

Boswellic Acids as Promising Leads in Drug Development against Alzheimer's Disease

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Article Info

Article History:

Received: 9 January 2020

Accepted: 11 March 2020

ePublished: 18 March 2020

Keywords:

- Alzheimer's disease
- Boswellic acids
- Disease-modifying therapy
- Multi-target drug
- Plant derived scaffolds

Abstract

Biological activity of Boswellia extract (BE) has been attributed to its main active ingredients; i.e. Boswellic acids (BAs). BE/BAs possess a promising therapeutic potential in neurodegenerative disorders; including Alzheimer's disease (AD). The multifactorial nature of AD pathophysiology necessitates the development of the disease-modifying agents (DMA). Recent multi-targeting approaches for the DMAs development have brought more attention to the plant-derived compounds regarding their better human compatibility because of their biological origin. This review addresses the current knowledge on the anti-AD activity of BE/BAs based on the available *in silico*, *in vitro*, *in vivo* studies and clinical trials. The contribution of BE/BAs in inflammatory pathways, Tau and β -amyloid proteins, microtubule functions, oxidative stress, cholinesterase and diabetes/insulin pathways involved in AD have been discussed. BAs efficacy in different AD-related pathways has been confirmed *in vitro* and *in vivo*. They can be considered as valuable scaffold/lead compounds for multi-targeted DMAs in anti-AD drug discovery and development.

Introduction

Boswellia plant is native to India, Arabia and the northeastern coast of Africa.^{1,2} *Boswellia* extract (BE) or Frankincense gum resin has been used in traditional medicine in India and Iran.^{3,4} Different species of *Boswellia* produce BE. BE is known as Kundur in Iran. Persian physician, Avicenna, has recommended BE for the memory function improvement and prevention of amnesia in elderly persons, in his book (the Canon).^{4,5} In addition to medical applications, it is also used as incense in religious ceremonies and cosmetic ingredients (antiseptic agents in mouthwash, a fixative in perfumes, soaps, creams, lotions, and detergents).³ Chemical composition and biological activities of BE has been studied for years.^{1,2,6} BE contains essential oil (5–15%), mucus-like cluster (12–23%) and a lipophilic part (55–66%). The composition varies across different species (*Serrata*, *Papyrifera*, *Carterii*) and different grades.^{6–9} The lipophilic part includes terpenoid compounds. Tri-terpenoids that are known as *Boswellic* acids (BAs) are the biologically active entities of BE. BAs have a carboxylic group which connected to a pentacyclic triterpene containing at least one other functional group.^{2,10} Figure 1 shows the chemical structure of the most studied BA derivatives; i.e. β boswellic acid (β BA), Acetyl β boswellic acid (A β BA), α boswellic acid (α BA), Acetyl

α boswellic acid (A α BA), Acetyl-11-keto-boswellic acid (AKBA), 11-keto-boswellic acid (KBA). These compounds are highly lipophilic and possess poor absorption characteristics.¹¹

Acidic forms of these derivatives have ionization constant around 4 which could be a reason for their poor absorption in contrast to their lipophilic nature. More details about the BAs chemical characteristics along with their synthesis

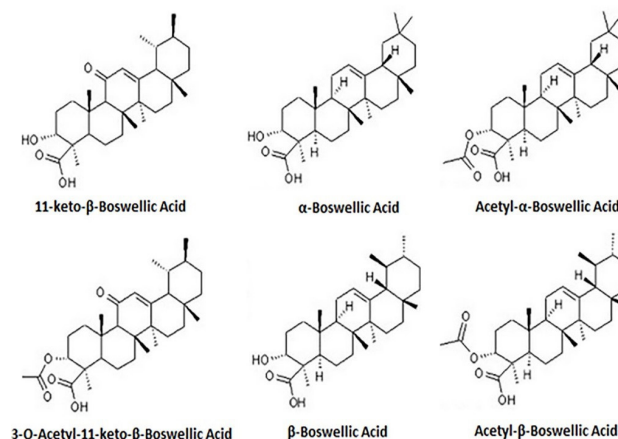


Figure 1. Chemical structures of Boswellic acid derivatives.

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and biosynthesis could be found in Al-Harrasi recent book about the BAs chemistry and bioactivity.¹²

AKBA and KBA are the most potent compounds and β BA is the most abundant derivative in extract.² Some derivatives of BAs are available commercially.¹³ BAs are responsible for the majority of the medical properties of *Boswellia*.¹ The therapeutic properties of for BE/BAs such as anti-inflammatory,^{14,15} antioxidant,^{16,17} immunomodulatory,¹⁸ chemotherapeutic,¹⁹ anti-hyperlipidemic and anti-obesity properties²⁰ have been reported. BEs/BAs efficacy in asthma, brain tumor edema, rheumatic diseases, and ulcerative colitis have been studied, and the promising applications have been suggested.^{1,7} BE/BAs role in neurodegenerative diseases (NDDs) has been investigated.^{4,21,22}

NDDs (also known as tauopathy disorders) are characterized by selective and progressive loss of structure or function of neurons. Alzheimer's disease (AD) is one of the most common types of NDDs. AD is characterized by progressive loss of memory and other cognitive functions.²³ A variety of co-pathologic cross-talks between different physiologic pathways and mechanisms lead to cognitive failure in AD. Abnormal neural network activity, functional impairment or loss of synapses and degeneration of specific neuronal populations are among the most studied factors that lead to cognitive failure.²⁴

The etiology of AD is unknown and the multifactorial pathogenesis of it has been discussed. Some of the pathophysiologic mechanisms of AD such as cholinergic mechanisms,²⁵ protein abnormalities,^{24,26} oxidative stress,²⁷ mitochondrial dysfunction^{28,29}, and neuroinflammation³⁰ have been studied for years. The available approved drugs against AD; i.e. acetylcholine esterase inhibitors (AChEIs: Donepezil, Galantamine) and N-methyl D-aspartate (NMDA) antagonists (Memantine), are symptomatic relief agents.³¹ The multifactorial nature of AD pathogenesis makes effective treatment development challenging. Recent approaches in AD treatment are suggesting multi-target agents with disease-modifying capabilities.³² Different synthetic and natural compounds with known multifunctional capabilities were studied as probable disease-modifying agents (DMA) in AD.³³

Different studies suggested an effective role for BE/BAs in AD-related pathways. Tau and β Amyloid ($A\beta$) pathways,²¹ cholinergic pathways,³⁴ inflammatory pathways,^{7,8} oxidative stress pathway²⁷ are among the most studied probable mechanism for BE/BAs anti-AD characteristics.

A number of studies suggested no steroidal anti-inflammatory drug (NSAID)-like activity for BAs,⁷ while related clinical trials are still in a relatively early phase.^{35,36} The inhibition of 5 lipoxygenases (5-LO)³⁷ and nuclear factor κ B (NF κ B)¹⁴ have been reported recently. The inhibition of acetylcholinesterase (AChE) enzyme activity^{34,38} and microtubule (MT) assembly dynamics for BAs^{39,40} have been reported. Also, possible beneficial effects of BAs on the experimental models of AD^{21,41} have been investigated. *In vivo* studies showed that oral administration of BAs

has resulted in the inhibition of $A\beta$ and Tau deposition in the brains of AD animal models.⁴² Also, improvements in behavioral impairment were observed in the same study.

