Genus *Boswellia* as a new candidate for neurodegenerative disorders

Aarezoo Rajabian 1, HamidReza Sadeghnia 2,3, Sahar Fanoudi 2, Azar Hosseini 1*

1Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran
2Department of Pharmacology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3Division of Neurocognitive Sciences, Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad

**Abstract**

Neurodegenerative diseases, characterized by progressive loss of neurons, share common mechanisms such as apoptotic cell death, mitochondrial dysfunction, inflammation, and oxidative stress. Genus *Boswellia* is a genus in the Burseraceae family. It comprises several species traditionally used for treatment of chronic inflammatory diseases, cerebral edema, chronic pain syndrome, gastrointestinal diseases, tumors, as well as enhancing intelligence. Many studies have been carried out to discover therapeutic approaches for neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, multiple sclerosis and amyotrophic lateral sclerosis, stroke, and concomitant cognitive deficits. However, no curative treatment has been developed. This paper provides an overview of evidence about the potential of the *Boswellia* species and their main constituents, boswellic acids, as modulators of several mechanisms involved in the pathology of the neurodegenerative diseases. *In vitro*, animal, and clinical studies have confirmed that *Boswellia* species contain bioactive components that may enhance cognitive activity and protect against neurodegeneration. They exert the beneficial effects via targeting multiple pathological causes by antioxidative, anti-inflammatory, antiamyloidogenic, and anti-apoptotic properties. The *Boswellia* species, having neuroprotective potential, makes them a promising candidate to cure or prevent the neurodegenerative disorders.

**Introduction**

Neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis, and stroke are age-related disorders (1, 2). A number of common pathophysiological features have been proposed for these diseases, including elevated oxidative/nitrosative stress, mitochondrial dysfunction, protein misfolding/aggregation, synapse loss, and decreased neuronal survival (3, 4). Considering limitation of effective treatments for these diseases, there is an urgent need for new strategies using natural products that act through novel biological targets (5). The genus *Boswellia* belonging to the Burseraceae family comprises about 20 species. Species include *B. serrata*, *B. sacra*, *B. frereana*, *B. neglecta*, *B. microphylla*, *B. papyrifera*, *B. ogadensis*, *B. pirottiae*, *B. rivae*, *B. madagascariensis*, *B. socotrana*, *B. popoviana*, *B. nama*, *B. ameero*, *B. bullata*, *B. dioiordis*, *B. elongata*, and *B. ovalifoliatata*. *B. neglecta* and *B. dalzielii* (6, 7). The genus is widespread in dry areas such as Arabia, northeastern coast of Africa, and India (8). The species have been useful in traditional medicine for treatment of inflammatory diseases, including asthma, arthritis, cerebral edema, chronic pain syndrome, gastrointestinal disease, tumors, and for enhancing memory and learning function (9-11). Frankincense, oleo-gum resins obtained from the genera *Boswellia*, is composed of essential oil (5-9%), mucopolysaccharides (20-23%), and resin (60%) (12, 13). The resinos part contains tetracyclic and pentacyclic triterpene acids. Boswellic acids (BAs) are considered the main biologically active components among the triterpene acids (Figure 1) (8, 14). Frankincense is responsible for anti-inflammatory and anti-cancer effects of BAs (15, 16). The anti-inflammatory mechanisms are applied through inhibition of 5-lipoxygenase, cathepsin G, and microsomal prostaglandin-E synthase (mPGES)-1 (17). Other mechanisms include suppression of nuclear transcription factor κB (NF-κB) and pro-inflammatory cytokines such as tumor necrosis factor (TNFα), interleukin (IL)-1β, IL-2, and IL-6 (15, 17). Also, BAs lead to induction of apoptosis in cancer cells via activation of caspase-8 and inhibition of topoisomerases-1 and H-alpha (16, 18).

In this review, the therapeutic effects of *Boswellia* and its major constituents on various neurodegenerative disease models have been summarized (Figure 2). Herein, pharmacological effects of the genus *Boswellia* in neurodegenerative diseases were classified as follows: 1. Alzheimer’s disease 2. Parkinson’s disease 3. Cognitive dysfunction 4. Multiple sclerosis 5. Central nervous system trauma and brain ischemia

**Methods**

To prepare this review, an online search was performed by using some databases, including PubMed, Google Scholar, Science Direct, and Scopus. This review mainly

*Corresponding author: Azar Hosseini. Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +98-38002283; Email: hoseiniaz@mums.ac.ir*
focuses on the therapeutic/or pharmaceutical effects of genus Boswellia and its main active constituents, AKBA, on neurodegenerative diseases (such as AD, PD, MS, and cerebral ischemia). The search terms included "Neuropharmacology", "Learning", "Memory", "Neurocognitive", "Neurodegenerative", "Neurological disorders", "Alzheimer's disease", "Parkinson's disease", "Multiple sclerosis", "Cerebral ischemia", "Boswellia", and "AKBA (3-acetyl-11-keto-β-boswellic acid)"

Alzheimer’s disease

Alzheimer’s disease is the most common type of neurodegenerative dementia in older people (19). It is characterized by amyloid-beta (Aβ) accumulation in plaques and neurofibrillary tangles of tau protein forming neurofibrillary tangles (20). Aβ aggregation and neurofibrillary tangles induce neuron and synapse loss and gross degeneration in the temporal lobe, parietal lobe, as well as parts of the frontal cortex and cingulate gyrus (21). The pathological alterations cause progressive memory loss, cognitive impairment and the inability to perform daily activities (21, 22). Aβ toxicity, cholinergic dysfunction, oxidative damage, apoptosis, synaptic dysfunction, and senile plaque-induced inflammation have been postulated to be involved in pathogenesis AD (21, 23). The possible prophylactic and therapeutic effects of B. serrate using an animal model AD induced by AlCl₃ (17 mg/kg for 4 weeks, orally) were assessed. In this study, rivastigmine (0.3 mg/kg/day), as standardized medicine, and B. serrata (45 and 90 mg/kg/day) were given for 2 weeks before AlCl₃ administration to rats. The results revealed that activity of rats increased, while the duration taken by rats to reach food in the T-maze test decreased. According to biochemical analysis, treatment with B. serrate led to elevation of acetylcholine (ACh) levels while acetylcholine esterase (AChE) activity was suppressed in brain homogenates. The histopathology findings indicated that amyloid plaques reduced in the hippocampus (24). In a preclinical study, therapeutic potential of B. serrate against neurodegeneration using an AlCl₃-induced rat model of AD was claimed. Following treatment of AD animals with B. serrata as resin methanolic extract (137.5 mg/kg, 3 months, orally), Aβ plaques in histopathological samples disappeared. Biochemical analysis showed brain and serum levels of AChE, C-reactive protein (CRP), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), monocyte chemoattractant protein-1 (MCP-1), and leukotriene B4 (LTB4) were suppressed while brain ACh and Bcl-2 were elevated. The data represented preventing efficacy of B. serrata against neuro-inflammatory and apoptosis insults (25). Also, co-administration of ginger (Zingiber officinale, 108 and 216 mg/kg) and B. serrata (45 and 90 mg/kg) in rats treated with ACl₃. The B. serrata and ginger improved histopathologic changes and also behavior stress tests, including activity cage, rotarod, T-maze, as well as restoring ACh and AChE levels in brain homogenate (26). Recent evidence revealed that insulin resistance and metabolic dysfunction play an important role in the pathology of sporadic Alzheimer’s disease (sAD) (27). Intracerebral-ventricular injection of streptozotocin (STZ, 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose) is applied to mimic sAD (28). STZ -induced insulin resistance causes several features characterizing AD including oxidative stress, neuroinflammation, and dysfunctions in adult neurogenesis that are followed by progressive deficits in learning and memory (29-31). A study explored whether aqueous extract of frankincense from B. carteri could have therapeutic effects on STZ- induced memory impairment. The evaluation of learning using passive avoidance task (PAT) indicated that chronic administration of aqueous extract of frankincense (50 mg/kg, 42 days) improved memory in rats receiving STZ (1.5 mg/kg/2 μl/side, i.c.v.) in a time-dependent manner (32). SuHeXiang Wan (SHXW) is a traditional Chinese medicine comprising Liquidambar orientalis, Saussurea lappa, Aquilaria agallocha, Santalum album, B. carteri, Eugenia caryophyllata, Cyperus rotundus, Sytrax benzoïn, and Dryobalanops aromatica that has been used orally for the treatment of seizures, infantile convulsions, and stroke (33). The potential beneficial effects of SHXW essential oil were investigated on SH-SYSY neuroblastoma cells and animal AD model induced by Aβ1-42 in mice. SHXW essential oil attenuated Aβ-induced cytotoxicity in SH-SYSY cells through inhibition of apoptosis and ROS generation. Up-regulation of heme oxygenase-1 (HO-1), nuclear factor erythroid 2-related factor (Nrf2) expression, and increased Bcl-2/Bax...
Table 1. A summary of pre-clinical and clinical studies on protective effects of genus* Boswellia* in the neurodegenerative diseases

