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Review Article

Promising role of Carob (*Ceratonia siliqua* L) phytochemical components against neurotoxicity induced by monosodium glutamate

Abstract

The phytochemical constituents of Carob (*Ceratonia siliqua* L) showed therapeutic medical importance especially concerning neurotoxicity which represents the major public health problem. Neurodegenerative disorders are developed from different metabolic diseases and chemical component such as monosodium glutamate. It is the widely used chense sodium salt of the non-essential glutamic amino acid. It is one of the most popular flavor enhancer. Monosodium glutamate is excitatory neurotransmitter in brain, increased the perception of wetness and saltiness as a taste sensation UMAMI. Treatment with the carob extract or their phytochemical constituents either protect or ameliorates these diseases which is promising.

Introduction

Phytotherapy is of medical importance due to the side effects of pharmaceutical drugs. Knowing the phytochemical components of plants and pharmacologic action of each constituents and standardization procedures for use and its clinical effective. Neurodegeneration is the progressive breakdown of neurons leading to neurological disorder such as Parkinson's and Alzheimer's, and Huntington's diseases [1]. Monosodium glutamate (MSG) is excitatory neurotransmitter in brain, mediating fast synaptic transmission and increased the perception of wetness and saltiness as a taste sensation UNAMI [2]. It is a water soluble bad chemical component showing a potent UNAMI comes from the fifth taste receptors on the tongue which are quite different from that of the brain [3]. This led individual to consume a large amount of food due to its characteristic flavor enhancer which alter physiological processes, especially the functioning of the nervous system [4,5].

The glutamate is produced by the brain and serves as a as a nerve impulse transmitter in the brain to manage the functional activity of body organs [6]. The brain generates its n glutamate with an intricate own transport system to protect the brain cells. The excess circulating glutamate derived from the food material is kept separated from the glutamate inside the brain. The shifted glutamate concentration being increased in the intracellular region and low in the extracellular ones. This may exert strokes and damage the blood–brain barrier [7,8].

Administration of glutamate to experimental animals and humans [9,10], led to the development of depression and anxiety in the form of imbalance of mood and emotions, abnormalities of limbic system structures [11], and disruption of the hypothalamic pituitary adrenal axis [12]. Glutamate was linked to many diseases such as Alzheimer's disease, Huntington's disease and Wernicke's encephalopathy [13,14], as well as retinal ischemia leading to loss of ganglion cells [15]. In vitro studies of MSG (20 mM) on astrocyte culture cells revealed increased a liberation of reactive oxygen species and apoptotic cell death [16].

The present review aimed to illustrate the neurologic disorders induced by monosodium glutamate and the promising role of carob extracts or their phytochemical constituents in treating or protecting the brain disorders.

Carob (*Ceratonia siliqua* L)

Carob fruit of *Ceratonia siliqua* L. is belong to Leguminosae family. It is widely cultivated in the Mediterranean region for ornamental and industrial purposes. Carob fruit is dark–brown with an elongated or curved shape and composed of two main components: the pulp (90%) and the seeds (10%). Its seeds contain approximately 90% galactomannans and used in food industry [17]. Papagiannopoulos et al. [18], reported that the carob pods contain 448 mg/kg polyphenols including gallic acid, hydrolyzable and condensed tannins, flavonol–glycosides, and traces of isoflavonoids. Carob powder contained Eleven

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phenolic compounds such as pyrogallol, catechol, chlorogenic and protocatechuic, coumarin, cinnamic, ferulic, gallic acid and vanillic are detected [19].

Sucrose represents about 70% of the carob pulp and composed mainly of fructose and glucose [20]. Protein is reached to about 7.6% and fat content is about 0.2 – 2.3% [21]. Fiber, cyclitols, polyphenols and tannins are the main constituents of carob fruits which possess anti-cancer, anti-diabetes, anti-diarrheal and anti-hyperlipidemic activity [22,23]. Also, carob is rich in micronutrients like amino acids including aspartic acid, glutamic acid, serine, glycine, histidine, arginine, threonine, alanine, tyrosine, valine, proline, methionine, isoleucine, leucine, cysteine, phenylalanine and lysine [24].