A number of review papers published in recent years which mentioned the anti-AD capabilities of BAs.^{3,11,43-47} Roy *et al.* reviewed the molecular targets attributed to BAs pharmacological uses and biological activities.⁴⁷ Along with a diverse range of diseases, they also discussed the contribution of BAs to AD treatment briefly. Phytochemistry and potential therapeutic actions of BAs were reviewed in the year 2017 by Iram *et al.*, in which they discussed BAs neuroprotective effects along with other medicinal effects.¹¹ The pharmacological activities of BE derived compounds were reviewed by Sultana and co-authors.³ They discussed the anti AD activity of BAs and suggested that it might be related to their anti-inflammatory activity. Neuropharmacological effects of triterpenoids were reviewed by Parmar *et al.* in the year 2013.⁴³ They listed BAs among the pentacyclic triterpenoids which possess behavioral and psychopharmacological effects that could be contributed to their anti-inflammatory activity. Hamidpour *et al.*⁴⁴ reviewed the *Boswellia* application as the novel phytotherapy for the prevention and treatment of serious diseases including memory function. Yoo and Park in the year 2012 reviewed the role of terpenoids in AD disease.⁴⁵ They discussed the anti-AD effect along with molecular targets of *Ginkgolides Panax ginseng*, *Bilobalide* from *Ginkgo biloba*, and *Cannabinoids* from *Cannabis sativa*. Terpenoids originated from *Boswellia* species omitted in their paper.⁴⁵ BAs biological efficacies were reviewed by Shah *et al.* in the year 2008⁴⁶ as a group of medicinally important compounds. The authors included the results of the publications from 1980-2008 in their study. They mentioned the anti-AD activity of BAs, and related to the BAs' anti-inflammatory activity. An evidence-based systematic review of *Boswellia*, published in the year 2004³⁶ in which the authors, discussed *Boswellia's* role in inflammatory disease, while no evidence or study relating its effect in NDDs such as AD were included.

BE/BAs as phytotherapy agents and lead compounds for AD treatment have not been reviewed and there is no publication including detailed mechanism-based discussion on their probable role in AD. The present study provides an overview of the BE/BAs role in AD treatment based on the pathophysiology of AD. The available studies, patents, clinical trials that provided information about the BE/BAs in AD pathways have been reviewed and discussed. The included publications have been discussed in 4 main categories; i.e. *in vitro* studies, animal studies, human studies, and clinical trials.

Methods

All published papers and patents from the year 1980 to 2020 were searched using different combinations of relevant keywords; i.e. *Boswellia*, boswellic acid, Alzheimer's disease, terpenoid, natural compounds, disease-modifying agents, multi-target. Google Scholar,

PubMed, Science Direct, ACS, Proquest, US patents, Clinical trials, were searched. Clinical trials were included in the review if they investigated the AD symptoms even in other diseases. Overall 165 papers were found that have investigated/reviewed the BA/BEs role in AD-related targets or pathways. Some of the included papers have not been investigated BE/BA in AD but they have reported the relevant molecular mechanisms of BE/BAs.

Pathophysiology of AD and Related Treatment Strategies

AD is a progressive NDD, in which cognitive function impairment followed by behavioral changes happens.⁴⁸ Although AD is known for about a century, effective medication to prevent, halt, or reverse of AD is not available yet.²⁴ One reason for such a failure in AD treatment development is due to the complicated pathophysiology of AD. The pathophysiologic mechanisms involved in AD was shown schematically in Figure 2. According to the Figure 2, different pathways and mechanisms have been identified for AD in which Cholinergic, A β /Tau and, inflammation pathways are among the most studied pathways. Due to various types of targets, different approaches have been utilized for AD drug development. Table 1 shows a summary of the available strategies for AD drug development. Most of the strategies are in the research phase. The most studied AD development mechanisms and the related drug development strategies are reviewed in the following sections.

Cholinergic pathway

Cholinergic neurons depend on choline for returning to

resting state after activation. Choline is provided to them mainly by acetylcholine (ACh) hydrolysis with AChE. The deficiency of choline, in AD patients, ended up with the cholinergic hypothesis.³³ Cholinergic neurons as the main players in AD neurotransmission are responsible for maintaining the cortical function, cerebral blood flow, cognitive/memory function, learning a task, cerebral cortex development, and sleep-wake cycle regulation. A part of the complexity of the symptoms in AD is due to the multifunctional nature of the cholinergic neurons.⁴⁹

The dysfunction of the cholinergic system in AD occurs at various levels including a decreased AChE activity, reduced choline uptake, decrease in ACh synthesis and altered levels of ACh receptors (AChR). AChEIs (e.g. Tacrine, Donepezil, Rivastigmine and Galantamine (enhance cholinergic neurotransmission, and are the major class of FDA approved drugs for AD.³¹ AChE possesses some choline independent roles in AD. Its contribution to inflammation-related mechanisms has been studied and considered as possible targets for AD drugs.⁵⁰⁻⁵⁵ The other mechanisms such as complex formation with A β and its contribution to cell toxicity have been studied.^{56,57}

Protein abnormalities

A β and Tau proteins are among the most studied proteins in AD.²⁴ Their aggregation is known as one of the main hallmarks in the AD brain.⁵⁸

Tau is an unfolded cytosolic protein located in the brain, specifically in the axon of neurons. Human Tau which is a microtubule-associated protein (MAP) encoded on chromosome 17q21.⁵⁹ It plays an important role in axonal

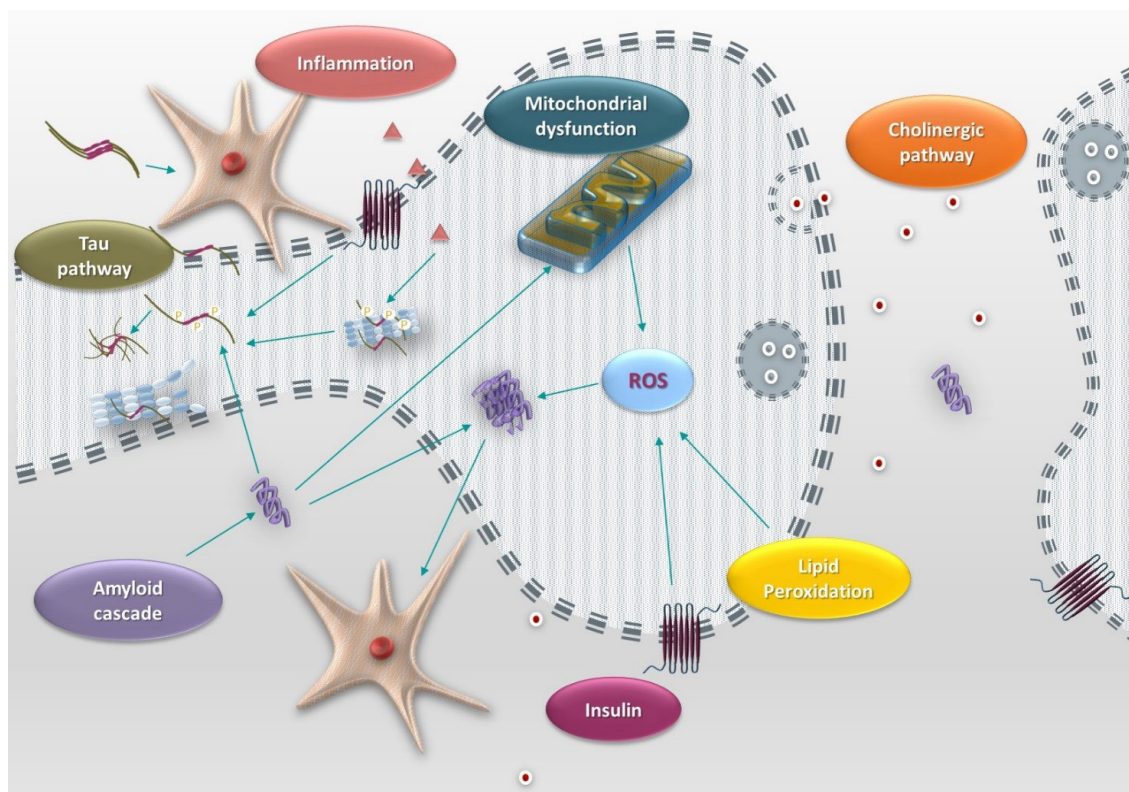


Figure 2. Probable Alzheimer's disease pathways affected by Boswellic acids

Table 1. AD treatment drug development strategie^{24,28,31,49,60}

Strategy	Involved mechanisms
Modulating neurotransmission	Acetylcholinesterase inhibitor (AChEI)*
	N-methyl D-aspartate (NMDA) antagonism*
	GABAergic modulation
	Serotonin receptor modulation
	Histaminergic modulation
	Adenosine receptor modulation
	Phosphorylation inhibition
Tau-based therapy	Microtubule stabilization
	Aggregation preventing
	Oligomerization blocking
	Enhancing Tau degradation
	immunotherapy
Amyloid based therapy	Secretase enzyme modulation
	Amyloid transport
	Aggregation preventing
	Clearance promoting
Intracellular signaling cascade	Immunotherapy
	Inhibition of the NF-κB system
Oxidative stress reduction	Inhibition of the production of ROS
Anti-inflammatory therapy	Inhibition of COX2, 5 lipoxygenase enzymes, interfering with complement pathway and reduction of inflammatory mediators
Mitochondrial targeting therapy	Microtubule stabilization
	Intranasal insulin
Others	Cell replacement
	Autophagy activators
	Metal chelators