| Protective agent/dose/reference | Study design or experimental model | Main results |
|--------------------------------|-----------------------------------|-------------|
| *B. serrata* (45 and 90 mg/kg/day, 2 weeks) (24). | Animal model AD induced by Aβ(1-42) in rat | Elevated ACh, suppressed AChE activity, improved histopathology changes, and reduced Aβ plaques in the hippocampus |
| *B. serrata* resin methanolic extract (137.5 mg/kg, 3 months) (25). | Animal model AD induced by Aβ(1-42) in rat | Induced anti-neuro-inflammatory and anti-apoptotic properties indicated by suppression of serum level of AChE, CRP, NF-κB, MCP-1, LTB4, and elevation of brain ACh and BCh E-2. Aβ plaques disappeared |
| Co-administration of ginger (*Zingiber officinale*; 216 mg/kg) and *B. serrata* (45 and 90 mg/kg) (26). | Animal model AD induced by Aβ(1-42) in rat | Improved histopathologic changes and behavior stress tests including activity cage, rotarod, and T- maze as well as restored ACh and AChE level in brain homogenate |
| Frankincense aqueous extract (50 mg/kg, 42 days) (32). | STZ (1.5 mg/kg/2 µl/side, i.c.v) - induced memory impairment | Evaluation of learning using passive avoidance task and improvement of memory |
| Sikkim essential oil (1, 10, 100 µg/ml) (34). | SH-SY5Y neuroblastoma under Aβ(1-42) (25 µM) toxicity | Improved Aβ-induced cytotoxicity through inhibition of apoptosis and ROS generation Up-regulated H0-1 and Nrf2 expression and Bcl-2/Bax protein ratio |
| Mouse AD models induced by Aβ(1-42) | Ameliorated cognitive dysfunction in mice associated with reduced p38, c-jun N-terminal kinases, and tau phosphorylation | |
| *Boswellia* resin extract (10 µg/ml) (38). | An in vitro PD model induced by MPTP in human dopaminergic SK-N-SH cell-line | Attenuated MPTP-induced neurotoxicity including inhibition of apoptosis |
| 1) *B. serrata* aqueous extract (0.1 g/kg/day) (47) 2) *B. serrata* (100 mg/kg/day) (48). | Assessment of cognitive dysfunction in young Wistar rats whose mothers received *Boswellia* during gestation (3 weeks) | Induced more dendritic segments and branching density in the neurites of CA3 hippocampal cells |
| Frankincense aqueous extract (50 and 100 mg/kg, 4 weeks) (49). | Assessment of learning and spatial memory in rats using Morris water maze test method | Facilitated the learning and spatial memory formation as reduction in escape latency and traveled distance |
| Frankincense aqueous extract (50 and 100 mg/kg) during gestation and lactation periods (50). | Assessment of the Frankincense efficacy on memory formation during development of the rat brain | Enhanced high performance memory and up-regulated CaMKII and CaMKIV mRNA levels in the hippocampus offloading rats |
| Frankincense aqueous extract (50 and 100 mg/kg/day, 4 weeks) (54). | Evaluation of the spatial memory parameters by MWM test | Improved spatial learning and memory and up-regulated expression of BDNF but not CREB |
| *Boswellia papyrifera* total extracts (300 mg/kg, three times a day) and boswellic acids fraction (100, 200, and 300 mg/kg) (55). | Assessment of spatial memory using MWM task | Enhanced the retention phase of spatial memory proposing the improvement of memory function |
| Olhumun (100 and 500 mg/kg, 180 days) (59). | Assessment of memory function using methimazole-induced hypothyroidism animal model | Countered memory deficit in the Morris water maze test |
| Ethyl acetate (0.1 mg/kg) and *N*-butanol (0.1 mg/kg) fractions of *B. carteri* gum resin (61). | Memory impairments induced by hyoscine-induced |
| Combined administration of *M. officinalis* and *B. serrata* (200 and 400 mg/kg) (62). | Spatial memory against cognitive impairment related to scopolamine | Ethyl acetate fraction was much more significant than other fraction in enhancing the memory ability indicated by the MWM task |
| Frankincense hydro-alcoholic extract (50 mg/kg) (67). | Memory loss following LPS administration (1 mg/kg) | Improved memory performance indicated by MWM method |
| Aqueous extracts of *B. serrata* (0.1, 0.5, and 1 g/kg, IP) (71, 72). | Pentyleneetetrazol-induced kindled rats were used to study epilepsy and its consequences on memory using shuttle box apparatus and step-through latency method | Enhanced step-through latency in a passive avoidance task accompanied by reduced TNF-α level in the hippocampus |
| *B. serrata* aqueous extract (100 mg/kg/d, for 8 weeks) (74). | Age-related morphological changes of hippocampal granule cells and concomitant cognitive deficits in escape latency and swimming distance | Improved passive-avoidance learning ability associated with an increase in the number of pyramidal neurons and dendritic spines in CA1 |
| A tablet containing *B. serrata* and *Melissa officinalis* extract (290 and 27 mg) (75). | A randomized, parallel, double-blind, placebo-controlled clinical trial performed among 70 older adults | Enhanced dendritict complexity in the dentate granule cells and spine density associated with improved spatial learning capability |
| Ethanolic extract of *B. serrata* oleo-gum resin (10, 20, 40, and 80 mg/ml) (79). | Oligodendroglia (OLN) cell injury induced by glutamate and quinolinic acid | Improved memory function |
| The extract mixture of *Portulaca oleracea*, *Uraria dioica*, and *B. serrata* (200 and 400 mg/kg) (81). | MS model induced by intra-hippocampal injection of ethidium bromide (sterotactic surgery) in rats | Attenuated oxidative stress |
| Capsule containing *B. papyrifera* (300 mg, twice a day, 2 months) (82). | A randomized, double-blind, clinical trial in MS patients | Induced neurogenesis and memory improvement in the shuttle box test |
| Capsule containing *B. serrata* extract (450 mg twice a day, two months) (83). | A double-blind clinical trial in MS patients with cognitive deficits | Indicated therapeutic efficacy for cognitive dysfunction as improved visual-spatial memory |
| *B. serrata* hydroalcoholic extract (1.5-6 µg/ml) and AKBA (0.5-2.5 µg/ml) (90). | Ischemia-induced cytotoxicity in PC12 cells following exposure to oxygen/glucose/serum deprivation condition | Improved cognitive deficits indicated by the improvement of auditory/verbal and visual/spatial memory in brief visuospatial memory test and California verbal learning test |
| BSE (25, 50, 100 µg/ml) and AKBA (5 μm) (91). | Cell culture model of neurodegeneration induced by glutamate toxicity in PC12 and Neuro-2a cell | Increased cell survival and counteracted oxidative stress (ROS, lipid peroxidation, and oxidative DNA damage) |
| *B. serrata* methanolic extract (50, 100, 256, 500, 1000, and 2000 µg/ml) (93). | In vivo assessment of antioxidant and anti-inflammatory activity | Exhibited DPPH free radical scavenging activity (IC50 = 54.06 µg/ml), ferric reducing power (IC50 = 62.12 µg/ml) stabilization towards human red blood cell membrane stabilization |
| Boswellia aqueous and ethanolic extracts (125, 250, and 500 mg/kg, IP) and AKBA (50 mg/kg, IP) (94). | An animal model of ischemia, MGA0 | Improved neurological deficits and reduced brain infarction volume, neuromatp apoptotic cell death accompanied by up-regulation of Bcl-2 and down-regulation of Bax and caspase-3. Reduced oxidative stress (counteracted lipid peroxidation and restored glutathione content and superoxide dismutase activity) in the cerebral cortex |