The carob powder is characterized by its natural sweetener with flavor and free from caffeine and theobromine which makes it suitable to be used in Europe instead of chocolate. It is widely used as a cocoa substitute in baking, cereal bars, ice creams and light products as CarovitTM (Alimcarat S.L., Spain) [25], as well as in cereal-derived foods for celiac people [26].

The pod and leaves of Ceratonia siliqua (carob) are rich in active compounds such as peripheral benzodiazepine receptor widely used as chemopreventive agents [27]. Its fruit is rich in flavonoids and condensed tannins [28], as well as contained of about 96.5% of protein and rich in glutamic acid, aspartic acid and arginine [29].The carob pods is a rich source of polyphenol reaching approximately 80% with high antioxidant activity [20,23,30]. Also, it is rich in linoleic and alpha-linolenic acid [31]. The antioxidant of ethyl acetate extracts of carob tree leaves scavenge 1,1-diphenyl-2-picrylhydrazyl liberated radicals than the diethyl ether and dichloromethane extracts [32].

Aqueous extract of carob (Ceratonia siliqua L.) (600 mg/kg body weight) pods protected against ethanol (6 g/kg bw)-induced hepatotoxicity characterized by elevated hepatic aspartate aminotransferase and alanine aminotransferase, lipid peroxidation and depletion of the antioxidant enzymes [33].

Ceratonia siliqua extracts, showed a potential DNA damage of murine leukaemia cells L1210 as well as protect against oxidative stress of H_2O_2 [34].

Monosodium glutamate related neurotoxicity

Monosodium glutamate (MSG) is the sodium salt of the glutamic acid. It is a non-essential amino acid, having unique flavor-enhancing widely used as a food additive (Figure 1).
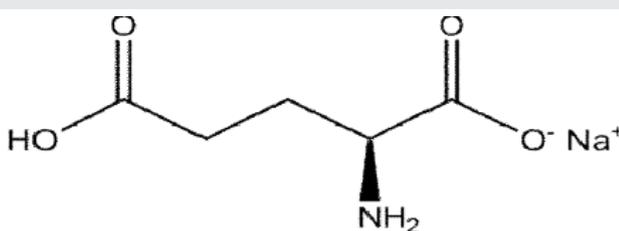

Figure 1: Chemical structure formula of monosodium glutamate.

Glutamic acid is abundant in protein rich food stuffs such as milk, meat, fish, cheese, tomato products, and soy sauces. It is one of the most popular flavor enhancer. It is excitatory neurotransmitter in brain, mediating fast synaptic transmission in one third of all CNS synapses. It increased the perception of wetness and saltiness as a taste sensation UMAMI and is used in many commercial packed food (Maggi Noddles, Knorr Soup etc), restaurant and household cooking. It is a natural components of many fermented or aged foods, such assoy sauce, fermented bean paste, and cheese, and is also in yeast extract [1]. In European countries, the intake of glutamate from food ranged from 5 to 12 g/day compared to Asian countries which reached from 1.2 to 1.7 g/day [35].

Administration of glutamate disrupted the biological function in experimental animals and humans causing depression and anxiety which are characterized by imbalance of mood and emotions, abnormalities of limbic system structures, associated by reduction in monoaminergic signaling, with depletion of serotonin (5-hydroxytryptamine, 5-HT) (Meyer et al. 2006).

Glutamate-induced neurotoxicity characterized by neuronal damage [36,37], via intracellular increase of Ca2C levels through increase liberation of the N-methyl-D-aspartate receptors [38], or enhancement secretion of glutaminase utilizing glutamate as a substrate [39].

