



Effects of *Boswellia serrata* resin on central nervous system: a mini review

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ABSTRACT

Medicinal plants are used for different purposes in traditional medicine. *Boswellia serrata* (*B. serrata*) from Burseracea family has been widely used for human medical purposes. This plant known as frankincense or olibanum has a resin with therapeutic properties. The main constituent of this resin is boswellic acid that plays an important role in various fields. From past to present, many studies had been shown that olibanum and its main constituent, boswellic acid, have antiinflammatory, antioxidant, antitumor, anti-arthritic, antimicrobial and anti-carcinogenic effects. In addition, many findings about effects of *B. serrata* and its ingredients on central nervous system (CNS) are available. Therefore, the aim this study is to review *in vivo* and *in vitro* evidence attributed to this plant and its constituents on CNS. Databases including Web of Sciences, Scopus, PubMed and Google Scholar were explored for entries from the beginning of January 2000 until the end of November 2020. Findings reveal that *B. serrata* and its constituents have neuroprotective effects and ameliorate learning and memory malfunction. These effects mainly are attributed to the antioxidant and anti-inflammatory properties of this plant.

Keywords:

Boswellia serrata
Frankincense
Olibanum
Central nervous system

Introduction

Boswellia serrata (*B. serrata*) is a tree with moderate height which flourishes in various regions of the world such as Middle East, North Africa and India (Kimmatkar et al., 2003, Hosseini-sharifabad and Esfandiari, 2015a). The extract of this plant is rich in gum, essential oils, resin, β -boswellic acid, phenolic compounds, terpenoids and polysaccharides (Yang et al., 2020). Elimination of free radical, reduction of pro-inflammatory cytokines, neutralization of pathogens and suppression of pain have

been attributed to resin presented in extract of *B. serrata* (Siddiqui, 2011, Beghelli et al., 2017). Based on animal and human researches, *B. serrata* gum resin extract ameliorated the diseases affected from inflammation including osteoarthritis, asthma and rheumatoid arthritis (Abdel-Tawab et al., 2011). Decline of peritumoral brain edema followed by glioma by this herb has been also documented (Winking et al., 2000). Most pharmacological properties of *B. serrata* have been related to boswellic acids, 11-keto- β -boswellic acid (KBA) and

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acetyl-11-keto- β -boswellic acid (AKBA), which can selectively inhibit 5-lipoxygenase (Kunnumakkara et al., 2009). These compounds have been reported to inhibit human leukocyte elastase and topoisomerases I and II α (Syrovets et al., 2005). Boswellic acids have been also shown to be able to diminish leukocyte–endothelial cell adhesive interaction and to reduce the number of rolling and adherent leukocytes when they were used orally in rats (Kriegelstein et al., 2001). In addition, these acids induced apoptosis in the abnormal cells like glioblastoma cells, liver and colon cancer by increasing the level of death receptors and activating caspase-8 (Moussaieff and Mechoulam, 2009). Besides all these therapeutic properties attributed to *B. serrata*, in this review we reviewed the effects of this plant and its constituents on nervous system.

Methods

PubMed, Scopus and Google Scholar databases were used to collect scientific information from the beginning of January 2000 until the end of November 2020 in this review. The terms “*Boswellia serrata*”, “boswellic acid”, “olibanum”, “frankincense”, “central nervous system”, “Learning and memory” were searched. Besides animal and human studies, in vitro searches were considered. Letters to Editor were excluded from this review.

B. serrata resin constituents

Frankincense is an oleo-gum resin extracted from *B. serrata*. It is constituted from 67% resin, 20–23% mucopolysaccharides and 5–9% essential oil (Rijkers et al., 2006). The resin of *B. serrata* contains terpenoides including α -thujene, α -pinene, β -pinene cis-verbenol, trans-pinocarveol, myrcene, borneol, verbenone, p-cymene, limonene and boswellic acids (Syrovets et al., 2000, Kasali et al., 2002). Boswellic acids were known as main active ingredient among terpenoides (Siddiqui, 2011). Boswellic acids include KBA, AKBA and incensole acetate (Weber et al., 2006).