*Note: AD: Alzheimer's disease, ACh: Acetylcholine, AChE: Acetylcholinesterase, Aβ: Amyloid β, BSE: Boswellia stanifera extract, AKBA: Acorus calamus basic alcohol, MCAO: Middle cerebral artery occlusion, MWM: Morris water maze model, PD: Parkinson’s Disease, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Sikkim: Sikkim, i.c.v: intracerebroventricular, T2: *T*2-weighted, R: *R*-weighted, MR: Magnetic Resonance, B: *B*-weighted, H: *H*-weighted, T1: *T*1-weighted, MS: Multiple sclerosis, STZ: Streptozotocin, HO-1: Heme oxygenase 1, TNF: Tumor necrosis factor, Aβ: Amyloid β, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IL: Interleukin, IL-6: Interleukin-6, IL-1β: Interleukin-1 beta, TNF-α: Tumor necrosis factor alpha, IL-1β: Interleukin-1 beta, IL-6: Interleukin-6, iNOS: Inducible NO synthase, NO: Nitric oxide, MPO: Myeloperoxidase, COX-2: Cyclooxygenase-2, CAT: Catalase, MnSOD: Mn-superoxide dismutase, SOD: Superoxide dismutase, AChE: Acetylcholinesterase, TMA: Trimethylamine, TBA: Thiobarbituric acid.
protein ratio have been shown to be involved in the protective effects (34). SHXW essential oil ameliorated cognitive dysfunction in Aβ1-42 treated mice, and it was associated with reduced p38, c-Jun N-terminal kinases, and tau phosphorylation (34). The findings suggested SHXW essential oil as a therapeutic agent for the prevention and treatment of AD and other tau protein pathology-related neurodegenerative diseases (34). Collectively, the experimental studies confirmed the inhibitory potential of Boswellia against formation of amyloid plaques and degeneration of cholinergic neurons induced by Aβ. The medicinal herbs were found to induce anti-apoptotic activity through modulation of Bcl-2/Bax protein ratio. In addition, they counteracted oxidative damages through enhancement of HO-1/Nrf2 protein expression and restoring oxidative stress markers (Table 1).

**Parkinson’s disease**

Parkinson’s disease (PD), a common chronic, progressive neurodegenerative disorder of the elderly, is characterized by motor (including bradykinesia, tremor, and rigidity) and non-motor symptoms (35). The symptoms of PD result from the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and dopamine (DA) deficiency in the striatum (36). Moreover, the presence of α-synuclein containing Lewy bodies in the surviving neurons is also proposed in the neuropathology of PD (37). Oxidative stress, mitochondrial dysfunction, excitotoxicity, calcium cytotoxicity, trophic factor deficiency, inflammatory processes, genetic factors, and apoptosis are now considered to be key mechanisms that contribute to neurodegeneration in PD (36). Some evidences has demonstrated the neuroprotective potential of *B. serrata* on dopaminergic neurons that can be applicable in PD. *Boswellia* resin extract (10 μg/ml) attenuated MPP+ (1-methyl-4-phenylpyridinium, 1000 μM) an active metabolite of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) induced toxicity in human dopaminergic SK-N SH cell-line. The protective effects were associated with increased cell viability and reduced apoptotic features (38) (Table 1).