Glutamate released its signal through ionotropic and metabotropic glutamate receptors. Ionotropic receptors promote the ion channel pore that activates when glutamate binds to the receptor meanwhile metabotropic receptors enhanced ion channels on the cell membrane via a signaling cascade that form G-protein-coupled receptors primarily on neurons and glial cells [40,41]. Ionotropic receptors divided into four subtypes depending on their ligand binding properties such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptors), kainite receptors, N-methyl-D-aspartate receptor (NMDA receptors) and delta receptors, They promote the excitatory synaptic transmission in the central nervous system for synaptic plasticity, which is important for learning and memory [42]. Thee synaptic receptors located primarily on the membranes of neuronal cells. The interactions of glutamate with its ionotropic NMDA receptors led to neurotoxic changes due to the release excessive amounts of calcium to enter the neuron [43,44] and consequently contributed to the development of neurodegenerative disorders [45-47].

The receptor AMPA located in the different parts of the brain mediating the synaptic transmission which categorized into four subunits including GluR1, GluR2, GluR3 and GluR4. Its dimerization start in the endoplasmic reticulum [48].

The second type is kinate receptors. They have both presynaptic and postsynaptic actions with a limited distribution in the brain comparing to the other types of ionotropic receptors. Kainic acid induced seizures, through the activation of kainate receptors containing both GluK2 subunit

and AMPA receptors [49], *N*-methyl-D-aspartate receptor is a glutamate receptor and ion channel protein found in brain cells. It is activated when glutamate and glycine (or D-serine) bind together and activated for permeability of positively charged ions to pass through the cell membrane. The NMDA receptor is responsible for controlling synaptic plasticity and memory function [50].

Ionotropic glutamate delta 2 receptor is a protein that encoded in the *human GRID2* gene. The receptors are expressed mainly in Purkinje cells in the cerebellum [51], and promote the synaptogenesis, synaptic plasticity, and motor coordination [52].

Glutamate is a naturally occurring amino acids reaching to 4 to 15% of all amino acids [53], and its level in the brain attained 10^4 μM. It is synthesized by neurons and not cross the blood–brain barrier [54]. It is responsible for maintaining developmental plasticity and memory [55]. However, intake diet containg MSG is followed by an increase in plasma glutamate level for 1 to 3 hours [56]. The first step of excitotoxicity is the release of Mg(2+) from mitochondria to the cytosol and accumulation of Ca(2+) [57]. Also, glutamate is then converted into glutamine in astrocyte through a glutamine-reuptake system and loss its function [58]. Most of the excitatory neurons in the brain are glutamatergic; moreover, it is found that many of the nerve-endings release glutamate. Presynaptic depolarization maintain vesicles to liberate glutamate into the synapses through exocytosis, which consequently bind to the post-synaptic ionotropic receptors and depolarize the synaptic cell. Neuronal cell death is come after the liberation of glutamate into the synaptic space which stimulates glutamate receptors of the NMDA subtype, leading to an influx of calcium and sodium and depolarization of the postsynaptic neuron. NMDA receptors become inactive for glutamate transport into cells. Neuronal ischemia impaired cell respiration through depletion of ATP coincides with failure of glutamate transport and neuronal depolarization. These led to activate NMDA R causing release of calcium, mitochondrial dysfunction and production of reactive oxygen species the cause of inflammation and neuronal cell death [59,60] (Figure 2).
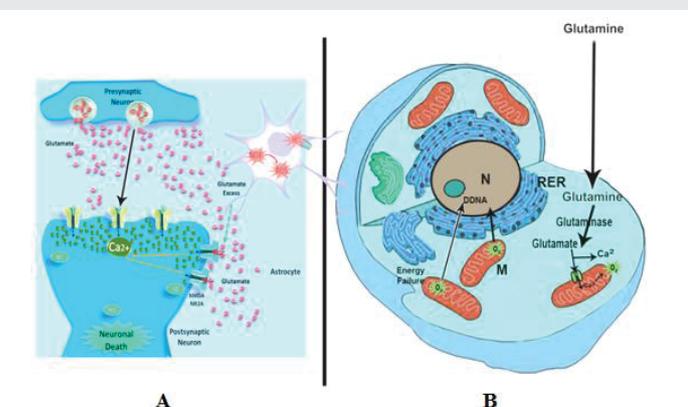
Figure 2: A. Synaptic vesicle showing hypertrophied astrocyte and release of glutamate which interfere with the synaptic vesicle. B. Showing architecture structure of cell illustrating the of glutamate in damaging mitochondria (M) and release of free radicals which induce cell death.