* Approved by FDA³⁰

microtubule (MT) stabilization, neuronal development, neuronal polarity⁶⁰ and maintenance of DNA.⁶¹ Tau aggregation is promoted by charge compensation of the basic middle part of Tau which is triggered by polyanions.⁶² Aggregates of hyperphosphorylated Tau makes intracellular neurofibrillary tangles (NFTs). Distribution of Tau oligomers correlates with the duration, progression and clinical stages of AD (Braak stages).^{61,63} In addition, impairment of axonal transport in the mature neurons is a common factor in many of the major NDDs, including AD.⁶⁴ MTs are cytoskeletal structures that are critical for stable neuronal morphology and physiologic functions of neurons. Impairment of axonal transport in mature neurons (that depends on normal functions of MTs), is a common factor in many of the NDDs, including AD.⁶⁴ Defects in MT assembly and organization have been reported in AD. Brandt and Bacota⁶⁵ described the involvement of structure and dynamics change (Tau dependent/independent) of MTs in the neurodegenerative triad of AD. They argued that MT dynamics modulation could be regarded as a potential target for AD drugs. Aβ is responsible for extracellular senile plaques.⁶⁶ At

physiological concentrations Aβ peptide (picomolar), improves memory function. The overproduction of Aβ in the brain of AD patients and individuals with Down's syndrome is known as a promoter of oxidative damage which produces a chain of damage in neurons and synapses and starting point for the AD development.⁶⁷⁻⁶⁹ The AD initiation is connected to Aβ accumulation. Aβ-induced neurotoxicity is dependent on NFTs. The levels of Aβ plaques is not a discriminative factor between normal aging and AD.^{61,62} Recent studies results are supportive of the idea of targeting Aβ and Tau, as a promising approach, for the development of disease-modifying therapies in AD.^{70,71} Inhibition of Aβ and Tau aggregation in the brain is one of the most studied strategies for the development of AD therapies. During the past decade, various phytochemical compounds (e.g. *Curcumin*, *Cinnamon*) have been reported to be able to interfere with both Aβ and Tau aggregation and evidence provided using *in vitro* studies.^{48,72,73}

Inflammation

Neuroinflammation exacerbates AD pathogenesis. Aβ, NFTs and neurodegeneration are the most likely

sources for inflammation in the AD brain. They induce inflammation via inflammatory cytokines and chemokines (e.g. IL-1 β , IL-6, IL-8, TNF- α , TGF- β , MIP-1 α , IFN- γ , NF- κ B) as well as the complement system activation mechanisms which are unique to the central nervous system (CNS).^{74,75} Joshi and Pratico reviewed the role of lipoxygenases (LOXs) in the pathogenesis of AD and tried to discuss LOX contribution in both oxidative and inflammatory pathways.⁷⁶ 5-LOX is playing a role in the metabolism of Tau and A β through FLAP (5-lipoxygenase activating protein),⁷⁶ γ -secretase,⁷⁷ protein kinases A and C (PKA, PKC) and MAP kinases (ERK1/ERK2, p38).⁷⁸ Different studies showed that microsomal prostaglandin E synthase-1 (mPGES-1) is upregulated in the AD brain of rats⁷⁹ and humans.⁸⁰ The results of the study of mPGES-1 upregulation in the human AD brain suggested a potential role for the functional replacement of cytosolic PGES or inactive mPGES-1 in later stages of AD.⁸⁰ The role of mPGES-1 in inflammatory brain diseases including AD was reviewed by Ikeda-Matsuo.⁸¹ They discussed the promising capability of mPGES-1 as a target for the new therapeutics in this area. Different studies suggested that treatment with anti-inflammatory drugs, such as NSAIDs, reduces the incidence and progression of AD.^{28,82}

Oxidative stress

Oxidative stress has an important role in the pathogenesis of AD through damage to vital cellular elements such as nucleic acids, lipids, and proteins.⁸³ It is well known that oxidative stress and oxidant/antioxidant imbalance is one of the hallmarks of AD. Oxidative stress pathway is one of the most interesting pathways in the multi-targeting anti-AD agents' development.⁸⁴⁻⁸⁶

Wojsiat *et al*⁸⁴ reviewed the impact of oxidative stress and oxidant/antioxidant imbalances in AD. They concluded that both the reactive oxygen species (ROS) generation and the cellular oxidative stress defense mechanisms are compromised in the brain as well as in the peripheral tissues in AD.⁸⁴

Mitochondria dysfunction is known as an important factor involved in the pathogenesis of AD, through the production of ROS,^{29,87,88} and modulation of Tau phosphorylation.^{63,89} A β and Tau-induced oxidative stress in neuronal cells is a cause of AD pathology and antioxidant therapy is one of the pharmacological approaches for AD treatment is.⁶³

Diabetes and Insulin

Evidence for the prevalence of diabetes and AD is getting higher.⁹⁰ There are a lot of studies which confirm the hyperglycemia as a potential risk factor in the development of AD. A lot of studies showed that diabetes-induced impairment of memory is associated with an increase in oxidative stress.⁹¹

Hyperglycemia induces brain insulin resistance, increases A β accumulation on brain lesions, neuroinflammation and mitochondrial dysfunction. It also impairs neuronal integrity and causes neurodegeneration.^{92,93} In both cell

culture and transgenic mice studies, high glucose condition increases A β production by inhibiting A β precursor protein (APP) degradation, not by increasing APP synthesis and abnormal insulin signaling in the brain. Insulin resistance increases A β accumulation and Tau phosphorylation in diabetic rodent models.⁹⁴ Systemic administration of insulin is associated with reduced penetration in the brain and a higher risk of hypoglycemia.^{95,96} In several clinical studies, intranasal administration of insulin has been tested.⁹⁷ After intranasal administration, insulin bypasses the Blood-Brain Barrier (BBB) and reaches significant biologic concentrations in the brain.^{95,97} Intranasal insulin administration improves memory and enhances the mood in AD patients in which improves cerebral glucose metabolism and preserves the volume of brain regions affected by AD pathology.^{96,97} *In vitro* studies showed that insulin inhibits neuronal apoptosis via activation of protein kinase B.^{96,98} *In vivo* studies revealed that insulin regulates Tau phosphorylation, APP metabolism and A β clearance.⁹⁹ Prevent or ameliorate cognitive dysfunction through Type 2 diabetes-specific treatment is one of the AD treatment approaches which has been interested in researches in recent years.⁹⁶ One of the main characteristics of this approach is the availability of a large number of common hallmarks between AD and diabetes in which oxidative stress and inflammation could be highlighted.

BEs' and BAs' Efficacy in AD

In Vitro studies

The probable molecular mechanisms of BE/BAs efficacy as anti-AD treatments were investigated *in vitro* and the results are discussed in different studies. Table 2 contains the AD-related *in vitro* studies of BE/BAs. The details of the related studies are discussed in the following sections.

Inhibition of AChE activity

Riazi and coworkers reported the effect of amino acid derivatives of β BA and AKBA on the inhibition of AChE in the *in vitro* studies.^{34,100} They showed that the coupling of AKBA and β BA with valine and leucine amino acids can successfully strengthen the effect of BAs on the decline of the AChE activity. Other studies suggested high AChEI activity (46-71% inhibition) for BE,³⁸ and the *Boswellia* oil (96% inhibition and IC₅₀ value 0.043 \pm 0.02 mg/ml).¹⁰¹ Ota and Houghton reported high AChEI activity (80%) for 11-hydroxy- β BA.¹⁰²

Microtubule stabilization

In an *in vitro* study, Karima *et al.*⁴⁰ reported the effect of β BA on hippocampal neurite outgrowth and branching. They showed that β BA has the capability of the enhancement of neurite outgrowth, branching, and tubulin polymerization dynamics. Following that study, they examined the effect of β BA on the assembly dynamics behavior of tubulin to address the mechanism of neurites outgrowth and branching enhancement by β BA.⁴ They reported that β BA could significantly enhance the MAP polymerization dynamic

and MT length, which may consequently prevent axonal degeneration and MT disruption. They concluded that β BA can be a useful agent against NDDs and memory loss.