**Cognitive dysfunction**

Learning means the process of acquiring knowledge from the outside environment while memory is retention and retrieval of learned information at a later date (39-41). Short-term plasticity (STP) and long-term potentiation (LTP), two types of synaptic plasticity, are mechanisms for memory storage (42-45). Learning and memory impairment are considered the most significant features of dementia (46). A number of experimental studies were conducted to evaluate the effect of maternal administration frankincense (an oleo-gum resin derived from trees of genus Boswellia) on the cognitive capabilities. Hosseini Sharifabadi et al. assessed learning and memory in two-month-old male Wistar rats whose mothers orally received aqueous extract of *B. serrata* (0.1 g/kg/day) during gestation (3 weeks) using active avoidance learning test. Frankincense enhanced power of learning at post-learning stage, short-term memory, and long-term memory (47). The results were relevant to the alteration in the neurites of CA3 hippocampal cells reported in another study. Analysis of morphology of dendritic architecture of CA3 hippocampal neurons indicated more dendritic segments and branching density in young rats whose mothers were treated with *B. serrata* (100 mg/kg/day) during gestation compared with untreated rats (48). Administration of aqueous extract of frankincense (50 and 100 mg/kg, 4 weeks) facilitated the learning and spatial memory formation in rats. The results were demonstrated as reduction in escape latency and traveled distance by the Morris water maze test method (49). An *in vivo* study was performed to assess the efficacy of frankincense for memory formation during development of the rat brain. For this purpose, aqueous extract of frankincense (50 and 100 mg/kg) was orally administered into female rats during gestation and lactation periods. Memory performance and hippocampal calcium/calmodulin kinase II (CaMKII) and CaMKIV mRNA levels in the offspring rats were evaluated to identify potential molecular change during gestation and lactation periods (50). CaMKII and CaMKIV are involved in many signaling cascades and are thought to be crucial mediators of learning and memory (51). CaMKII, as an important component of the postsynaptic density of glutamatergic synapses (52), plays a role in regulation of synaptic transmission and induction of long-term potentiation (LTP) (53).
According to the results, up-regulation of CaMKII-α mRNA expression of the hippocampus was concomitant with improvement of spatial memory retrieval in offspring rats (50). Evaluation of the spatial memory parameters by the Morris water maze (MWM) test revealed improvement of spatial learning and memory in rats treated with aqueous extract frankincense (50 and 100 mg/kg/day for 4 weeks). Frankincenseup-regulated expression of brain-derived neurotrophic factor (BDNF) transcripts but not cAMP response element-binding (CREB). Therefore, the effects of the extract on memory formation may be attributed to another BDNF-related (CREB). Therefore, the effects of the extract on memory function may be attributed to another BDNF-related pathway other than BDNF–CREB–BDNF cycle (54). B. papyrifera total extracts (300 mg/kg, three times a day, orally) and boswellic acids fraction (100, 200, and 300 mg/kg) enhanced the retention phase of spatial memory of adult male rats in the MWM task. The results of the investigation proposed improving potential of Boswellia and boswellic acid fraction in memory function in normal subjects or neurodegenerative disorders (55). Impairment of cognitive function including memory, visuospatial organization, attention, and reaction time in overt hypothyroidism has been recognized for more than a century (56-58). Olibanum (resin of B. serrata) exhibited beneficial effects on memory deficit in methimazole-induced hypothyroidism model. Oral administration of olibanum (100 and 500 mg/kg, 180 days) improved memory and learning impairment in hypothyroid rats by the Morris water maze test (59). Animal models of amnesia induced by scopolamine are widely used to screen potential therapeutic value of compounds in treatment of dementia (60). Another study aimed to assess the effect of ethyl acetate and N-butanol fractions of B. carterii gum resin on intact memory and hyoscine-induced memory impairments using the MWM task. Ethyl acetate (0.1 mg/kg) and N-butanol (0.1 mg/kg) fractions remarkably enhanced intact memory. The ethyl acetate fraction was much more significant than other fractions in enhancing the memory (61). The combination of Melissa officinalis and B. serrata improved scopalamine-induced cognitive impairment. The MWM method revealed co-administration of M. officinalis and B. serrata (200 and 400 mg/Kg body weight) before scopalamine injection (0.1 mg/kg) led to improvement of memory function (62). Neuro-inflammation can cause cognitive deficits since it affects memory processing during consolidation and retrieval stages (63, 64). Considering anti-inflammatory activity of frankincense has been approved with an (15). Lipopolysaccharide (LPS) triggers the neuro-inflammatory process through activation of nuclear factor kappa B (NF-κB) pathway in microglia in the central nervous system (CNS) (65, 66). Administration of hydro-alcoholic extract of frankincense (50 mg/kg; orally) before LPS (1 mg/kg; IP) enhanced step-through latency (STL) in a passive avoidance task (PAT) via decreasing the TNF-α level in the hippocampus. Therefore, anti-inflammatory effects of frankincense may be involved in inhibition of memory loss (67). Clinical and pre-clinical studies have shown that prolonged frequent seizures cause cognitive, memory, and emotional impairments (68). These recurrent seizures affecting the hippocampus may lead to cell damage and death in the cornu ammonis (CA1) region (69). Function of CA1 neurons in the hippocampus plays a vital role in converting short-term memory to long-term memory (70). Pentyleneterazol (PTZ)-induced kindled rats animal model was used for evaluation of epilepsy and its consequences on memory (71). The aqueous extracts of B. serrata (0.1, 0.5, and 1 g/kg, IP) improved passive-avoidance learning ability in kindled animals indicated by using shuttle box apparatus and step-through latency method. The findings were associated with increasing number of pyramidal neurons and dendritic spines in CA1 (71, 72). Therefore, consumption of B. serrata may be a therapeutic strategy for decreasing harmful effects of seizures on cognitive function (71). Age-related spatial learning deficits have been suggested to be due to changes that appear mostly in hippocampal connectivity and plasticity (73). The three main fields of the hippocampal region, CA1, CA3, and particularly dentate gyrus are vulnerable to aging (73). An experimental study conducted by Hosseini-Sharifabad et al. investigated the effects of chronic administration of B. serrata hydroalcoholic extract (BSE) on the learning performance and the morphology of hippocampal granule cells in aged rats (74). The rats (24 months old) received the aqueous extract of BSE (100 mg/kg/d, for 8 weeks, intragastrically), after this time, dentritic complexity in the dentate granule cells and spine density on the dentritic tree of the cells increased (74). These findings were observed along with improvement of spatial learning capability indicated as decrease in escape latency and swimming distance (74). Neuroprotective potential of Boswellia resin in age-related morphological changes and concomitant cognitive deficits may suggest it as a therapeutic agent in neurodegenerative diseases (74). In a randomized, parallel, double-blind, placebo-controlled clinical trial, administration of B. serrata and Melissa officinalis extracts (290 mg and 27 mg, for a month) improved memory in 70 older adults (75). Overall, this evidence provides preliminary support for the cognitive-enhancing efficacy of genus Boswellia. Potential beneficial actions may be attributed to BDNF up-regulation (Table 1).

**Multiple sclerosis**

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the CNS, which leads to the destruction of myelin, oligodendrocytes, and axons (76). Quinolinic acid (2, 3-pyridine dicarboxylic acid), a neuroactive metabolite of the kynurenine pathway, is an agonist of N-methyl-D-aspartate (NMDA). Inappropriate activation of the kynurenine pathway may increase quinolinic acid levels, which is often implicated in the pathogenesis of a number of neurological diseases such as MS (77, 78). *In vitro* study revealed that 24 hr pre-treatment of oligodendroglia (OLN-93) cells with ethanolic extract of B. serrata oleo-gum resin (10, 20, 40, and 80 µg/ml) prior to glutamate exposure reduced glutamate and quinolinic acid-induced oxidative injury (8 mM)(79). A mixture extract of Portulaca oleracea, *Urtica dioica*, and B. serrata (200 and 400 mg/kg) has protective effects against ethidium bromide-induced MS model (80). The results revealed neurogenesis and memory improvement using the shuttle box test following treatment with the mixture (81). Cognitive deficits have been reported in up to 70% of MS patients (80). A clinical trial study was carried out in 80 patients...
### Table 2. A summary of in vitro and animal studies on neuroprotective potential of AKBA in the neurodegenerative diseases