Glutamate is linked to many neurological diseases such as Alzheimer's disease, Huntington's disease, glaucoma and Wernicke's encephalopathy [61]. Also, it is associated with "kindling" limbic seizures in hippocampus of rodent and cerebral cortex of patients via repeated electrical stimulation dependent on the activation of N-methyl-D-aspartate (NMDA) receptors. Microdialysis increased the extracellular concentration of glutamate and aspartate before or during seizure onset, as a result of either enhanced amino acid release or impaired uptake contributed to seizure occur [60].

In vitro studies revealed that the excitatory amino acids such as L-aspartate and L-glutamate and micromolar kainic acid induced massive shedding of the rod photoreceptor disc and loose the contact with the pigment epithelium in eye cups of Xenopus laevis [62]. In postnatal rodents, daily injection of MSG led to impairment of vision via increase of retinal lesions and optic nerve degeneration [63]. Acute retinal ischemia was incorporated in retinal damage associated with accumulation of glutamate in aqueous humor [64] leading to retinal detachment in patients [65], and increase retinal damage in neonatal rats [66].

Intra-vitreal injections of glutamate induced overexpression of the excitatory amino acid transporter 1 (EAAT-1), thinning of retina and reduction of ganglion and increase glial fibrillary acidic protein (GFAP) in Müller cells, CD11b in microglia, and iNOS and GRP78 in glial cells [67]. MSG-treatment induced a marked increase in β-amyloid in the hippocampus by >4-fold and >5-fold after 10 days in both oral and subcutaneous administration [68].

Monosodium glutamate have the great ability to penetrate the placental barrier and accumulate in the embryonic tissues especially in the brain tissue of fetal mice [69], and cause acute necrosis of the acetylcholinesterase-positive neurons in the area postrema in the mother rats and their fetuses [70]. Monosodium glutamate (4mg/g body weight)- treatment decreased the antioxidant capacity of midbrain region and increased lipid peroxidation [71], via increasing thiobarbituric acid reactive substances and delay the acrophases of GSH and catalase as a result of increased glutamate levels [72].

Also, it led to an increase of neuronal cell death of the medial basal hypothalamic (arcuate nucleus) neurons of neonatal mice associated with overexpression of the *N*-methyl-D-aspartate glutamate receptor subunit of the damaged neurons [73].

Monosodium glutamate and amyloid deposition

Monosodium glutamate (MSG) is the main cause of excitotoxicity associated with brain disorders including brain ischemia and neurodegenerative disorders [74]. In Alzheimer's disease temporal cortex, there was a marked decrease of glutamate uptake comparing with non-changed NMDA receptor [75]. Its treatment led to stimulation of neurotransmitters and consequently nitric oxide (NO)-mediated neurotransmission pathway as a result of increased NO synthase produced from the arginine. Increased release of NO in endothelial cells vasodilated neighboring vascular smooth

muscle cells and consequently induce Chinese restaurant syndrome and/or glutamate-induced asthma, 'hot dog headache, and Alzheimer's disease [76], Acute MSG(500 mg/kg i.p.) administration disrupted norepinephrine, dopamine, glycine , glutamate, asparate neurotransmitter contents led to apparent reduction in both the hypothalamus (16%) and cerebellum of adult rats, but was increased in aged rats (24 month old). Cortical serotonergic deficits were reported in aged rats. Aged rats possessed alterations in amino acids, especially the excitatory amino acids such as glutamate and aspartate [77]. Glutamate excitotoxicity is greatly associated with neurodegenerative disorders including amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease [78].