Neuroprotective effects

Hydro-alcoholic extract of *B. serrata* (3 and 6pg/ml) and its constituent AKBA (1 and 2.5pg/ml) protected PC12 neural cells against oxygen-glucose-serum deprivation-triggered cell injury. This neuroprotective effect was due to the alleviation of oxidative stress. In this study both the extract and AKBA could decrease

DNA oxidative damage, free radical concentration, lipid peroxidation (Sadeghnia et al., 2017). Aqueous and ethanolic extract of *B. serrata* (125, 250 and 500mg/kg) and AKBA (50mg/kg) have been shown to lessen brain damage and to save the neurons of cerebral cortex against stroke in rats. This protective property was associated with reduction of lipid peroxidation, elevated level of glutathione and increased activity of superoxide dismutase in cerebral cortex (Forouzanfar et al., 2016). Intraperitoneal injection of KBA (10 or 50mg/kg) could lower glutamate concentration stimulated by kainic acid and prevent neuronal death in CA3 area of hippocampus in rats. It was proposed that suppression of glutamate release happened via inhibiting N- and P/Q-type Ca²⁺ channels from hippocampal synaptosomes and suppressing the activity of protein kinase A (Lu et al., 2020). Intraperitoneal injection of AKBA (5mg/kg) and dexamethasone (1mg/kg) attenuated noxious impacts of lipopolysaccharide (LPS) on neuroinflammation in mice. This protective effect was due to decrement of inflammatory cytokines level as well as anti-amyloidogenic properties (Sayed et al., 2018). Acetyl-11-keto- β -boswellic acid (20mg/kg) could also ameliorate neuronal damage in a rat model of middle cerebral artery occlusion. Treatment with AKBA was associated with enhancing the activity of nuclear factor-2-related factor 2/hem oxygenase -1 pathway. This pathway reported to be as a main goal in brain protection against stroke (Ding et al., 2014). Assessment of neuroprotective properties of AKBA on neuronal damage caused by glutamate in neuron-like cells PC12 and N2a were examined. The results showed that 2.5–10 μ M of this compound rescued these cells from programmed cell death via down-regulating the expression ratio of Bax/Bcl2 and inhibiting of caspase 3. These effects are also attributed to antioxidant properties of 3-Acetyl-11-keto- β -boswellic acid (Rajabian et al., 2020b). Researchers investigated the effects of *B. serrata* gum resin on the morphology of pyramidal neurons in CA1 area of hippocampus in aged rats. Based on the results, administration of 100mg/kg of *B. serrata* gum resin for 8 weeks could increase the density of dendritic tree (Hosseini-sharifabad and Esfandiari, 2015b). The neuroprotective effects of *B. serrata* and its constituents were summarized in Table 1.

Effects on learning and memory

It has been documented that usage of 50 and 100mg/

TABLE 1: Neuroprotective effects of *B. serrata* and its constituents

Extract/Constituent	Dose	Study model	Effects	Ref.
Hydro-alcoholic AKBA	3 and 6 pg/ml 5mg/kg	PC12 cells	Decrease of DNA oxidative damage, free radical concentration and lipid peroxidation	Sadeghnia et al., 2017
Aqueous and ethanolic AKBA	125, 250 and 500mg/kg 50mg/kg	Rat	Protection of neurons of cerebral cortex against stroke through reducing lipid peroxidation, elevating the level of glutathione and increasing activity of superoxide dismutase	Forouzanfar et al., 2016
KBA	10 or 50mg/kg	Rat	Prevention of neuronal death in CA3 area of hippocampus through inhibiting N- and P/Q-type Ca ²⁺ channels and suppressing glutamate release	Lu et al., 2020
AKBA	5mg/kg	Mice	Attenuation of noxious impacts of lipopolysaccharide on neuro-inflammation	Sayed et al., 2018
AKBA	20mg/kg	Rat	Prevention of neuronal damage in middle cerebral artery occlusion via enhancing the activity of nuclear factor-2-related factor 2/hem oxygenase-1 pathway	Ding et al., 2014
AKBA	2.5-10 μM	Neuron-like cells PC12 and N2a	Inhibition of programmed cell death via down-regulating the expression ratio of Bax/Bcl2 and inhibiting of caspase 3	Rajabian et al., 2020b