| Agent            | Type of study                           | Protocol                                                                 | Results                                                                 | Ref. |
|------------------|-----------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------|------|
| AKBA             | In vivo (MCAO)                          | 20 mg/kg AKBA were given immediately after the onset of reperfusion     | Treatment of AKBA:                                                     | (99) |
|                  |                                         |                                                                         | -reduced infarct volumes and apoptotic cells                            |      |
|                  |                                         |                                                                         | -increased neurologic scores by elevating the Nrf2 and HO-1 expression in brain |      |
| AKBA             | In vitro (OGD in primary cultured cortical neurons) | Incubation with AKBA for 24 hr                                           | -In primary cultured neurons:                                         | (100) |
|                  |                                         |                                                                         | -increased the Nrf2 and HO-1 expression,                                 |      |
|                  |                                         |                                                                         | -protection against OGD-induced oxidative stress                        |      |
| AKBA             | In vivo (MCAO)                          | KBA (25 mg/kg) applied 1 hr after reperfusion                            | -reduced infarct volumes and apoptotic cells                            | (100) |
|                  |                                         |                                                                         | -increased neurologic scores                                             |      |
|                  |                                         |                                                                         | -decreased MDA levels                                                   |      |
|                  |                                         |                                                                         | -restored the superoxide dismutase (SOD) activity                       |      |
|                  |                                         |                                                                         | -increased the protein Nrf2 and HO-1 expression in brain tissues         |      |
| AKBA             | In vitro (OGD in primary cultured astrocytes) | Incubation with KBA for 24 hr                                           | -increased the Nrf2 and HO-1 expression                                 | (101) |
|                  |                                         |                                                                         | -protection against OGD-induced oxidative stress                        |      |
| AKBA             | In vivo (cognitive impairment in mice induced by LPS) | Dual therapy with AKBA (at a dose of 5 mg/kg, IP for 4 days) and celecoxib (at a dose of 30 mg/kg, IP for 7 days) | -reversed the behavioral and molecular changes                           | (102) |
|                  |                                         |                                                                         | -anti-inflammatory effect                                                |      |
| AKBA             | In vivo (kainic acid-induced excitotoxicity and oxidative and nitrosative damage in mice) | The effects of COX inhibitors (indomethacin, nimesulide, and celecoxib) and a 5-LOX inhibitor (AKBA) and the combination of these inhibitors in this model | -AKBA, indomethacin, and nimesulide did not produce any change in the behavioral parameters |      |
| Nano formulation of AKBA | In vivo (MCAO)                       | AKBA-NPs (containing AKBA 10 mg/kg), intravenously                      | AKBA-NPs had better:                                                   | (103) |
|                  |                                         |                                                                         | -brain delivery efficacy                                                |      |
|                  |                                         |                                                                         | -neuroprotection in OGD and MCAO models                                 |      |
|                  |                                         |                                                                         | -modulation of antioxidant and anti-inflammatory pathways               |      |
| AKBA             | In vivo (OGD)                           | OGD + AKBA-NP (10 mg/ml) treatment                                       | AKBA and DEX reversed the behavioral dysfunction                         | (104) |
|                  |                                         |                                                                         | AKBA:                                                                   |      |
|                  |                                         |                                                                         | -decreased P-IκB-α, miRNA-155 expression level, and carbonyl protein content |      |
|                  |                                         |                                                                         | -restored normal cytokine level                                          |      |
|                  |                                         |                                                                         | -increased SOCS-1 expression level                                       |      |
|                  |                                         |                                                                         | -showed anti-apoptotic and anti-amyloidogenic effects                   |      |
| AKBA             | In vivo (young and aged mice)           | Chronic administration of AKBA (100 mg/kg, p.o.) and nimesulide (2.42 mg/kg, p.o.) for 15 days | -enhanced the cognitive performance                                      | (105) |
|                  |                                         |                                                                         | -reduced oxidative damage                                               |      |
|                  |                                         |                                                                         | -reversed the aging-induced motor dysfunction                            |      |
| AKBA             | In vivo (MCAO)                          | AKBA (50 mg/kg) was administered IP after MCAO induction                | improved neurological deficit                                            | (94)  |
|                  |                                         |                                                                         | -reduced brain infarction                                                |      |
|                  |                                         |                                                                         | -decreased neuronal cell loss and apoptosis                              |      |
|                  |                                         |                                                                         | -attenuated lipid peroxidation                                           |      |
|                  |                                         |                                                                         | -increased glutathione content and superoxide dismutase activity         |      |
| AKBA             | In vitro (glutamate toxicity induced in PC12 and N2a cells) | Co- and pretreatment with AKBA (5 mM) was done on PC12 and N2a cells under glutamate toxicity (8 mM) | - decreased ROS                                                         | (91)  |
|                  |                                         |                                                                         | -decreased lipid peroxidation                                            |      |
|                  |                                         |                                                                         | -decreased superoxide dismutase activity                                 |      |
|                  |                                         |                                                                         | -decreased oxidative DNA damage                                         |      |

MCAO: middle cerebral artery occlusion; OGD: oxygen-glucose deprivation; AKBA: acetyl-11-keto-β-boswellic acid; Nrf2: nuclear factor erythroid 2-related factor; MDA: malondialdehyde; LPS: lipopolysaccharide; COX: cyclooxygenase; DEX: dexamethasone; ROS: reactive oxygen species.
Cognitive impairments (83) (Table 1).

Central nervous systems trauma and brain ischemia

Stroke is the fourth cause of death and one of the main causes of disability worldwide (84). Ischemic stroke is the most common type of stroke, accounting for about 80 percent of all strokes, which results from transient or permanent cessation of cerebral blood flow (85, 86). Following brain ischemia, the level of glutamate increases, leading to over-activation of its receptors, including NMDA receptors and raised intracellular calcium (87). Brain ischemia also can trigger inflammatory responses and subsequently neuro-inflammation. Therefore, strategies targeting these pathways involve NMDA receptor antagonists, calcium channel blockers, and anti-inflammatory and antioxidant agents, which may be used as prophylactic or therapeutic for ischemia damage of brain tissue (87, 88). *B. serrata* and its constituent, AKBA (3-acetyl-11-keto-β-boswellic acid), exhibited potential neuroprotective and anti-oxidant activity (89). Neuroprotective potential of BSE and AKBA against ischaemia-induced cytotoxicity was investigated. The survival of PC12 neural cells, pretreated with BSE (1.5-6 µg/ml) and AKBA (0.5-2.5 µg/ml) for 2 hr before exposure to oxygen/glucose/serum deprivation (OGSD) condition, increased. Moreover, BSE and AKBA counteracted oxidative stress indicated as restoring of intracellular reactive oxygen species content, lipid peroxidation, and oxidative DNA damage (90). Pre- and co-treatment with BSE and AKBA prevented glutamate-induced PC12 and Neuro-2a cell toxicity. The protective effect may be related to their inhibitory effects against oxidative damage and apoptotic cell death (91). An *in vitro* investigation aimed to explore anti-glycation and anti-oxidant potentials of *B. sacra* oleo-gum resin. Dichloromethane (CH₂Cl₂) fraction of the resin, 40% dichloromethane (CH₂Cl₂)/n-hexane sub-fraction, and frankincense oil exhibited 1,1-Diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity. In addition, moderate superoxide anion scavenging activity was exhibited by polar fraction, while the highest anti-glycation activity for polar fractions were reported (92). Another study was designed to investigate phytochemical screening, *in vitro* antioxidant activity of leaf extract of *B. serrata*. The methanolic extract of *B. serrata* contains alkaloids, terpenoids, saponins, and flavonoids (93). Methanolic extract exhibited significant DPPH free radical scavenging activity (IC₅₀ = 54.06 µg/ml) and ferric reducing power (IC₅₀ = 62.12 µg/ml) in a dose-dependent manner (93). Administration of the aqueous and ethanolic extracts of *B. serrata* (125, 250, and 500 mg/kg, IP) and AKBA (50 mg/kg, IP) just after middle cerebral artery occlusion (MCAO), for 50 min and reperfusion for 24 hr improved neurological deficits and reduced brain infarction volume. The extract diminished neuronal apoptotic cell death through up-regulation of Bcl-2 and down-regulation of Bax and caspase-3. The modulated cerebral redox status was also indicated as inhibition of lipid peroxidation while increasing glutathione content and superoxide dismutase activity in the cerebral cortex (94). The neuroprotective effects of Boswellia against brain stroke were further confirmed by the reduction of infarction volume and neurological impairments. The aqueous extract of frankincense was administrated (50, 100, and 150 mg/kg, orally for 30 days). Two hours after the last treatment with frankincense extract, the rats were subjected to MCAO for 60 min followed by reperfusion for 24 hr. The level of blood-brain barrier (BBB) permeability and stroke-induced brain edema decreased in rats treated with aqueous extract of frankincense at doses of 100 and 150 mg/kg (95). The results of a prospective, randomized, placebo-controlled, double-blind, pilot trial confirmed the efficacy of BS on cerebral edema following brain radiotherapy (96). In this trial, forty-four patients with primary or secondary malignant cerebral tumors randomly received BS (4200 mg/day) or placebo during radiotherapy. Administration of BS suppressed the edema volume which was evaluated by T2-weighted magnetic resonance imaging (MRI) (96). To investigate the effect of *B. serrata* on neuro-recovery following diffuse axonal injury (DAI), a double-blind, randomized, cross-over study was designed. The outcome of diffuse axonal injury was assessed using the disability rating scale, a surrogate clinical marker for the pace of neuro-recovery. 38 patients randomly received either placebo or BS capsules (containing 215 mg BS gum resin) for 6 weeks. The BS resin enhanced the cognitive outcome of patients with DAI (97). The protective effects of the condor against cerebral inflammation after induction of diffuse traumatic brain injury were investigated. *B. serrata* (250 and 500 mg/kg) attenuated brain edema and disruption of blood-brain-barrier induced by traumatic brain injury. The results were accompanied by improvement of vestibulomotor dysfunction as well as modulation of IL-1β and I-10 in brain tissue. Anti-inflammatory properties were suggested to be involved in the neuroprotective effects (98). Boswellia exhibited therapeutic potential for brain ischemia and injuries, which is most likely related at least in part to its anti-inflammatory, anti-apoptotic, as well as anti-oxidative and free radical scavenging activities (Table 1).