Tau and A β proteins

Different studies reported the effect of terpenoids on A β /Tau aggregation, and Tau hyperphosphorylation.^{45,91} Investigation of the effect of α BA on human astrocytes revealed its capability to reduce hyperphosphorylated Tau.¹⁰³

Our investigation on the probable direct interaction between Tau (hTau34) protein and β BA using Surface Plasmon Resonance (SPR) technique, suggested the formation of Tau- β BA complex under physiologic pH.¹⁰⁴ Molecular docking investigation in two different studies revealed that terpenoids are the most potent and safe inhibitor of both AChE and A β aggregation.^{105,106}

We investigated the Tau interaction with β BA and the results showed the capability of β BA binding to Tau via PGGG loops by hydrophobic interactions as the main driving force for the binding.¹⁰⁴ Additional studies are required to investigate the precise activity of BAs on A β and Tau related AD treatment.

Antioxidant activity

Antioxidant activity of BEs was studied using methanol extract of *Salvia macrochlamys* and the results confirmed their antioxidant potency and capability for use in pharmaceutical as antioxidant agents.¹⁶ Antioxidant activity (free radical scavenger capacity) of *B.serrata* aqueous extracts were studied and the results revealed a dose-dependent antioxidant activity.¹⁰⁷ The similar results were obtained for *Boswellia* oil¹⁰⁸, and methanolic leaf

extract.¹⁰⁹ A recent *in vitro* study on the antioxidant power of BEs revealed the higher antioxidant potency for the extracts with higher concentrations of polyphenols and AKBA.¹¹⁰

Anti-inflammatory activity

BE/BAs anti-inflammatory activity has been reported in different studies.^{8,19,111} Different studies showed that AKBA reduces chronic inflammation through the inhibition of the NF κ B system¹⁴, while other inflammatory targets; e.g. LL-37 (cathelicidin related peptides) and Human leukocyte elastase (HLE) have been reported¹¹² as well. Also, BAs inhibit the 5-LOX enzyme and consequent inhibition of 5-hydroxyicosatetraenoic (5-HETE) and leukotriene B4 (LTB4) production^{36,113}, HLE.^{1,112} They also reversibly suppress the transformation of prostaglandin (PG) H2 to E2 mediated by mPGES-1 (IC₅₀ = 3–10 mM).¹¹⁴ As discussed earlier in this paper 5-LOX plays a significant role in Tau and A β metabolism and its inhibition with BAs could be considered as one of the main AD treatment mechanisms of BAs.

The results of some BAs and their semisynthetic derivatives 5-LOX inhibitory activity showed that AKBA and KBA are more potent inhibitors than β BA and 3-O-acetyl-BA.^{8,111,115,116}

Suppression of PGE2 formation by BAs (AKBA, KBA, and β BA) via interference with mPGES-1, was studied using a protein fishing approach and the results showed that BAs could reduce PGE2 formation by inhibiting mPGES-1.¹¹⁴ Also, they reported concentration-dependent blocking of PGE2 biosynthesis in intact A549 cells.¹¹⁴ The results of a cell-based assay in the same study suggested a functional role for BAs in PGE2 formation reduction, in which β BA

Table 2. The *in vitro* studies of BE/BAs on the AD related targets

Strategy	Assay method	Studied ingredient	Results	Ref.
Microtubule stabilization effect	Embryonic hippocampal cells	10,20,30 nM β BA	β BA could increase both MT length and axonal outgrowth and branching	4,40
	Spectroscopy	β BA/ AKBA	Inhibited AChE activity	34,102
Inhibition of AChE activity	Mass and NMR spectroscopy	BE, AChE-I	Only 11 α -hydroxy- β -boswellic acid and KBA have AChE-I activity	110
		AKBA, BE	Antioxidant and Anti-inflammatory activity	110
Anti-oxidative activity	Free radical scavenging assay	<i>B.serrata</i> 500 μ g/mL	Antioxidant activity in a concentration dependent manner	107
		<i>Boswellia</i> oil	Antioxidant and antimicrobial activity	108
Anti-inflammatory activity	Human neutrophils	AKBA, KBA, β BA and α BA	Inhibition of 5-LOX product formation and Cat-G	15,114
	HLE, 5-HETE, LTB4 production by spectroscopy	AKBA, BE	Inhibition of 5-LOX	8,11,36, 112, 113
	NF- κ B-dependent cytokine expression	BE	Inhibiting NF- κ B activity, decrease NO production	19,43, 111,117
	Human whole blood, A549 cells	β BA	Suppressed levels of PGE2 mediated by mPGES1	114

selectively reduced the PGE2 formation.¹¹⁴ This evidence suggests the contribution of the anti-inflammatory activity of BEs/BAs, as a part of their promising effect in AD treatment.

Anti-diabetic activity

Both type 1 and type 2 diabetes activity of BE and KBA have been studied.¹¹⁸ Ammon¹¹⁸ reviewed the present evidence of the therapeutic effects and the underlying molecular mechanisms of BE and/or KBA in the prevention/ treatment of diabetes mellitus recently. The author concluded that the BE and/or KBA may prevent insulin resistance in type 1 and type 2 diabetes by inhibiting the expression of proinflammatory cytokines from immunocompetent cells. There is no *in vitro* study which specifically studies the effect of BE/BAs on shared mechanisms of AD and Diabetes. We studied the effect of β BA-Tau interaction in the presence and absence of the glucose in which the results showed that the presence of glucose interferes with the β BA-Tau complex formation in a way that affinity decreased significantly by the enhancement of glucose concentration.¹⁰⁴

Preclinical studies of BEs/BAs role in AD

BE/BAs effect in AD has been studied extensively in animal models. Some of the reported *preclinical* studies are summarized in Table 3. According to the table, most of the conducted studies confirmed the capability of BE/BAs in the AD treatment.

BBB permeability of BAs studied using a rat model and the results revealed the highest brain/plasma ratio for β BA compared to KBA and AKBA which indicates facilitated BBB permeability for β BA.¹¹⁹ The crossing of the BAs from the BBB and improvement of A β ¹²⁰ and NFTs formation studied in AD induced rats. Oral administration of BE (90 mg/kg) to the adult male Sprague Dawley rats had protective effects against oxidative damage.²¹ Also returning to the healthy neurons in the affected brain regions and NFTs level reduction was reported in their study.

The different probable underlying mechanisms for the contribution of BE in AD treatment were studied on adult male Wistar rats with AD (induced using AlCl₃).⁴² Oral administration of BE resulted in a significant reduction in brain ACh along with significant elevation in serum and brain AChE. Also, a significant decrease in brain CRP, NF κ B, MCP-1, and LTB4 levels was observed.⁴² They concluded that the potent effect of *B.serrata* against AD stems from its ability to ameliorate cholinergic dysfunction, inhibit the inflammatory mediators and promote neuronal survival. A group of researchers reported the increased level of ACh and decreased level of AChE enzyme in AD rats (induced using AlCl₃) after oral treatment with BE. The reported variation in the cholinesterase pathway showed a dose-dependent activity.²¹

In a recent study, the effect of BE on the cognitive impairment of diabetic rats was investigated.⁹¹ The results showed that hippocampal elevated levels of AChE were

significantly decreased due to BE consumption.

Different studies showed that oral BE reduces inflammatory mediators (IL-1 β , IL-6, TNF- α , IFN- γ , cathepsin G (Cat G) and PGE2 level significantly, and increases the level of IL-10.^{11,15,43,120} The effect of *B.carterii* on memory loss in rats (induced by lipopolysaccharide (LPS)) was studied and the results showed a significant reduction of TNF- α in the hippocampus of rats as well as a significant increase in the step-through latency.¹²¹ The authors concluded that the hydroalcoholic extract of the *Boswellia* was able to retrieve the memory of studied rats probably due to anti neuro inflammatory property.