Dief et al. [58], reported that oral or subcutaneous administration of MSG increased b-amyloid accumulation in the rat hippocampus and FAS ligand and decreased adenosine monophosphate-activated protein kinase which is associated with increased anxiety. Soluble oligomers of the amyloid-β peptide (AβOs) was found to accumulate in brain of Alzheimer's disease and promote extracellular accumulation of glutamate and d-serine, a co-agonist at glutamate receptors of the N-methyl-d-aspartate subtype (NMDARs), in hippocampal neuronal cultures [79]. Amyloid-β peptide was involved in generating reactive oxygen species (ROS), leading to inhibition of the glutamate transporter protein by the glutamatergic neurons [80].In patients with amyotrophic lateral sclerosis, Alzheimer's and Huntington's disease, there was a marked decrease of transmission of glutamate uptake in synaptosomes from spinal cord, motor cortex, and somatosensory cortex, and missing in visual cortex, striatum, or hippocampus [81].

Administration of monosodium glutamate to rat newborn led to dramatic cerebral and striatum neuronal cell death by either apoptosis or via MAPK p38 pathway activation in 8, 10, and 14 day-old. This drastic alterations was inhibited by pre-treatment with SB203580 (p38 inhibitor). These findings led the authors to explain that neuronal death induced by glutamate was promoted by p38 pathway activated by TNF-alpha [82].

Individual or combined monosodium glutamate (8mg/kg) and aspartame-treatment (32 mg/kg) for one month led to significant disruption of cognitive responses, memory retention and learning capabilities as well as decreased significantly the levels of neurotransmitters (dopamine and serotonin) and increased lipid peroxidation [83].

Investigating hippocampal slice cultures of rat, characterized by high branched axons and overexpression of glutamate transporters. Using confocal microscopy, the mobility of mitochondria within the astrocytic processes and neuronal dendrites was markedly greater compared to astrocytes. Inhibition of glutamate transport and Na(+)/Ca(2+) exchange activated the mobility of mitochondria in astrocytes [84].

Six-month-old mice treated with monosodium glutamate (MSG) developed a model of obesity-induced pre-diabetes, characterized by increased tau phosphorylation at Ser396 and Thr231 in the hippocampus which contributed to the formation of neurofibrillary tangles related to cognitive dysfunction and Alzheimer's disease. Subcutaneous administration of a lipidized analog of prolactin-releasing peptide (palm-PrRP31) for two weeks increased phosphorylation of the insulin cascade kinases PDK1 (Ser241), Akt (Thr308), GSK-3β (Ser9) and attenuated phosphorylation at Ser396, Thr231, and Thr212 of tau kinases in the hippocampi [85].

Monosodium glutamate treatment increased the [3H] serotonin (5-HT) uptake in the cerebral cortices of rats and induced a deregulation of hypothalamic pituitary adrenal axis function (by increasing serum MSG treatment increased the [3H]5-HT uptake in the cerebral cortices of rats and induced a deregulation of HPA axis function (by increasing serum ACTH and corticosterone levels) [86].

The brain need high-energy requirements and blockage of blood flow causes rapid deterioration of brain cells. Acidosis and liberation of excess glutamate are of two excitotoxic mechanism for induction of brain ischemia. Overexpression of channelrhodopsin-2 in glial cells led to glial acidification and to release of glutamate and increase the severity of brain damage. However, glial alkalization via optogenetic activation of a proton pump, archaerhodopsin (ArchT), led to cessation of glutamate release and improve the disease [87].

High concentration of glutamate (Glu) is excitotoxic for nervous system structures. This may lead to glial reactivity ie. increased expression of glial fibrillary acidic protein (GFAP) and S100β protein, and also to hypertrophy and proliferation of cells which are determined by the presence of Ki-67 antigen. Its administration to young rats (2 g/kg b.w. and 4 g/kg b.w.) caused marked alterations of astrocytes with the GFAP expression in the SLM of the hippocampal CA1 region. Also, there is marked increase in the number of GFAP and S100β immunopositive astrocytes and nuclei with Ki-67 expression [88].