kg of aqueous extract of frankincense fortified spatial memory retrieval dose-dependently in offspring rats. In this study treatment with extract heightened the level of mRNA expression of calcium/calmodulin kinase II (CaMKII) as a crucial player in memory formation in hippocampus tissue (Beheshti et al., 2018). The aqueous extract of *B. serrata* (1g/kg) was reported to increase dendritic processes of CA1 neurons in hippocampus. In this study *B. serrata* also augmented learning in pentylenetetrazol-kindled rats in passive avoidance task (Jalili et al., 2014). The useful effects of mixed extract of *B. serrata* (200mg/kg) and *Melissa officinalis* (400mg/kg) on scopolamine-induced memory impairment have been also documented. The results of Morris Water Maze (MWM) test showed an enhancing effect in spatial memory in rats treated by extracts. This memory enhancing effect was attributed to antineuroinflammatory, antioxidant and anti-acetylcholine esterase properties these plants (Mahboubi et al., 2016). Oral administration of *B. serrata* extract (300 and 400mg/kg) could promote spatial learning ability in diabetic rats by streptozotocin. Improving effect of *B. serrata* was linked to suppress the activity of glycogen synthase kinase 3 beta (GSK-3β), to alleviate oxidative stress status and to inhibit inflammatory responses in the brain of rats. Based on the results of this research the accumulation of amyloid plaques and neurofibrillary tangles in hippocampal tissue was also attenuated by extract (Gomaa et al.,

2019). Olibanum is a resin of *B. serrata*. Scientific evidences reveal that olibanum (100 and 500mg/kg) could restore hypothyroidism-triggered spatial memory deficits in rats. Based on the results of MWM test, traveled distance and delay to reach the hidden platform in rats treated with olibanum were lower than those of methimazole group (Hosseini et al., 2010). According the previous studies, boswellic acid (160mg/kg, IP) presented in gum resin of *B. serrata* restored cognitive dysfunction stimulated by trimethyltin in male Wistar rats in MWM test. These effects probable were mediated via reducing brain oxidative stress and inhibiting acetylcholine esterase enzyme (Ebrahimpour et al., 2017). In a study the effect of co-administration of AKBA (5mg/kg) and celecoxib (30mg/kg) as selective cyclooxygenase-2 inhibitor on LPS-agitated cognitive malfunction was checked in mice. In this work, the animals injected by AKBA and celecoxibe were more successful in performing behavioral tests including Y maze, radial maze and novel object recognition in comparison with mice treated by LPS. According the biochemical results of this study the memory repairmen followed by simultaneous use of AKBA and celecoxib likely resulted from diminishing the level of TNF-α, glutamate and amyloid beta peptide in brain tissue of mice (Sayed et al., 2016). It has been documented that administration 5 and 10mg/kg of AKBA 30min before LPS amplified retrieval memory in MWM and passive avoidance tasks by rats. Successful