Werts *et al.* investigated the BAs' contribution to the reduction of PGE2 formation. They studied carrageenan-induced rat pleurisy and mouse paw edema after intraperitoneal or oral administration of BAs.¹¹⁴ They found that β BA selectively suppresses the production of PGE2, while cyclooxygenase (COX) pathway metabolites' levels were not altered. According to their results β BA clearly exhibited anti-inflammatory activity. They concluded that interference with mPGES-1 might represent a reasonable molecular mechanism contributing to some of the anti-inflammatory properties of BE.

Increased or decreased level of cathepsin as a lysosomal protein, can lead to functional impairment and gradual death of neurons.¹²² A systematic review published recently¹²³ provided an overview of the role of cathepsins in AD. According to their review, the main role of cathepsins is related to their contribution to A β degradation. Another review paper discussed the positive and negative contribution of cathepsin B in AD which mostly is related to the A β degradation/metabolism.¹²⁴ Other researchers reported the upregulation of cathepsin D in the AD human brain neocortex¹²⁵ and inducing of AD-like phenotype in LPS treated mice, by cathepsin B.¹²⁶ Most of the other similar studies investigated the role of cathepsins B and D (cysteine cathepsins) in AD and another aging-related disease.^{122,123} The BAs effect on cathepsin G was investigated using cell-based and computational methods, and the results showed that BAs interact directly and functionally with Cat G.¹⁵ There are few reports about the contribution of cathepsin G in AD which are against the probable role for it in AD.¹²⁷⁻¹²⁹ There is no report on the probable interaction of BAs with other cathepsins.

The effect of the combination therapy of AKBA, as a 5-LOX inhibitor and Celecoxib as a selective COX-2 inhibitor on LPS cognitive dysfunction mice model, was studied and the results showed improved cognitive-behavioral functions for dual enzyme inhibitors compared to monotherapies.¹¹⁹ Histochemical study of the mice brain showed a reduction of the A β deposition in the cerebral cortical region in the same study.¹¹⁹ According to the results, the effect of AKBA on cognitive behavior improvement was comparable with Celecoxib.

The effect of BE on the cognitive impairment reduction of diabetic rats was investigated recently, and the results showed the probable contribution of the antioxidant

effect of the active compounds on the preventive effect of BE on cognitive impairment.¹³⁰ According to this study BE treatment produced a significant reduction in an oxidative damage marker (Malondialdehyde (MDA)), in the hippocampus of diabetic rats and enhanced the antioxidant enzyme activities of glutathione peroxidase (GSH) and Superoxide dismutase (SOD).

Neuroprotective effect of BE due to the antioxidant effect was studied in a rat model and the results showed reduced GSH content and increased MDA level in the cerebral cortex that suggests the antioxidant activity as a mechanism of anti-AD efficacy.¹³¹

Some studies reported that BEs can improve behavioral and anatomical deficits.^{132,133} Beheshti and Aghaei investigated the effect of BE in streptozotocin-induced AD models of adult male Wistar rats.⁵⁵ Their results showed

that chronic administration of BE improves dementia type AD in a time-dependent manner.⁵⁵ In another study,¹²¹ the results of the administration of BE before LPS injection to the male Wistar rats indicated that BE reduces the LPS induced memory. Also, the reduction of TNF- α levels in the hippocampus of rats was reported in the same study. They suggested that the anti neuroinflammatory activity of BEs could be involved in their Anti AD effect.

Protective effects of BE against AD in male Albino rats (AlCl₃ induced AD) were studied, and the results were in agreement with previous findings of the probable anti AD activity of BE.¹³⁴ The results showed that in addition to the memory and learning improvement, *B.carteri* extract can possess a neuroprotective effect on rats with AD. Prevention of lipid peroxidation (LPO) rising, increased levels of GSH, Glutathione disulfide (GSSG) and SOD,

Table 3. The *in vivo* studies of BE/BAs anti-AD effects in animal models

Animal model	Treatment	Neuropathological and biochemical investigation	Behavioral investigation	Ref.
Wistar rats	BSE (68.75 , 137.5 mg/kg/d) orally for 3 months	A significant increase in brain ACh, a significant decrease in brain and serum AChE activity, CRP, NF κ B, MCP-1, LTB ₄ , Bcl-2 and A β plaque burden in hippocampus and striatum	ND	42
Sprague Dawley rats	BSE (90 mg/kg /day) orally for two weeks	A significant increase in Brain ACh, a significant decrease in brain AChE activity and decrease A β , NFT plaque burden	Retrieval of memory in the behavioral tests	21
Wistar rats	BSE(50 mg/kg; orally for 6 weeks)	Significant reduction in hippocampal TNF- α level	Significant facilitation of spatial learning and memory	55,115
CD1 mice, Wistar rats	β BA (1 mg/kg; I.P. or orally 30 min before carrageenan) mouse paw edema and pleurisy	Markedly lower PGE2 levels by inhibition of mPGE ₁ , inhibition of cathepsin G and 5-LOX activity	ND	114
Albino diabetic rats	BE(500 mg /kg/day) orally for 5 weeks	Ameliorate the NDDs characteristics of AD. Significant increase GSH content	Improve memory and learning	130
Wistar rats	<i>B.Carterii</i> (40, 80 and 160 mg/kg/d, I.P for 3 weeks)	Significant inhibitory effect against AChE increased the GSH content and reduced the MDA level	Significant improvement in learning and memory	131
Wistar rats	BSE (100 mg/kg/d; orally for 8 weeks)	Neuro-anatomical basis for memory improvement, attenuate dendritic regression in CA1 of Hippocampus.	ND	132,135
Wistar diabetic rats	BAs (200-400 mg/kg/d; orally for 8 weeks)	Reduced significantly the hippocampal elevated levels of caspase-3, AChE, GSK-3 β , TNF- α , IL-1 β , IL-6, MDA and GSH, SOD, glutamate receptor expression also inhibited extracellular deposits of amyloid plaques and the intracellular NFT	Significantly ameliorates cognitive decline	91
NMRI mice, Wistar rats	<i>B. Papyrifera</i> (50-150 mg/kg, orally)	ND	Facilitation of spatial learning and memory	133,136
Albino Wistar rats	<i>B. Carteri</i> (500 mg /kg/day) orally for 8 weeks	Significant decrease brain neurotransmitters as DA, NE, GABA, GSH, GSSD, SOD and AChE activity. Improve hippocampus histopathological changes	Improve the learning and memory	134

N.D (not described) - *Boswellia Serrata* extracts (BSE) - Intraperitoneal(I.P)

enhancement in the neurotransmitter (Norepinephrine, Dopamine and gamma-Aminobutyric acid (GABA)) formation in the brain and decreased AChE activity was detected in BE treated AD rats in this study.¹³⁴ According to these results, the authors suggested the contribution of antioxidative stress activity of the BE in its potential protective and therapeutic role in AD.

The effect of *B.papyrifera* extract on learning and memory of male Wistar rats and male NMRI mice was studied and the results showed that its oral administration significantly decreased the number of days required to make the mice learned as per set criteria and time took to find the food by the learned mice in the radial arm maze model.¹³³ In addition, *B.papyrifera* extract leads to a decrease in escape latency as well as an increase in the animal swimming speed in the morris water maze model. Spatial memory retention in male rats was studied after administration of total extract of *B.papyrifera* and the results were compared with BAs fraction administration in the same study.¹³⁵

According to the results, both total extract and BAs fraction reduced escape latency and distance traveled in studied rats significantly. In addition, their findings indicated a dose-dependent manner for the BAs fraction in spatial memory retention enhancement. Recently a group of researchers investigated the effects of chronic administration of BAs on the learning performance and the morphology of hippocampal granule cells in the aged rats.¹³² Their results showed that BE improved learning capability in the aged male Wistar rats. Also, their data showed the enhancement of dendritic arbors and dendritic spines in hippocampal granule cells.

