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Evaluation of Neuroprotective Properties of Ellagic Acid and Caffeic Acid Phenethylester

*Nitin Bansal[1] and Manish Kumar[2]**

[1]Department of Pharmacology, ASBASJSM College of Pharmacy, India

[2]Department of Pharmacology, Swift School of Pharmacy, India

Mini Review

In recent times naturally occurring therapeutically active biomolecules and secondary plant products have gained attention largely due to their potent therapeutic actions. This led to screening of plethora of natural products finding their utility in diverse disorders such as cancer, malaria, diabetes, urinary disorders, and joint disorders. Numerous naturally obtained drugs such as quinine, penicillin, theophylline, vincristine, doxorubicin, digoxin, morphine and paclitaxel are cornerstones of pharmaceutical care. Natural products having beneficial effects on brain functions are particularly sought after due to lack of potent and safe drugs for various CNS ailments including psychiatric disorders (e.g. depression, anxiety, psychosis) and neurodegenerative disorders (e.g. Alzheimer's disease, Huntington's disease, dementia). Several classes of natural products such as flavonoids, tannins, phenols, and terpenes have undergone intensive stuffy for their activities on brain. Many of these natural products are still under clinical trials. In this review we will focus on two naturally occurring molecules (ellagic acid and caffeic acid phenethylester) that have most recently received significant focus due to their beneficial actions on brain.

Ellagic Acid

Ellagic acid is a polyphenol compound abundantly present in berries (strew berry, raspberry, cloudberry, and blueberry), grapes, pomegranate, almonds, walnuts, and beverages [1]. EGA and EGA enriched extracts such as Ellagic Active tablets®, PomActiv™ and Biotech Nutritions Ellagic Acid Capsules® are widely consumed as dietary supplements owing to its health promoting activities [2]. EGA (2,3,7,8-tetrahydroxy[1]-benzopyranol[5,4,3-cde]benzopyran-5,10-dione) is a lactonised product (four hydroxyl groups and two lactone groups) of sugar (mostly glucose) esterified hexahydroxydiphenoic acid complexes (e.g. ellagitannins). In Gastro Intestinal Tract (GIT) ellagitannins are hydrolytically converted to EGA upon dietary consumption of whole fruits. EGA and ETs are converted to urolithins (dibenzopyranones) aided by pH and gut micro biota, and urolithin A and B have been detected in intestine [3,4]. Systemically EGA is metabolised through glucuronidation, catechol-*O*-methyl transferase and conversion to urolithin A, B, C and D. Although the bioavailability of EGA from whole fruit is reported low, however, several studies depict that EGA is widely distributed in body and significant amounts are detected in brain tissue upon oral consumption of EGA enriched extracts [5]. The bioavailability of EGA is comparable to that of resveratrol and significantly higher than choloro genic acid [6]. Despite of limited lipophilicity EGA (weak acid) is absorbed mostly from upper GIT (~1-2 h), has a half-life of ~ 8.4 ± 1.8 h and ~50% plasma-protein binding [7,8]. After (~1 h) the oral intake of 400 mg pomegranate extract (330 mg ETs and 22 mg EGA) the presence of free EGA in the plasma of human subjects (concentration 33 ng/ml) have been detected. EGA is detectable in plasma ~ 30-60 min after intake of pomegranate juice by human volunteer (C_{max} 31 ng/ml) and rats (concentration 93.6 ng/ml) [9,10].

Several studies demonstrated that pomegranates, berries and walnuts possess potent health promoting properties mostly attributed to EGA. EGA has shown anti atherogenic [11], anti-thrombotic [12], anti-diabetic [13], anti-obesity [14], antihypertensive [15], Hepato protective [16], antioxidant [17], anti-inflammatory [18], neuro restoration [19] and immuno modulatory [20] activities in pre-clinical studies [21,22]. Several evidences indicate that EGA targets the adipogenic markers (e.g. PPARγ and Kruppel-like factor 4/5), suppresses the adipogenic genes (e.g. fatty acid synthase, fatty acid–binding protein 4), and activate AMPK and cholesterol efflux mechanisms [23]. Attenuation of hyper lipidemia by EGA is demonstrated in transgenic (C57BL/6J/HFD mice) and non-transgenic (streptozotocin) animal models that may afford therapeutic benefits in AD. The EGA induced activation of AMPK vitalizes the glucose metabolism in diabetic rats [24]. The

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Correspondence:
Manish Kumar, Department of Pharmacology, Swift School of Pharmacy, Ghaggar Sarai, Rajpura, 140401, India, Tel: +91-9050757400; E-mail: mkpharmacology@gmail.com

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significant bioactivities of EGA prompted its use as nutraceutical in different food supplements [25]. The modulation of cholinergic function and LTP in brain indicates the neuroprotective ability of EGA [26-28]. EGA potently inhibits the AChE activity (IC_{50} ~ 13.79 µg/mL) and thereby up regulates the cognitive abilities through acetylcholine [29,30]. EGA has shown therapeutic benefits in experimental models of depression. EGA modulates the brain mono aminergic and GABA ergic transmission that have profound effects on learning and memory. The facilitation of serotonergic and nor-adrenergic transmission in brain is correlated with anti-depressant activity of EGA [31].

