Mehan S, Sharma N, Bedi KL. Amelioration of intracerebroventricular streptozotocin induced cognitive dysfunction and oxidative stress by vinpocetine - a PDE1 inhibitor. Eur J Pharmacol. 2009; 620:49-56.

117. Messier C, Gagnon M. Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. Behav Brain Res. 1996; 75:1-11.

118. Beal MF. Energetics in the pathogenesis of neurodegenerative diseases. Trends Neurosci. 2000; 23:298-304.

119. Lampson MA, Racz A, Cushman SW, McGraw TE. Demonstration of insulin-responsive trafficking of GLUT4 and vpTR in fibroblasts. J Cell Sci. 2000;113 (Pt 22):4065-4076.

120. Hayashi T, Hirshman MF, Kurth EJ, Winder WW, Goodyear LJ. Evidence for 5'AMP-activated protein kinase mediation of the effect of muscle contraction on glucose transport. Diabetes. 1998; 47:1369-73.

121. Poulose N, Prasad CNV, Haridas PAN, Anilkumar G. Ellagic acid stimulates glucose transport in adipocytes and muscles through AMPK mediated pathway. J Diabetes Metab. 2011; 2:7 doi:10.4172/2155-6156.1000149. http://dx.doi.org/10.4172/2155-6156.1000149

122. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM et al. The hormone resistin links obesity to diabetes. Nature. 2001; 409:307-12.

123. Makino-Wakagi Y, Yoshimura Y, Uzawa Y, Zaima N, Moriyama T, Kawamura Y. Ellagic acid in pomegranate suppresses resistin secretion by a novel regulatory mechanism involving the degradation of intracellular resistin protein in adipocytes. Biochem Biophys Res Commun. 2012; 417:880-5.doi:10.1016/j.bbrc.2011.12.067

124. Fazliana M, Wan Nazaimoon WM, Gu HF, Ostenson CG. Labisia pumila extract regulates body weight and adipokines in ovariectomized rats. Maturitas. 2009;62(1):91-97. doi: 10.1016/j.maturitas.2008.10.004.

125. Huang SW, Seow KM, Ho LT, Chien Y, Chung DY, Chang CL, Lai YH, Hwang JL, Juan CC. Resistin mRNA levels are downregulated by estrogen in vivo and in vitro. FEBS Lett. . 2005; 579(2):449-454. doi:10.1016/j.febslet.2004.12.010.

126. Bhatia IS, Bajaj KL. Chemical constituents of the seeds and bark of Syzygium Cumin. Planta Med. 1975; 28:346-52.

127. Stanely Mainzen Prince P, Kamalakkannan N, Menon VP. Syzigium cumini seed extracts reduce tissue damage in diabetic rat brain. J Ethnopharmacol. 2003; 84:205-9.

128. Dhingra D, Chhillar R. Antidepressant-like activity of ellagic acid in unstressed and acute immobilization-induced stressed mice. Pharmacol Rep. 2012; 64:796-807.

129. Madsen K, Neumann WJ, Holst K, Marner L, Haahr MT, Lehel

S et al. Cerebral serotonin 4 receptors and amyloid-β in early Alzheimer's disease. J Alzheimers Dis. 2011; 26:457-66.doi: 10.3233/JAD-2011-110056.

130. Ciranna L. Serotonin as a modulator of glutamate- and GABA-mediated neurotransmission: implications in physiological functions and in pathology. Curr Neuropharmacol. 2006; 4:101-14.

131. Girish C, Raj V, Arya J, Balakrishnan S. Evidence for the involvement of the monoaminergic system, but not the opioid system in the antidepressant-like activity of ellagic acid in mice Eur J Pharmacol. 2012; 682:118-25. doi: 10.1016/j.ejphar.2013.04.003.

132. Nadkarni AK, Nadkarni KM. Indian Materia Medica 3rd ed. Vol.I Popular Prakashan, New Delhi, 1992.

133. Pemminati S, Gopalakrishna HN, Shenoy AK, Sahu SS, Mishra S, Meti V et al. Antidepressant activity of aqueous extract of fruits of Emblica Officinalis in mice. IJABPT. 2010; 1:449-54.

134. Tamashiro Filho P, Sikiru Olaitan B, Tavares de Almeida DA, Lima JC, Marson-Ascêncio PG, Donizeti Ascêncio S et al. Evaluation of antiulcer activity and mechanism of action of methanol stem bark extract of Lafoensia pacari A. St.-Hil. (Lytraceae) in experimental animals. J Ethnopharmacol. 2012; 144:497-505. doi: 10.1016/j.jep.2012.09.019

135. Galdino PM, Nascimento MV, Sampaio BL, Ferreira RN, Paula JR, Costa EA. Antidepressant-like effect of Lafoensia pacari A. St.-Hil. Ethanolic extract and fractions in mice. J Ethnopharmacol. 2009; 124:581-5. doi:10.1016/j.jep.2009.05.001.

136. Dhingra D, Valecha R. Evaluation of antidepressant-like activity of aqueous and ethanolic extracts of Terminalia bellirica Roxb. fruits in mice. Indian J Exp Biol. 2007; 45:610-6.

137. Garcia-Alloza M, Tsang SW, Gil-Bea FJ, Francis PT, Lai MK, Marcos B et al. Involvement of the GABAergic system in depressive symptoms of Alzheimer's disease. Neurobiol Aging. 2006; 27:1110-7.doi:10.1016/j.neurobiolaging.2005.06.003

138. Choudary PV, Molnar M, Evans SJ, Tomita H, Li JZ, Vawter MP et al. Altered cortical glutamatergic and GABAergic signal trans-

mission with glial involvement in depression. Proc Natl Acad Sci. 2005; 102:15653-8.

139. Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. Mol Psychiatry. 2003; 8:721-37. doi: 10.1038/sj.mp.4001362

140. Girish C, Raj V, Arya J, Balakrishnan S. Evidence for the involvement of the monoaminergic system, but not the opioid system in the antidepressant-like activity of ellagic acid in mice Eur J Pharmacol. 2012; 682:118-25. doi:10.1016/j.ejphar.2012.02.034.

141. Lue LF, Walker DG, Brachova L, Beach TG, Rogers J, Schmidt AM et al. Involvement of microglial receptor for advanced glycation endproducts (RAGE) in Alzheimer's disease: identification of a cellular activation mechanism. Exp Neurol. 2001; 171:29-45.

142. Cheng X, Wu J, Geng M, Xiong J. The role of synaptic activity in the regulation of amyloid beta levels in Alzheimer's disease. Neurobiol Aging. 2014; 35:1217-32.

143. Sun X, Meng X, Zhang J, Li Y, Wang L, Qin X, Sui N, Zhang Y. GABA attenuates amyloid toxicity by downregulating its endocytosis and improves cognitive impairment. J Alzheimers Dis. 2012;31(3):635-649.doi: 10.3233/JAD-2012-120535

144. Taghi Mansouri M, Naghizadeh B, Ghorbanzadeh B, Farbood Y. Central and peripheral antinociceptive effects of ellagic acid in different animal models of pain. Eur J Pharmacol. 2013; 707:46-53.http://dx.doi.org/10.1016/j.ejphar.2013.03.031

145. Gainok J, Daniels R, Golembiowski D, Kindred P, Post L, Strickland R et al. Investigation of the anti-inflammatory, antinociceptive effect of ellagic acid as measured by digital paw pressure via the randall-selitto meter in male sprague-dawley rats. AANA J. 2011; 79:S28-34.