According to the results of a recent study, *B.serrata* treated aged rats, had greater stratum pyramidal volumes and stratum radiatum lacunosum molecular.¹³⁶ The Results also indicated more numerical branching density in the apical dendrites of CA1 pyramidal neurons for the rats *B.serrata* extract treated rats. A recent study investigated the effect of BE on the cognitive impairment of diabetic rats, and the results showed that BE prevents cognitive impairment.⁹¹ The authors reported a significant decrease in A β deposits and p-Tau positive cells after BE consumption.

Clinical studies

Few number of clinical trials have been reported the results of BE/BAs efficacy study in patients (Table 4). Most of the available trials are related to the inflammatory diseases such as bronchial asthma,^{137,138} osteoarthritis of the knee,^{35,129,139,140} joint discomfort,¹⁴¹ Crohn disease,^{142,143} collagenous colitis,¹⁴⁴ chronic colitis,¹⁴⁵ moderate plaque-induced gingivitis,¹⁴⁶ erythematous eczema and psoriasis¹³ osteo muscular pain,¹³⁷ while other diseases such as heavy menstrual bleeding,¹⁴⁷ diabetes,^{20,148} prevention of adjuvant radiotherapy skin damage,¹⁴⁹ multiple sclerosis (MS),¹⁵⁰ osteoarthritis (as pain reliever)¹⁵¹ are studied too.

The safety profile of BEs/BAs was investigated by monitoring of the vital signs or measuring the hematological and biochemical parameter and no safety perturbation was

observed.¹⁴² Overall good tolerability was reported in different trials. Only a few adverse effects (diarrhea, abdominal pain, and nausea) were reported.⁷ A prospective, placebo-controlled, and a double-blind pilot clinical trial was conducted on 27 patients with brain edema. 14 patients received a high dose of BEs (4.2 g per day) orally, while 13 patients received placebo. The results showed that BE was well tolerated after oral administration.¹⁵²

Phase II studies for anti-inflammatory/anti-arthritis effects of BEs provide proof of the efficacy.⁴¹ The effect of a tablet containing *B.serrata* and *M.officinalis* extract, on older adults (70 years and older) memory, was studied through a randomized controlled trial and the results suggested beneficial effects for the administered tablets.

In a randomized clinical trial, a study in type 2 diabetic patients, administration of 400 mg *Boswellia* gum resin capsules two times a day after meal, leads to the reduced fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c) and insulin. Also, cholesterol (Chol), LDL and triglyceride (TG) levels significantly decreased without any significant effects on the other blood lipid levels and liver/kidney function tests compared with the placebo at the endpoint.²⁰

A recent study of *B.serrata* extract effect on the blood glucose and lipid profile of diabetic patients showed considerable reduction after the intervention in the field of FBS, HbA1c, and TG in the BE administered group, while no significant difference was observed in all outcome measures between the two groups at the end of study.¹⁴⁸

The effect of *B.papyrifera* extract on cognitive impairment in MS patients was investigated on 80 patients.¹⁵³ The results showed that *B.papyrifera* significantly improved visuospatial memory, but it had no effect on verbal memory and information processing speed.

The efficacy of a mixture of *B.carterii*, *Z.officinale*, and *A.millefolium* was investigated on the severity of symptoms, anxiety, and depression in irritable bowel syndrome (IBS) patients.¹⁵⁴ The results suggested a reduction of pain, anxiety, and depression in studied patients. Analgesic activity of *B.serrata* was investigated in healthy volunteers and the results suggested a significant enhancement in the pain threshold, pain tolerance force and time compared to placebo.¹⁵⁵

Researchers investigated the effect of herbal medicine, D.Loban (DL: a mixture of *C.rotundus* L., *Z.officinale*, *Acorus calamus* L., *P.nigrum* L., and *B.carterii*) on 24 patients with mild to moderate AD. The results showed the improvement of memory in DL treated patients compared with the placebo group. But they didn't report any data on the application of *B.carterii* alone.¹⁵⁶ There is no published or submitted clinical trial to investigate the effect of BAs independently on AD.

Patents

There is one patent¹⁵⁷ in the USA that mentioned the application of incense and different forms of BAs derivatives in the treatment of AD.

Table 4. Studies of the BEs/BAs efficacy in different disease in patient and healthy volunteers

Condition	Treatment	Findings	Ref.
Asthma	23 males and 17 females (18 - 75 y)- BSE 300 mg/tid for 6 w	Disappearance of physical symptoms and signs	138
Knee osteoarthritis	440 patients with - BSE 24 w 75 patients- BSE tid for 4 w 105 patients- BSE for 90 d 210 patients-Curcumin+ BSE 150mg/ tid for 12 w	Reduced knee pain and improved knee function	129,140,141,151
Crohn's disease (CD)	108 patients- BSE 1200 mg/bid for 52 w 102 patients- BSE	Good tolerability, safety and efficacy in long-term treatment	142,143
Collagenous colitis	31 patients- BSE 400 mg/tid for 6 w	Efficacy in treatment	144
Chronic colitis	30 patients- BSE 300 mg/tid for 6 w	Effective in the treatment	145
Gingivitis	75 patients (15-18 y)-BSE for 2 w	Improve inflammation	146
Erythematous eczema and psoriasis	BSE 30 d tropical oil	Promising effect for treatment of erythematous eczema and psoriasis	13
Osteo-muscular pain	BSE 4-week for 52 healthy young rugby players with acute knee pain and inflammation	Effective and safe treatment	137
Menstrual bleeding	102 patients- <i>ginger</i> + BSE 300 mg/tid for 1 w	Effective complementary treatments	147
Diabetes	56 patients- BSE 250 mg/bid for 8 w 71 patients- BSE 400 mg/bid for 12 w	Had no better glucose and lipid-lowering effect than placebo as a safe anti-oxidant, anti-hyperglycemic and anti-hyperlipidemic agent	20,148
Adjuvant radiotherapy skin damage	114 women with breast cancer patients- <i>Boswellia</i> cream	Prevent or alleviate radiation-induced skin reactions	149
Multiple sclerosis (MS)	80 MS patients -BSE 300 mg/bid for 2 months	Significant improvement in visuospatial memory	153
Irritable bowel syndrome (IBS)	60 IBS patients- mixture of <i>B. Carterii</i> , <i>Z. officinale</i> , and <i>A. millefolium</i>	Effective in eliminating IBS symptoms	154
Analgesic	12 healthy subjects- BSE 250 mg/ single dose	Significantly increased the pain threshold and pain tolerance force	151,155

tid: three times a day, bid: two times a day, w: weeks, BSE: *Boswellia serrata* extract

BAs as Disease-Modifying Scaffolds

Today, drug discovery for AD is one of the most challenging and difficult tasks in medicinal chemistry. AD has multifactorial etiology and complex pathophysiology. Understanding the pathogenesis of AD, the critical elements underlying the mechanism of it and the disease process are crucial bottlenecks of AD drug discovery. Accordingly, over the last decade, a growing number of researches has focused on DMAs¹⁵⁸ in which more than 80% of phase II and III DMAs are belonging to the anti-A β and anti Tau drugs. Anti-inflammatory agents and cell-protecting drugs are also studied frequently. The drug-target space in AD still is not completely understood and more information is needed about the underlying mechanisms of AD beginning, progression and ameliorating. Interdisciplinary and collaborative approaches along with a correlation between clinical outcomes and biomarkers are the main facilitators of DMAs development. Researchers

are using a combination of diverse drug discovery tools such as phenotypic based drug discovery (better tools are developing by the application of advanced assay tools, organoids, and artificial intelligence-based data translation), poly-pharmacology based screening and multi-target drug design methods to develop DMAs for AD. They are hopeful about the potential of these strategies to develop new promising AD treatment drugs.