TABLE 2: Effects of *B. serrata* and its constituents on learning and memory

Extract/Constituent	Dose	Study model	Effects	Ref.
Aqueous extract	50 and 100mg/kg	Rat	Improvement of spatial memory retrieval, increase the level of mRNA expression of CaMKII in hippocampus tissue	Beheshti et al., 2018
Aqueous extract	1 g/kg	Rat	Enhancement of dendritic processes of CA1 neurons in hippocampus, augmentation of learning in PTZ-kindled in passive avoidance task	Jalili et al., 2014
extract	200mg/kg	Rat	Betterment of spatial memory in scopolamine-induced memory impairment via reducing inflammatory responses, attenuating oxidative stress and inhibiting acetylcholine esterase	Mahboubi et al., 2016
Extract (extracted with petroleum ether)	300 and 400mg/kg	Rat	Promotion of spatial learning ability in streptozocin -induced diabetes through suppressing the activity of GSK-3 β , alleviating oxidative stress status and inhibiting inflammatory responses and decreasing the accumulation of amyloid plaques and neurofibrillary tangles in hippocampus tissue.	Gomaa et al., 2019
Olibanum	100 and 500mg/kg	Rat	Repairment of hypothyroidism-triggered spatial memory deficits	Hosseini et al., 2010
boswellic acid	160mg/kg	Rat	Improvement of cognitive dysfunction stimulated by trimethyltin via reducing brain oxidative stress and inhibiting acetylcholine esterase enzyme	Ebrahimpour et al., 2017
AKBA	5mg/kg	Mice	Reinforcement the performance of behavioral tests including Y maze, radial maze and novel object recognition through diminishing the level of TNF- α , glutamate and amyloid beta peptide in brain tissue	Sayed et al., 2016
AKBA	5 and 10mg/kg	Rat	Amplification of retrieval memory in MWM and passive avoidance tasks, elevation of IL-10, BDNF, superoxide oxide dismutase and catalase and lowering TNF- α , IL-6, NO, glial GFAP and malondialdehyde in hippocampal tissue	Marefati et al., 2020
AKBA	5mg/kg	Mice	Improvement of cognitive disturbances through reinforcing the signaling pathway of Nrf2/Ho-1 and intercepting inflammatory pathways related to NF- κ B	Wei et al., 2020
Olibanum and ethanolic extract	1 μ m 2 μ g/ml	B65 cell line	Regulation of gene expression of CREB-1 and CREB2	Jebelli et al., 2019

learning was accompanied with elevating IL-10, BDNF, superoxide oxide dismutase and catalase and lowering TNF- α , IL-6, nitric oxide, glial fibrillary acidic protein and malondialdehyde (MDA) in hippocampal tissue of rats (Marefati et al., 2020). AKBA (5mg/kg) has been also found to ameliorate cognitive disturbances through reinforcing the signaling pathway of Nrf2/Ho-1 and intercepting inflammatory pathways related to NF- κ B in APPswe/PS1dE9 mice (Wei et al., 2020). CREB-1 and CREB2 are two main transcription factors which can promote memory-linked genes transcription and potent long term memory. It has been found that olibanum (1 μ m) and ethanolic extract of *B serrata* (2 μ g/ml) reg-

ulated gene expression of CREB-1 and CREB2 in B65 cell line (Jebelli et al., 2019). The effects of *B. serrata* and its constituents on learning and memory were exhibited in Table 2.

Effects on neurodegenerative diseases

Alzheimer’s disease (AD) is well-known neurodegenerative disease in which memory is lost and person is unable to perform the daily activities (Brookmeyer et al., 2007). Beneficial effect of *B. serrata* and its constituents on AD was documented (Rajabian et al., 2020a). In a study the effect of aqueous extract of *B. serrata* (45 and 90 mg/kg/day) on AD induced by aluminum chloride

TABLE 3: Effects of *B. serrata* and its constituents on neurodegenerative disorder