In this review, Tables 1 and 2 represent the brief description of pre-clinical and clinical studies on protective effects of genus Boswellia and AKBA in the neurodegenerative diseases, respectively.

**Conclusion**

Considering lack of effective therapy for clinical applications, pharmacologically active natural products, having neuroprotective activities are being focused, which makes them potential candidates for neurodegenerative disorders. The genus Boswellia has been suggested to target various molecular pathways involved in pathogenesis of neurodegenerative diseases. The genus regulates neurotrophic factors (including BDNF), apoptotic proteins (pro-apoptotic caspase-3 and anti-apoptotic bcl-2), and redox status. They were shown to be therapeutically effective at controlling inflammatory and cholinergic systems. Therefore, evidence suggests the importance of the genus in the prevention and treatment of neurodegenerative diseases even though further studies and clinical trials on these promising medicinal plants and their constituents should be strongly encouraged in the future.

**References**

1. Ayooobi F, Shamsizadeh A, Fatemi I, Vakilian A, Allahtavakoli...
M. Hassanshahi G, et al. Bio-effectiveness of the main flavonoids of Achillea millefolium in the pathophysiology of neurodegenerative disorders-a review. Iran J Basic Med Sci 2017; 20:604-612.

2. Durães F, Pinto M, Sousa E. Old drugs as new treatments for neurodegenerative diseases. Pharmaceuticals 2018; 11:44.

3. Finkel T. Signal transduction by reactive oxygen species. J Cell Biol 2011; 194:7-15.

4. Winner B, Kohl Z, Gage FH. Neurodegenerative disease and adult neurogenesis. Eur J Neurosci 2011; 33:1139-1151.

5. Shirooie S, Nabavi SF, Dehpour AR, Behvaid T, Hambaramian S, Argüelles S, et al. Targeting miRNAs by omega-3 fatty acids: a possible novel therapeutic strategy for neurodegeneration?. Pharmaco Res 2018; 135:37-48.

6. Mertens M, Buettner A, Kirchhoff E. The volatile constituents of frankincense–a review. Flavour Fragr J 2009; 24:279-300.

7. Morikawa T, Matsuda H, Yoshikawa M. A review of anti-inflammatory terpenoids from the incense gum resins frankincense and myrrth. J Oleo Sci 2017; 66:805-814.

8. Siddiqui M. Boswellia serrata, a potential antiinflammatory agent: an overview. Indian J Pharm Sci 2011; 73:255-261.

9. Finkel T. Signal transduction by reactive oxygen species. J Cell Biol 2011; 194:7-15.

10. Hamidpour R, Hamidpour S, Hamidpour M. The effect of Rhodiola crenulata gum extract on learning and memory in mice and rats. Iran J Basic Med Sci 2010; 13:9-15.

11. Hamidpour R, Hamidpour S, Hamidpour M, Shahhari M. Frankincense (Boswellia species): from the selection of traditional applications to the new phytotherapy for the prevention and treatment of serious diseases. J Tradit Complement Med 2013; 3:221-226.

12. Takahasi M, Sugiura Y, Ueno H, Kuro K, Matsuoka Y, et al. Anti-inflammatory effects of boswellic acid on colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. Carcinogenesis 2012; 33:2441-2449.

13. Liu J-J, Nilsson A, Oredsson S, Badmaev V, Zhao W-Z, Duan J. The effects of Boswellia resin extract on dopaminergic cell signaling pathways implicated in the pathogenesis of Parkinson’s disease: a systematic review and meta-analysis. Mov Disord 2015; 30:759-769.

14.  Qu Zq, Zhou Y, Zeng YS, Lin YK, Li Y, Zhong Zq, et al. Protective effects of a Rhoioldia crenulata extract and saudioside on hippocampal neurogenesis against streptozotocin-induced neural injury in the rat. PLoS One 2012; 7:e29641.

15. Sun P, Kuzovkina A, Parlak M, Cuber J, M Karabeg M, Deckert J, et al. Long-term effects of intracerebroventricular streptozotocin treatment on adult neurogenesis in the rat hippocampus. Curr Alzheimer Res 2015;12:772-84.

16. Beheshti S, Aghaie R. Therapeutic effect of frankincense in a rat model of Alzheimer’s disease. Avicenna J Phytomed 2016; 6:468-475.

17. Bensky D, Gamble A, Kaptchuk TJ. Chinese herbal medicine: materia medica. Eastland Press Seattle; 2004.

18. Jeon S, Hur J, Jeong HJ, Koo BS, Pak SC. SulHExiang van essential oil alleviates amyloid beta induced memory impairment through inhibition of tau protein phosphorylation in mice. Am J Chin Med 2011; 39:917-932.

19. den Brok MG, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RM, Richard E. Apathy in Parkinson’s disease: a systematic review and meta-analysis. Mov Disord 2015; 30:759-769.

20. Yuan H, Zhang ZW, Liang LW, Shen Q, Wang XD, Ren SM, et al. Treatment strategies for Parkinson’s disease. Neurouzi Bol 2010; 26:66-76.

21. Gaki GS, Papavassiliou AG. Oxidative stress-induced signaling pathways implicated in the pathogenesis of Parkinson’s disease. Neurovascular Med 2014; 16:217-230.

22. Kazmi S, Kafami L, Ebrahimi A, Jameie B, Joghataee MT. The effects of Boswellia resin extract on dopaminergic cell line, SK-N-SH, against MPP+-induced neurotoxicity. Basic Clin Neurosci 2011; 3:16-21.

23. Baudry M, Qi X. Learning and memory: an emergent property of cell motility. Neurobiol Learn Mem 2013; 104:64-72.

24. Colciago A, Casati L, Negri-Cesi P, Pelotti E. Learning and memory: steroids and epigenetics. J Steroid Biochem Mol Biol 2015; 150:64-85.