The reduction in $A\beta_{40-42}$-plaque deposition in brain and improvement in memory of rodents by pomegranate juice [32] and walnut extracts [33] has been attributed to EGA. The prevention of Aβ-peptide neurotoxicity [5], fibrillar aggregation of Aβ-peptides in brain [34] and inhibition of BACE-1 activity [35,36] are associated with EGA. A recent study demonstrated that EGA protects from $A\beta_{25-35}$ neurotoxicity in rats. The $A\beta_{25-35}$ induced elevation in oxidative stress, inflammation (NFκB activity) and AChE activities were significantly abrogated by EGA in rat brain. EGA reduced the cerebral infarct size and improved the memory of rats in passive avoidance and radial arm maze tests [37]. The antioxidant activity of EGA is due to direct free radical scavenging property and potentiation of endogenous antioxidants like NADPH: quinone oxido reductase 1 (NQO1), heme oxygenase-1(HO-1), GSH, SOD, catalase, glutathione reductase and glutathione peroxidase [38]. The hydroxyl group and lactone ring directly detoxify superoxide, hydroxyl free radical, hydrogen peroxide and per oxy nitrites [39]. EGA positively regulates the Nrf2 pathway which is a downstream target of PI3-kinase-Akt signalling and negatively regulates the Nrf2 repressor Kelch-like ECH-associated protein 1 (Keap1) [40]. EGA can protect the brain from inflammation by down regulating he expression of several pro-inflammatory cytokines (e.g. TNF-α) [41]. A number of evidences indicate that EGA negate the activities of iNOS, COX-2, 5-LOX, ICAM-1 and VCAM-1 [5]. The suppression of overt microglial response portrays the therapeutic benefit of EGA in AD. *In vivo* and *in vitro* studies supported the EGA induced inhibition of release of inflammatory cytokines by microglia and amyloid-plaques in APP/PS1 transgenic mice model and cultured primary murine cortical microglia [42]. Several reports suggest that EGA suppresses the NFκB pathway in different experimental models of cancer, renal, lungs and liver diseases [39].

In vitro treatment with EGA (30 micro molar) shows protection of rat brain astrocytes against cadmium (Cd^{2+}) toxicity [43]. The chelation of metal ions by EGA is involved in protection of nickel induced oxidative stress [44]. The anti-apoptotic and anti-inflammatory effects of EGA are attributed to modulation of PI3-kinase-Akt signalling [45]. The ability of EGA to restore the endothelial dysfunction in mice depicts involvement of eNOS which is a key downstream effector of PI3-kinase-Akt pathway [46]. Administration of EGA ameliorated the scopolamine and diazepam triggered memory deficits in rats [27]. In streptozotocin diabetes model EGA (50 mg/kg) prevented the progression of neuro degeneration. The STZ induced oxidative stress and lipid peroxidation was potently suppressed by EGA in rat brain [47]. The 2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD)-induced lipid peroxidation and genotoxicity in rat hippocampus were also prevented by EGA (1 mg/kg, *p.o.*) [48].

Amelioration of Bcl-2/Bax ratio in rat brain by EGA abates the ischemia induced neuron damage. EGA enhances the neuron viability in ischemic rats which highlights the involvement of PI3-kinase-Akt pathway [49]. In a novel photo thrombosis-induced model of brain injury in rats EGA imparted protective effects on nerves and abated the morphological changes and infarct volumes in brain of rats [19]. The inhibition of GSK-3β and FoxO transcriptional activity by EGA also implies the role of Akt signalling in EGA action. Furthermore, existing evidences indicate that EGA modulates several pathways such as MAPK, PPARγ, JNK1/2, NOTCH and STAT that bear significant impact on brain functions [39]. The present data suggests that EGA may hold benefits in the management of AD type dementia.

Caffeic Acid Phenethyl Ester (CAPE)

Caffeic acid phenethyl ester (2-phenylethyl (2*E*)-3-(3,4-dihydroxyphenyl) acrylate; $C_{17}H_{16}O_4$) is bioactive polyphenol present in honey and propolis of honeybees hive (15-29 mg/g) [50]. The other constituents of propolis are caffeic acid, quercetin, kaempferol, galangal and cinnamic acid esters. CAPE is ester derivative of caffeic acid which is a cinnamic acid derivative (3,4-dihydroxycinnamic acid) present in abundance in coffee drinks, berries, apples and cider [51]. Several other derivatives (alkyl esters) of caffeic acid are synthesized from phenyl propanoid scaffold having significant antioxidant and anti-inflammatory activities. Although CAPE is converted to caffeic acid after ~ 6 h *in vivo*, however, it provides better pharmacokinetic parameters (e.g. clearance 42-172 ml/min/kg, elimination $t_{1/2}$ 21.24–26.71 min, *i.v.*) highly desired for optimum therapeutic effects [52]. The high lipophilicity of CAPE renders wide distribution (V_d 1555-5209 ml/kg) in body including the brain [53].