The cellular and optical densities of GFAP-immunoreactive sections of suprachiasmatic nucleus were significantly increased in neonatal rats received monosodium glutamate (3.5 mg/g/day,sc) for 3-10 days [89].

In vitro studies of MSG (20 mM) on astrocyte culture cells revealed increased liberation of reactive oxygen species and apoptotic cell death and attenuated by N-acetylcysteine (500 µM)-treatment restoration of mitochondrial membrane potential and intracellular reduced glutathione and up-regulation of endoplasmic reticulum stress markers [90].

Within the neurons, there is a greater percentage of mobility of mitochondria than in astrocytes and are present at sites of high metabolic activity. Glutamate transport and the concomitant activation of the Na(+)/K(+)-ATPase represent a substantial energetic demand on astrocytes. Similar to inhibitory effect of glutamate, inhibiting neuronal activity with tetrodotoxin (TTX) increased the percentage of mobile mitochondria in astrocytes [91].

Phytotherapy of glutamate neurotoxicity

Phytotherapy involve the wide application of medicine which is of great importance and less side than the organochemical compounds. Hydrogen peroxide and peroxynitrite impaired glutamate uptake by astrocytes dependent on the concentration level and increased following inhibition of catalase. This led to marked increase of neurotoxicity. Carob-supplementation before or followed monosodium glutamate treatment reduced the accumulation of hydrogen peroxide in the extracellular space of the assayed brain tissues, and exerted a potential therapeutic effects [92].

Administration of MSG to neonatal rats increased body mass index and serum glucose Špolcová et al. [85], mentioned abnormally hyperphosphorylated tau protein at Ser396 and Thr231 in the hippocampus in monosodium glutamate-obese mice post-6-month-treatment and improved post palm-PrRP31 and liraglutide-treatment.

Cinnamon (CE) (the phenolic component of carob fruit) supplementation improved Alzheimer's disease (AD) previously induced by MSG-treatment for 10 months. It is characterized by insulin sensitivity, decreased phosphorylated glycogen synthase kinase-3β (pGSK3β), and increased the cholinesterase activity, cognition and hippocampus neuronal cell loss in non-transgenic rat model of AD rats [93].

Ferulic acid (carob polyphenol) [21], is a novel neuroprotector. It is protected against the MSG-induced hippocampal lesions characterized by intracellular edema, degeneration and necrosis of neurons, and hyperplasia [94]. It inhibited apoptotic morphology, active caspase-3 protein expression, and PARP cleavage induced by glutamate-treatment [95].

Many plant- extracts and their chemical constituents are reported to have beneficial effects on brain function [96], (Kennedy and Wightman, 2011). Carob-supplementation before or followed monosodium glutamate treatment reduced the accumulation of hydrogen peroxide in the extracellular space of the assayed brain tissues, and exerted a potential therapeutic effects [97].

Several phytochemical components such as ferulic acid [98], and epigallocatechin-3-gallate [99], protects against free radical mediated cell damage. Also, carob constituents ferulic acid improved AD through reduction of amyloid beta (Abeta) and AChE levels in the hippocampus related to development of cognition induced by glutamate [100].

Alzheimer and Parkinson are developed from increased oxidative stress. Ferulic acid is a natural antioxidant [101]. Its clinical importance in treatment Alzheimer's disease resulted from maintaining cell viability, increased superoxide dismutase, and inhibited the production of tumor necrosis factor-α and interleukin -1β induced amyloid-beta peptide 25-35(Aβ25-30) formation [102].

One-year-old mice with established β-amyloid plaques received daily doses of OG and FA alone or in combination for 3 months. APP/PS1 mutant transgenic mice received dimeric derivatives of ferulic acid KMS4001 at doses of 3 and 30mg/kg/day via drinking water showed the significantly enhanced novel-object recognition memory at both 1.5 and 3 months and decreased amyloid peptide Aβ1-40 and Aβ1-42 levels in the frontal cortex [103].