25. Gallistel CR, Balsam PD. Time to rethink the neural
mechanisms of learning and memory. Neurobiol Learn Mem 2014; 108:136-144.
42. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993; 361:31-39.
43. Kandel ER, Schwartz JH, Jessell TM, Jessell MBT, Siegelbaum S, Hudspeth AJ. Principles of neural science. McGraw-hill New York; 2000.
44. Martin SJ, Grimwood PD, Morris RG. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu Rev Neurosci 2000; 23:649-711.
45. Whitlock JR, Heynen AJ, Shuler MG, Bear ME. Learning induces long-term potentiation in the hippocampus. Science 2000; 313:1093-1097.
46. Arlt S. Non-Alzheimer’s disease-related memory impairment and dementia. Dialogues Clin Neurosci 2013; 15:465-473.
47. Hosseini SM, Esfandiari E, Aalai H. Effects of frankincense aqueous extract during gestational period on increasing power of learning and memory in adult offsprings. J Isfahan Med School 2004; 21:16-20.
48. Hosseini Sharifabad M, Esfandiary E. A morphometric study on CA3 hippocampal field in young rats following maternal administration of Boswellia serrata resin during gestation. Iran J Basic Med Sci 2007; 10:176-182.
49. Sharifabad MH, Esfandiary E. The effects of maternal administration of boswellia gum resin (Frankincense) during lactation on stereological parameters of rat hippocampus. J Isfahan Med School 2012; 29:1-9.
50. Beheshti S, Shalakomi AG, Ghadki E, Dehestani H. Frankincense upregulates the hippocampal calcium/calmodulin kinase II-a during development of the rat brain and improves memory performance. Int J Dev Neurosci 2018; 69:44-48.
51. Kang H, Sun LD, Atkins CM, Soderling TR, Wilson MA, Tonegawa S. An important role of neural activity-dependent CaMKII signaling in the consolidation of long-term memory. Cell 2001; 106:771-783.
52. Petersen JD, Chen X, Vinade L, Dosemeci A, Lisman JE, Reese TS. Distribution of postsynaptic density (PSD)-95 and Ca2+/calmodulin-dependent protein kinase II at the PSD. J Neurosci 2003; 23:11270-11278.
53. Lisman J, Schulman H, Cline H. The molecular basis of CaMKII function in synaptic and behavioural memory. Nat Rev Neurosci 2002; 3:175-190.
54. Khajeh-Kondori M, Sadeghi F, Hosseinporfeizi MA, Shaikhzadeh-Hesari F, Nakhlab M, Rahmati-Yamchi M. Boswellia serrata gum resin aqueous extract upregulates BDNF but not CREB expression in adult male rat hippocampus. Turk J Med Sci 2016; 46:1573-1578.
55. Mahmoudi A, Hosseini-Sharifabad A, Monsef-Esfahani HR, Yazdinejad AR, Kavani N, Roghani A, et al. Evaluation of systemic administration of Boswellia papyrifera extracts on spatial memory retention in male rats J Nat Med 2011; 65:519-525.
56. Begin M, Langlois M, Lorrain D, Cunnane S. Thyroid function and cognition during aging. Curr Gerontol Geriatr Res 2008; 2008:474868.
57. Miller KJ, Parsons TD, Whybrow PC, Van Herle K, Rasgon N, Van Herle A, et al. Verbal memory retrieval deficits associated with untreated hypothyroidism. J Neuropsychiatry Clin Neurosci 2007; 19:132-136.
58. Paz-Baruch N, Leikin M, Leikin R. Visual processing and attention abilities of general gifted and excelling in mathematics students. , Charles University in Prague, Faculty of Education; ERME, Feb 2015, Prague, Czech Republic. pp.1046-1051.
59. Hosseini M, Hadjizadeh MA-R, Derakshesh M, Havakhan S, Rassouli FB, Rakhshandeh H, et al. The beneficial effects of olibanum on memory deficit induced by hypothyroidism in adult rats tested in Morris water maze. Arch Pharm Res 2010; 33:463-468.
60. Bejar C, Wang R-H, Weinstock M. Effect of rivastigmine on scopolamine-induced memory impairment in rats. Eur J Pharmacol 1999; 383:231-240.
61. Hosseinizadeh H, Ramezani M, Akhtar Y, Ziaei T. Effects Boswellia carterii gum resin fractions on intact memory and hyoscine-induced learning impairments in rats performing the Morris water maze task. J Medicinal Plants 2010; 2:95-101.
62. Mahboubi M, Taghizadeh M, Talaei SA, Firozeh SM, Rashidi AA, Tamtaji OR. Combined administration of Melissa officinalis and Boswellia serrata extracts in an animal model of memory. Iran J Psychiatry Behav Sci. 2016; 10:e681.
63. Czerniawski J, Miyashita T, Lewandowski G, Guzowski JF. Systemic lipopolysaccharide administration impairs retrieval of context-object discrimination, but not spatial, memory: evidence for selective disruption of specific hippocampus-dependent memory functions during acute neuroinflammation. Brain Behav Immun 2015; 5:159-166.
64. Kranjac D, McLinden KA, Deodati LE, Papini MR, Chumley MJ, Bohlman GW. Peripheral bacterial endotoxin administration triggers both memory consolidation and reconsolidation deficits in mice. Brain Behav Immun 2012; 26:109-121.
65. Lehnardt S, Massillon L, Follett P, Jensen FE, Ratan R, Rosenberg PA, et al. Activation of innate immunity in the CNS triggers neurodegeneration through a Toll-like receptor 4-dependent pathway. Proc Natl Acad Sci 2003; 100:8514-8519.
66. Zhao M, Zhou A, Xu L, Zhang X. The role of TLR4-mediated PTEN/PI3K/AKT/NF-κB signaling pathway in neuroinflammation in hippocampal neurons. Neuroscience 2014; 269:93-101.
67. Beheshti S, Karimi B. Frankincense improves memory retrieval in rats treated with lipopolysaccharide. J Herbined Pharmacol 2016; 5:12-16.
68. Dodrill CB. Neuropsychological effects of seizures. Epilepsy Behav 2004; 5:21-24.
69. Babb TL. Axonal growth and neosynaptogenesis in human and experimental hippocampal epilepsy. Adv Neurol 1997; 72:45-51.
70. Portavella M, Vargas J, Torres B, Salas C. The effects of telencephalic pallial lesions on spatial, temporal, and emotional learning in goldfish. Brain Res Bull 2002; 57:397-399.
71. Jalili C, Salahshoor M, Pourmotabbed A, Moradi S, Roshankhah S, Darehdori AS, et al. The effects of aqueous extract of Boswellia serrata on hippocampal region CA1 and learning deficit in kindled rats. Res Pharm Sci 2014; 9:351-358.
72. Jalili C, Salahshoor MR, Moradi S, Pourmotabbed A, Motaghi M. The therapeutic effect of the aqueous extract of Boswellia serrata on the learning deficit in kindled rats. Int J Prev Med 2014; 5:563-568.
73. Burger C. Region-specific genetic alterations in the aging hippocampus: implications for cognitive aging. Front Aging Neurosci 2010; 2:140.