Several pharmacological activities such as antioxidant [54], anti-inflammatory [55], immuno-modulatory [56] and neuro protection [57] by CAPE ensues high utility in many disorders [58,59]. The anti-inflammatory activity of CAPE is attributed to inhibition of expression and activity of COX-1/2 and suppression of NFκB [60], nuclear factor of activated cells (NFAT) and activator protein-1 (AP-1) transcriptional activity [61]. The pro-survival function of CAPE is evident by inhibition of Bak, Bax, p53 MAPK, c-Jun, c-Jun N-terminal kinase and Fas ligand, and caspases. Furthermore, activation of Bel-2, X-linked inhibitor of apoptosis protein, release of cytochrome C, loss of mitochondrial trans membrane potential, and decrease in Mcl-1 demonstrate the anti-apoptotic effects of CAPE [58]. The immunosuppressant action of CAPE suggests inhibition of T-cell activation and release of IL-2 [62]. In a study CAPE attenuated the release of TNF-α and IL-1 in LPS stimulated neutrophils [63]. The cardio protection, nephron protection, Hepato protection and prevention of bone-marrow toxicity from several chemotherapeutic toxic agents like cisplatin, bleomycin, tamoxifen, doxorubicin and methotrexate in humans and animals show the pro-survival effects of CAPE [58]. It is demonstrated that CAPE can directly suppress the iNOS gene expression through modulation of NFκB sites in promoter region of iNOS gene [64]. The iNOS mediated pathogenic rise in NO is detrimental for the neuron survival.

The antioxidant activity of CAPE owing to the catechol ring [65] is found better than that of vitamin E [66]. The existing data indicates that CAPE reduces lipid peroxidation, and enhances the endogenous antioxidant defence (e.g. glutathione, SOD, catalase, glutathione peroxidase) against streptozotocin induced diabetes [67] and thermal trauma [68]. The antioxidant activity of CAPE is attributed to activation of Nrf2/ARE pathway [69] that is a downstream target of PI3-kinase-Akt signalling. The inhibition of Kelch-like ECH-associated protein 1 (a repressor of Nrf2) by CAPE

is another mechanism for activation of Nrf2 signalling [70]. The neuroprotective potential of CAPE was evaluated in 3-nitropropionic acid (3-NP) induced striatal toxicity in male C57BL/6 mice, a model of Huntington's disease. The study depicted direct free radical scavenging activity of CAPE, and reduction in neuro degeneration, LDH release and microglia activation by CAPE against 3-NP [57]. CAPE prevents the mouse HT22 hippocampal neurons from acrolein toxicity through reduction in ROS and increase in GSH levels [71]. The protection of dopaminergic neurons against LPS/IFN-γ toxicity by CAPE is attributed to increase in HO-1 and release of BDNF [72]. CAPE has shown substantial neuro protection against other neurotoxins like pentylenetetrazole [73] and cigarette smoke and mouse model of amyotrophic lateral sclerosis [74].

A recent study demonstrated that CAPE protected the memory functions of mice in $A\beta_{1-42}$ oligomers induced AD model. CAPE (10 mg/kg) countered the oxidative stress, inflammation and triggered activation of Nrf2/HO-1 pathway through GSK-3β modulation in hippocampus of $A\beta_{1-42}$ oligomers treated mice [75]. Protective action of CAPE on PC12 cells against dopaminergic neurotoxin MPP^+ has been observed. CAPE increased the neuritogenesis, synaptogenesis; expression of GAP-43, synapsin and synaptophysin in MPP^+ treated PC12 cells [76]. In an animal model of Parkinson's disease CAPE bestowed considerable neuro protection against MPTP by inhibiting the expression of iNOS, caspase-9, and release of cytochrome c and Apoptosis Inducing Factor (AIF) from mitochondria [77]. In addition it has been stressed that CAPE can prevent mitochondrial dysfunction which is a key feature in AD pathology [78].

An *in vitro* study demonstrated CAPE induced decrease in BACE-1 activity and increase in α-secretase activity in hippocampal cell culture [71]. Amelioration of insulin induced glucose metabolism and decrease in expression of pro-apoptotic factors by CAPE have been associated with PI3-kinase-Akt pathway [79,80]. CAPE restores the TBI triggered disruption of neurovascular integrity and relieves the cerebral vasospasm which implies involvement of eNOS-NO signalling through PI3-kinase-Akt pathway [81,82].

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