PSAPP mice receiving combination therapy of octyl gallate (OG) and ferulic acid (FA) for 3 months had statistically significantly improved cognitive function through reductions of β-amyloid deposits in brain parenchymal and cerebral vascular tissues the main cause of Alzheimer's disease [104]. A series of novel Novel Tacrine-Ferulic Acid Hybrids [105], and ferulic acid-O-alkylamines derivatives were proved to be a good choice against Alzheimer's disease [106].

Cinnamon (CE) (the phenolic component of carob fruit) supplementation improved Alzheimer's disease (AD) induced by MSG-treatment in non-transgenic rat model of AD rats [107].

Chloroform: methanolic (80:20) extract of C. asiatica (CA; 100 and 200 mg/kg),improved monosodiumglutamate impaired locomotor activity and CAl a region of the hippocampus coincides with impaired lipid peroxides and ameliorated catalase, super oxide desmutase and lipid peroxides levels in hippocampus and striatum regions [108]. MSG (2 g/kg, 7 days i.p.) -treatment for seven days decreased the activities of SOD and increased malondialdhyde in serum, brain, liver and kidney of Sprague-Dawley female rats and improved after tannic acid-treatment (50 mg/kg, 3 days) [109].

Catechol is known as pyrocatechol or 1,2-dihydroxybenzene, Its derivatives including 3-methylcatechol, 4-methylcatechol, and 4-tert-butylcatechol exerted downregulation of lipopolysaccharide (LPS)-induced NO and tumor necrosis factor (TNF)-alpha production in BV-2 microglia cells through inhibition of inducible nitric oxide synthase (iNOS) and TNF-alpha at mRNA or protein levels [110].

Protocatechuic acid was found to protect neurotoxicity against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) through the depletion of dopamine (DA) and its metabolites in striatum. It is ameliorated the histopathology in substantia nigra and the downexpression of tyrosine hydroxylase in f C57BL/6J mice [111].

Chlorogenic acid a polyphenol of carob fruit protect against glutamate-induced neuronal cell death in invitro cultures of mouse cerebral cortex through inhibition of release of intracellular concentrations of Ca(2+) and nitric oxide the causes of neuronal cell death [112].Several dtudies reported that the Chlorogenic acid exerted therapeutic potential including neuroprotection, cardioprotection, weight loss, chemopreventive properties, anti-inflammatory activity, decreased blood pressure, decreased diet-induced insulin resistance, decreased blood pressure, anxiolytic effects, and antihyperalgesic effects [113]. The neuroprotective properties of Chlorogenic acid is occurred by inhibiting acetylcholinesterase and butyrylcholinesterase, activities as well as preventing oxidative stress-induced neurodegeneration [114,115].

Glutamate and nitric oxide (NO) are active regulators of dendrite and axon development in the brain. Excess glutamatergic stimulation induced neuronal atrophy and shrinkage with eventual neurodegeneration and cell death. Twenty-four hours-treatment of cultured primary cortical rat neurons with glutamate (500μM) or N-methyl-d-aspartate (NMDA) (100-500μM) combined with glycine impair neurite outgrowth [116].

It is known that glutamate is the main excitatory neurotransmitter in the brain and over-activation of the glutamate receptors, NMDA, AMPA and kainate (KA), led to neuronal death in epilepsy, seizures and neurodegenerative diseases. Mitochondria is responsible for neuronal excitability, including managing Ca(2+) homeostasis and ATP production to maintain Na(+)K(+)-ATPase in the central nervous system. Also, it is the primary site of reactive oxygen species production enhancing cell damage and causing oxidative stress. Resveratrol was found to decrease intracellular ROS production, through NMDA, AMPA/KA, intracellular Ca(2+) and the heme oxygenase 1 (HO1) pathway [117].

The author finally concluded that carob micro-constituents showed phytotherapeutic potential against neurotoxicity.

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