At the same time, the enterprise of drug discovery for AD is still challenging with respect to addressing potency, toxicity, and pharmacokinetic problems during the hit optimization. The availability of the relevant cellular and animal models that closely mimic human clinical conditions in AD is another challenging issue. The absence of effective tests to monitor the course of treatment and certify the cure of patients is also a very serious problem that must be faced in parallel with efforts to develop new drugs. To address one of the main challenges of multi-target

drug discovery; i.e. small drug discovery, researchers have been used natural products as a valuable source of excellent small molecule scaffolds. Chemical entities originated from nature are among the most valuable lead compounds in drug design and discovery especially for complex diseases like AD. Natural compounds could be regarded as biologically pre-validated platforms for the design of compound libraries in the search for new drug candidates.¹⁵⁹ In addition, their incredible diversity provides a higher possibility of candidate compound selection in the current paradigm of drug discovery (i.e. multi-targeting approach rather than one molecule one target approach),¹⁶⁰ especially for the complex disease.^{161,162} A large number of studies have used natural compounds and related databases in the design and discovery of multi-targeted anti AD agents.^{104,161,163-165}

The current review provided a comprehensive summary of the available evidence on the effectiveness of BEs and BAs in AD. The biologic activities of BAs have been studied extensively confirming their multi-targeting nature. Al Harrasi *et al.* discussed *Boswellia's* diversity and biological activity within a recently published book.⁶

Our review showed that although there are a vast number of *in silico*, *in vitro* and *in vivo* preclinical studies on the probable contribution of BE/BAs in AD treatment. Clinical trials that are investigating the effect of BE/BAs in AD patients are rare. We believe that translation of the results obtained from preclinical studies to the clinical applications needs rigorous pharmacokinetic/ pharmacodynamic analysis and more molecular and mechanistic studies. Fortunately, the drugability of the BAs has been examined and described in different diseases which facilitates and accelerates AD drug designing from BAs. In addition, animal studies have confirmed the effectiveness of BAs in AD treatment.

Due to acceptable potency and diversity in targets and mechanisms of action, BAs are regarded as a valuable scaffold for multi-target based DMAs development for AD. Both additive (act on different targets in one pathway) and synergistic (act on different targets on different pathways) approaches in DMAs development for AD can be covered by BAs.

Conclusion

To the best of our knowledge, most of the available studies related to the BE/BAs efficacy in AD were reviewed and included in this paper. According to the current comprehensive review, BEs along with their active ingredients; i.e. BAs, are promising agents for AD treatment. Their anti-oxidative stress, anti-inflammatory, and anti-diabetic efficacies along with their AChE inhibitory and anti-A β activities together with their effects on the modulation of Tau deposition and hyperphosphorylation in the brain have introduced them as powerful multi-targeting lead compounds. These wonderful natural compounds could be considered as successful scaffolds in DMA discovery and development, for AD treatment. Although no clinical trial

has been reported to approve the actual benefits of BE/BAs in AD patients, according to the traditional medicine of Iran and India, BE/BAs are efficient in the reinforcement of memory, especially in elderly people. Also, clinical trials approved BE/BAs efficacy in some diseases with shared hallmarks with AD (e.g. inflammation, oxidative stress, diabetic symptoms, memory function, etc). In conclusion, further *in vitro* and *in vivo* studies are needed to clarify the detailed mechanistic contribution of BAs to AD treatment. In addition, detailed *in silico* studies are needed to discuss BAs structure-activity relationships and apply the results for rational DMA development against AD.

Acknowledgments

The authors would like to thank the Vice Chancellor for Research, Tabriz University of Medical Sciences, under grant number of D/P/3 which was a part of the Ph.D. thesis of Dr. Hossein Haghaei.

Conflict of Interest

The authors claim that there is no conflict of interest.

References

1. Ammon HP. Boswellic acids in chronic inflammatory diseases. *Planta Med.* 2006;72(12):1100-16. doi:10.1055/s-2006-947227
2. Zhang Y, Ning Z, Lu C, Zhao S, Wang J, Liu B, Xu X, Liu Y. Triterpenoid resinous metabolites from the genus *Boswellia*: pharmacological activities and potential species-identifying properties. *Chem Cent J.* 2013;7(1):153. doi:10.1186/1752-153X-7-153
3. Sultana A, Padmaja AR. *Boswellia serrata* Roxb. a traditional herb with versatile pharmacological activity: a review. *Int J Pharm Sci Res.* 2013;4(6):2106-17.
4. Karima O, Riaz G, Khodadadi S, Yousefi R, Mahnam K, Mokhtari F, et al. An *in vitro* study of the role of β -boswellic acid in the microtubule assembly dynamics. *FEBS Lett.* 2012;586(23):4132-8. doi:10.1016/j.febslet.2012.10.007
5. Ahmadian-Attari MM, Ahmadiani A, Kamalinejad M, Dargahi L, Shirzad M, Mosaddegh M. Treatment of Alzheimer's disease in Iranian traditional medicine. *Iran Red Crescent Med J.* 2014;17(1):e18052. doi:10.5812/ircmj.18052
6. Al-Harrasi A, Rehman NU, Khan AL, Al-Broumi M, Al-Amri I, Hussain J, et al. Chemical, molecular and structural studies of *Boswellia* species: β -Boswellic Aldehyde and 3-epi-11 β -dihydroxy BA as precursors in biosynthesis of boswellic acids. *PLoS One.* 2018;13(6):e0198666. doi:10.1371/journal.pone.0198666
7. Abdel-Tawab M, Werz O, Schubert-Zsilavec M. *Boswellia serrata*: an overall assessment of *in vitro*, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet.* 2011;50(6):349-69. doi:10.2165/11586800-000000000-00000