Extract/Constituent	Dose	Type of neurodegenerative disorder	Study model	Effects	Ref.
aqueous	45 and 90 mg/kg	AD	Rat	Improvement of behavioral impairments caused by AlCl ₃ in rotarod and T-maze tests, increase of acetylcholine and decrease of acetylcholinesterase in the brain	Yassin et al., 2013
aqueous	50mg/kg	AD	Rat	Attenuation of dementia resulted from AD caused by chronic intracerebroventricular infusion of streptozotocin	Beheshti et al., 2016
Boswellic acid	250mg/kg	AD	Rat	Decrease of glucose, tau protein expression, MDA and an increase superoxide dismutase, catalase and glutathione peroxidase in hippocampus tissue	Mohamed et al., 2021
Ethylalcoholic	125, 250 and 500mg/kg	PD	Rat	Mitigation of motor deficits resulted from 6-OHDA in rotational and elevated narrow beam tasks	Doaee et al., 2019
Boswellia resin	10µg/ml	PD	SK-N-SH-cell line	Protection against MPP ⁺	Kazmi et al., 2011

was checked in rats. The results showed that high dose of extract improved behavioral impairments caused by aluminum chloride in rotarod and T-maze tests. In addition, both doses could increase the concentration of acetylcholine and decrease the level of acetylcholinesterase in the brain of rats (Yassin et al., 2013).

Researchers also reported that aqueous extract of frankincense (50mg/kg for 42 days) time dependently restored dementia resulted from AD caused by chronic intracerebroventricular infusion of streptozotocin. According to the results of passive avoidance test, the latency time to enter the dark chamber was high and time spent in dark compartment also was low in rats treated by extract (Beheshti et al., 2016).

Boswellic acid has been also shown to have improving effects on AD. It has been shown that boswellic acid (250mg/kg for 3 weeks) could ameliorate AD in an A β -induced rat model of this neurodegenerative disease. In this study the rats pretreated by boswellic acid had a decreased level of glucose, tau protein expression, MDA and an increased of antioxidant indexes such as superoxide dismutase, catalase and glutathione peroxidase in hippocampus tissue (Mohamed et al., 2021).

Parkinson's disease (PD) is a neurodegenerative disease accompanied with reduction or lack of dopamine in the brain and was characterized by muscle stiffness,

bradykinesia and resting tremor (Rocha et al., 2015). The results of studies exhibit that *B. serrata* and its ingredients can debilitate PD symptoms (Rajabian et al., 2020a). Ethylalcoholic extract of *B. serrata* (125, 250 and 500mg/kg) has been reported to mitigate motor deficits in rotational and elevated narrow beam tasks in a 6-hydroxydopamine triggered rat model of PD. This protective effect on nigrostriatal dopaminergic neurons has been linked to anti-inflammatory and antioxidant properties of *B. serrata* extract (Doaee et al., 2019).

In an in vitro study the effect of boswellia resin on neuronal death of SK-N-SH- cell line exposed by 1-methyl-4-phenylpyridinium (MPP⁺) was investigated. Based on results of this study 10µg/ml of boswellia resin could protect this human dopaminergic cells against MPP⁺ (Kazmi et al., 2011). The effects of *B. serrata* and its constituents on neurodegenerative disorder were presented in Table 3.

Anti-anxiety and anti-depressant effects

Anxiety disorders are psychiatric disorders which are known by restlessness, presentiment and fear. It has been understood that 50 and 200mg/kg of *B. serrata* could ameliorate anxiety behaviors in Swiss albino mice in light and dark arena and elevated plus maze tests. (Adake et al., 2015). In a clinical trial oral

administration of *B. serrata* reduced the intensity and frequency of headaches in patients with chronic cluster headaches (Lampl et al., 2012). Incensole acetate as a major component of boswellia resin has been reported to have the anti-depressive and anxiolytic effects (Moussaieff and Mechoulam, 2009). In addition, it has been found that incensole acetate induced anti-anxiety and anti-depressant effects in behavioral mice models (Moussaieff et al., 2008).

Conclusion

Based on the results of this literature review, *B. serrata* and its constituents especially boswellic acid exert protective effect on central nervous system and improve learning and memory impairments. Scientific evidences reveal that neuroprotective effects of this medicinal plant mainly are attributed to its antioxidant and anti-inflammatory properties. In addition, it was understood that *B. serrata* reinforces learning and memory via increasing acetylcholine and decreasing the level of acetylcholinesterase in brain.

Conflict of interest

Not declared

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