74. Hosseini-Sharifabad M, Kamali-Ardakani R, Hosseini-Sharifabad A. Beneficial effect of Boswellia serrata gum resin on spatial learning and the dendritic tree of dentate gyrus granule cells in aged rats. Avicenna J Phytomed 2016; 6:189-197.
75. Taghizadeh M, Maghaminejad F, Aghajani M, Rahmani M. The effect of tablet containing Boswellia serrata and Melissa officinalis extract on older adults’ memory: A randomized controlled trial. Arch Gerontol Geriatr 2018; 75:146-150.
76. Noseworthy JH, Luchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. New Engl J Med 2000; 343:938-952.
77. Lopez YP, Kenis G, Rutten BP, Myint AM, Steinbusch HW, van den Hove DL. Quinolinic acid-immunoreactivity in the naive mouse brain. J Chem Neuroanat 2016; 71:6-12.
78. Sundaram G, Brew BJ, Jones SP, Adams S, Lim CK, Guilleneau GJ. Quinolnic acid toxicity on oligodendroglial cells: relevance for multiple sclerosis and therapeutic strategies. J Neuroinflammation 2014; 11:204.
79. Rahimi VB, Askari VR, Mehrdad A, Sadeghnia HR. Boswellia serrata has promising impact on glutamate and quinolnic acid-induced toxicity on oligodendroglial cells: in vitro study. Acta Pol Pharm 2017; 74:1803-1811.
80. Chiavaralli ND, DeLuca J. Cognitive impairment in multiple sclerosis. The Lancet Neurology 2008; 7:1139-1151.
81. Mirhosseini G, Tehrani-pour M, Shahri NM. The synergistic effects of mixture extract Portulaca oleracea, Urtica Dioica, Boswellia serrata on multiple sclerosis in rats. J Gorgan Univ Med Sci 2018; 21:57-61.
82. Sedighi B, Pardakhty A, Kamali H, Shafee K, Hasani BN. Effect of Boswellia papyrifera on cognitive impairment in multiple sclerosis. Iranian J Neurol 2014; 13:149-153.
83. Majdinasab N, Siahpush A, Mousavinejad SK, Malayeri A, Sajedi SA, Bizhanzadeh P. Effect of Boswellia serrata on cognitive impairment in multiple sclerosis patients. J Herb Med 2016; 6:119-127.
84. Minino AM, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. Natl Vital Stat Rep. 2011; 59:1-126.
85. Della-Morte D, Guadagni F, Palmirotta R, Testa G, Caso V, Paciariono M, et al. Genetics of ischemic stroke, stroke-related factors, stroke precursors and treatments. Pharmacogenomics 2012;13:595-613.
86. Mahajan S, Kashyap R, Sood B, Jaret P, Mokta J, Kaushik N, et al. J Assoc Physicians’s India 2004;52:699-702.
87. Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. Prog Neurobiol 2014; 115:157-198.
88. Chamorro À, Dírgau L, Urre X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurology 2016; 15:869-881.
89. Assimopoulou A, Zlatanos S, Papageorgiou V. Antioxidant activity of natural resins and bioactive triterpenes in oil substrates. Food Chem 2005; 92:721-727.
90. Sadeghnia HR, Arjmand F, Ghorbani A. Neuroprotective effect of Boswellia serrata and its active constituent acetyl 11-keto-β-boswellic acid against oxygen-glucose-serum deprivation-induced cell injury. Acta Pol Pharm 2017; 74:911-920.
91. Rajabian A, Boroushaki MT, Hayatdavoudi P, Sadeghnia HR. Boswellia serrata Protects Against Glutamate-Induced Oxidative Stress and Apoptosis in PC12 and N2a Cells. DNA Cell Biol 2016; 35:666-679.
92. Al-Harrasi A, Ali L, Ceniviva E, Al-Rawahi A, Hussain J, Hussain H, et al. Antiglycation and antioxidant activities and HPTLC analysis of Boswellia sacra oleogum resin: the sacred frankincense. Trop J Pharm Res 2013; 12:597-602.
93. Afsar V, Reddy YM, Saritha K. In vitro antioxidant activity and anti-inflammatory activity of methanolic leaf extract of Boswellia serrata. Int J Life Sci 8 & Pharm Res 2012; 4:15-23.
94. Forouzanfar F, Hosseinzadeh H, Ebrahimzadeh Bideskan A, Sadeghnia HR. Aqueous and ethanolic extracts of Boswellia serrata protect against focal cerebral ischemia and reperfusion injury in rats. Phytother Res 2016; 30:1954-1967.
95. Rahman M. Effect of treatment with aqueous extracts of Boswellia serrata on blood-brain barrier permeability and brain edema in experimental model of stroke in rats. Qom Univ Med Sci J 2017; 11:56-65.
96. Kirtse S, Treier M, Wehrle SJ, Becker G, Abdel-Tawab M, Gerbeth K, et al. Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors: A prospective, randomized, placebo-controlled, double-blind pilot trial. Cancer 2011; 117:3798-3795.
97. Moein F, Abbasi Fard S, Asnaashari A, Baratian H, Barekatain M, Tavakoli N, et al. The effect of Boswellia Serrata on neurorecovery following diffuse axonal injury. Brain Res 2013; 1460:1245-1466.
98. Sheykhiyeh Golzadi Mashid, Rezaenejad Rezvan, Kachouei Emadeddin Y, Siahposht-Khachali A. Neuroscience J Shefaye Khatan 2018; 6:64.
99. Ding Y, Chen M, Wang M, Wang M, Zhang T, Park J, et al. Neuroprotection by acetyl-11-keto-β-boswellic acid, in ischemic brain injury involves the Nrf2/HO-1 defense pathway. Sci Rep 2014; 4:7002-7010.
100. Ding Y, Chen M, Wang M, Li Y, Wen A. Post treatment with 11-keto-β-boswellic acid ameliorates cerebral ischemia-reperfusion injury: Nrf2/HO-1 pathway as a potential mechanism. Mol Neurobiol 2015; 52:1430-1439.
101. Sayed AS, El Sayed N. Co-administration of 3-acetyl-11-keto-beta-boswellic acid potentiates the protective effect of celecoxib in lipopolysaccharide-induced cognitive impairment in mice: possible implication of anti-inflammatory and antiglutamatergic pathways. J Mol Neurosci 2016; 59:58-67.
102. Bishnoi M, Patil C, Kumar A, Kulkarni SK. Co-administration of acetyl-11-keto-beta-boswellic acid, a specific 5-lipoxygenase inhibitor, potentiates the protective effect of COX-2 inhibitors in kainic acid-induced neurotoxicity in mice. Pharmacology 2007; 79:34-41.
103. Ding Y, Qiao Y, Wang M, Zhang H, Li L, Zhang Y, et al. Enhanced neuroprotection of acetyl-11-keto-β-boswellic acid (AKBA)-loaded O-carboxymethyl dithioan nanoparticles through antioxidant and anti-inflammatory pathways. Mol Neurobiol 2016; 53:38-42.
104. Sayed AS, Gomaa IEO, Bader M, El Sayed N. Role of 3-acetyl-11-keto-beta-boswellic acid in counteracting LPS-induced neuroinflammation via modulation of miRNA-155. Mol Neurobiol 2018; 55:5798-5808.
105. Bishnoi M, Patil C, Kumar A, Kulkarni S. Protective effects of nimesulide (COX Inhibitor), AKBA (5-LOX Inhibitor), and their combination in aging-associated abnormalities in mice. Methods Find Exp Clin Pharmacol 2005; 27:465-470.