8. Siddiqui MZ. *Boswellia serrata*, a potential antiinflammatory agent: an overview. *Indian J Pharm Sci.* 2011;73(3):255-61. doi:10.4103/0250-474X.93507
9. Schmiech M, Lang SJ, Werner K, Rashan LJ, Syrovets T, Simmet T. Comparative analysis of pentacyclic triterpenic acid compositions in oleogum resins of different *Boswellia* species and their in vitro cytotoxicity against treatment-resistant human breast cancer cells. *Molecules.* 2019;24(11):2153. doi:10.3390/molecules24112153
10. Hill RA, Connolly JD. Triterpenoids. *Nat Prod Rep.* 2018;35(12):1294-1329. doi:10.1039/c8np00029h
11. Iram F, Khan SA, Husain A. Phytochemistry and potential therapeutic actions of Boswellic acids: A mini-review. *Asian Pac J Trop Biomed.* 2017;7(6):513-23. doi:10.1016/j.apjtb.2017.05.001
12. Al-Harrasi A, Hussain H, Csuk R, Khan HY. Chemistry of Boswellic acids and other terpenoids of the genus *Boswellia*. Amsterdam: Elsevier; 2019. p. 9-66. doi:10.1016/B978-0-08-102441-6.00002-5
13. Togni S, Maramaldi G, Di Pierro F, Biondi M. A cosmeceutical formulation based on boswellic acids for the treatment of erythematous eczema and psoriasis. *Clin Cosmet Investig Dermatol.* 2014;7:321-7. doi:10.2147/CCID.S69240
14. Cuaz-Pérolin C, Billiet L, Baugé E, Copin C, Scott-Algara D, Genze F, et al. Antiinflammatory and antiatherogenic effects of the NF- κ B inhibitor acetyl-11-keto- β -boswellic acid in LPS-challenged APOE $^{-/-}$ mice. *Arter Thromb Vasc Biol.* 2008;28(2):272-7. doi:10.1161/ATVBAHA.107.155606
15. Tausch L, Henkel A, Siemoneit U, Poeckel D, Kather N, Franke L, et al. Identification of human cathepsin g as a functional target of boswellic acids from the anti-inflammatory remedy frankincense. *J Immunol.* 2009;183(5):3433-42. doi:10.4049/jimmunol.0803574
16. Assimopoulou A, Zlatanov S, Papageorgiou V. Antioxidant activity of natural resins and bioactive triterpenes in oil substrates. *Food Chem.* 2005;92(4):721-7. doi:10.1016/j.foodchem.2004.08.033
17. Topcu G, Ertas A, Kolak U, Ozturk M, Ulubelen A. Antioxidant activity tests on novel triterpenoids from *Salvia macrochlamys*. *Arkivoc.* 2007;7:195-208. doi:10.3998/ark.5550190.0008.716
18. Mehta M, Satija S, Nanda A, Garg MJAJDDD. Nanotechnologies for Boswellic acids. *Am J Drug Disc Dev.* 2014;4:1-11. doi:10.3923/ajdd.2014.1.11
19. Shah BA, Qazi GN, Taneja SC. Boswellic acids: A group of medicinally important compounds. *Nat Prod Rep.* 2009;26(1):72-89. doi:10.1039/B809437N
20. Azadmehr A, Ziaee A, Ghanei L, Fallah Huseini H, Hajiaghvae R, Tavakoli-Far B, et al. A randomized clinical trial study: Anti-oxidant, anti-hyperglycemic and anti-hyperlipidemic effects of olibanum gum in type 2 diabetic patients. *Int J Pollut Res.* 2014;13(3):1003-9.
21. Yassin N, El-Shenawy S, Mahdy KA, Gouda N, Marrie A, Farrag A, et al. Effect of *Boswellia serrata* on Alzheimer's disease induced in rats. *J Arab Soc Med Res.* 2013;8:1-11.
22. Jiang XW, Zhang BQ, Qiao L, Liu L, Wang XW, Yu WH. Acetyl-11-keto-beta-boswellic acid extracted from *Boswellia serrata* promotes schwann cell proliferation and sciatic nerve function recovery. *Neural Regen Res.* 2018;13(3):484-91. doi:10.4103/1673-5374.228732
23. Nieoullon A. Neurodegenerative diseases and neuroprotection: Current views and prospects. *J Appl Biomed.* 2011;9:173-83. doi:10.2478/v10136-011-0013-4.
24. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. *Cell.* 2012;148(6):1204-22. doi:10.1016/j.cell.2012.02.040
25. Terry AV, Jr., Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: Recent challenges and their implications for novel drug development. *J Pharmacol Exp Ther.* 2003;306(3):821-7. doi:10.1124/jpet.102.041616
26. Tramutola A, Lanzillotta C, Perluigi M, Butterfield DA. Oxidative stress, protein modification and Alzheimer disease. *Brain Res Bull.* 2017;133:88-96. doi:10.1016/j.brainresbull.2016.06.005
27. Huang WJ, Zhang X, Chen WW. Role of oxidative stress in Alzheimer's disease. *Biomed Rep.* 2016;4(5):519-22. doi:10.3892/br.2016.630
28. Wang J, Tan L, Wang HF, Tan CC, Meng XF, Wang C, et al. Anti-inflammatory drugs and risk of Alzheimer's disease: An updated systematic review and meta-analysis. *J Alzheimers Dis.* 2015;44(2):385-96. doi:10.3233/JAD-141506
29. Selfridge JE, Lezi E, Lu J, Swerdlow RH. Role of mitochondrial homeostasis and dynamics in Alzheimer's disease. *Neurobiol Dis.* 2013;51:3-12. doi:10.1016/j.nbd.2011.12.057
30. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 2015;14(4):388-405. doi:10.1016/s1474-4422(15)70016-5
31. Anand R, Gill KD, Mahdi AA. Therapeutics of Alzheimer's disease: Past, present and future. *Neuropharmacology.* 2014;76:27-50. doi:10.1016/j.neuropharm.2013.07.004
32. Zhang HY, Yang DP, Ji HF. Naturally occurring multipotent anti-Alzheimer's agents. *Expert Opin Drug Discov.* 2006;1(3):269-77. doi:10.1517/17460441.1.3.269
33. Williams P, Sorribas A, Howes M-JR. Natural products as a source of Alzheimer's drug leads *Nat Prod Rep.* 2011;28(1):48-77. doi:10.1039/c0np00027b
34. Esmaeili S, Naeini FB, Nezhati MN, Afrasiabi A, Modaresi SMS, Dadras A, et al. Synthesis and the inhibitory effects of amino acid derivatives of β -boswellic acid on acetylcholinesterase. *Int J Pharm Sci Rev Res.* 2014;28(1):200-6.
35. Kimmatkar N, Thawani V, Hingorani L, Khyani R.

- Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial. *Phytomedicine*. 2003;10(1):3-7. doi:10.1078/094471103321648593
36. Basch E, Boon H, Davies-Heerema T, Foppo I, Hashmi S, Hasskarl J, et al. Boswellia: An evidence-based systematic review by the natural standard research collaboration. *J Herb Pharmacother*. 2004;4(3):63-83. doi:10.1080/J157v04n03_06
37. Safayhi H, Boden SE, Schweizer S, Ammon HP. Concentration-dependent potentiating and inhibitory effects of boswellia extracts on 5-lipoxygenase product formation in stimulated PMNL. *Planta Medica*. 2000;66(2):110-3. doi:10.1055/s-2000-11136
38. Bakthir H, Ali NA, Arnold N, Teichert A, Wessjohann L. Anticholinesterase activity of endemic plant extracts from soqotra. *Afr J Tradit Complement Altern Med*. 2011;8(3):296-9. doi:10.4314/ajtcam.v8i3.65292
39. Kohoude MJ, Gbaguidi F, Agbani P, Ayedoun M-A, Cazaux S, Bouajila J. Chemical composition and biological activities of extracts and essential oil of *Boswellia dalzielii* leaves. *Pharm Biol*. 2017;55(1):33-42. doi:10.1080/13880209.2016.1226356
40. Karima O, Riaz G, Yousefi R, Movahedi AAM. The enhancement effect of β -Boswellic acid on hippocampal neurites outgrowth and branching (an in vitro study). *Neurol Sci*. 2010;31(3):315-20. doi:10.1007/s10072-010-0220-x
41. Taghizadeh M, Maghaminejad F, Aghajani M, Rahmani M, Mahboubi M. The effect of tablet containing *Boswellia serrata* and *Melisa officinalis* extract on older adults' memory: A randomized controlled trial. *Arch Gerontol Geriatr*. 2018;75:146-50. doi:10.1016/j.archger.2017.12.008
42. Ahmed H, Mohamed E, El-Dsoki S. Evidences for the promising therapeutic potential of *Boswellia serrata* against Alzheimer's disease: Pre-clinical study. *Int J Pharm Pharm Sci*. 2014;6(11):384-92.
43. Parmar SK1, Sharma TP1, Airao VB, Bhatt R, Aghara R, Chavda S. Neuropharmacological effects of triterpenoids. *Phytopharmacology*. 2013;4(4):354-72.
44. Hamidpour R, Hamidpour S, Hamidpour M, Shahleri M. Frankincense (rǔ xiāng; boswellia species): From the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases. *J Tradit Complement Med*. 2013;3(4):221-6. doi:10.4103/2225-4110.119723
45. Yoo K Y, Park S YJM. Terpenoids as potential anti-Alzheimer's disease therapeutics. *Molecules*. 2012;17(3):3524-38. doi:10.3390/molecules17033524
46. Bhahwal AS, GhulamNQ, SubhashCT. Boswellic acids: A group of medicinally important compounds. *Nat Prod Rep*. 2008:72-89. doi:10.1039/B809437N
47. Roy NK, Parama D, Banik K, Bordoloi D, Devi AK, Thakur KK, et al. An update on pharmacological potential of boswellic acids against chronic diseases. *Int J Mol Sci*. 2019;20(17):4101. doi:10.3390/ijms20174101
48. Hamaguchi T, Ono K, Yamada M. Curcumin and Alzheimer's disease. *CNS Neurosci Ther*. 2010;16(5):285-97. doi:10.1111/j.1755-5949.2010.00147.x
49. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: A review of progress. *J Neurol Neurosurg Psychiatry*. 1999;66(2):137-47. doi:10.1136/jnnp.66.2.137
50. Yasumasa Y, Ayako K, Chieko I, Kimihito A. Antiinflammatory action of donepezil ameliorates tau pathology, synaptic loss, and neurodegeneration in a tauopathy mouse model. *J Alzheimers Dis*. 2010:295-306. doi:10.3233/JAD2010100681
51. Nizri E, Hamra-Amitay Y, Sicsic C, Lavon I, Brenner T. Anti-inflammatory properties of cholinergic up-regulation: A new role for acetylcholinesterase inhibitors. *Neuropharmacology*. 2006;50(5):540-7. doi:10.1016/j.neuropharm.2005.10.013
52. Burčul F, Generalić Mekinić I, Radan M, Rollin P, Blažević I. Isothiocyanates: Cholinesterase inhibiting, antioxidant, and anti-inflammatory activity. *J Enzyme Inhib Med Chem*. 2018;33(1):577-82. doi:10.1080/14756366.2018.1442832
53. Kamal MA, Greig NH, Reale M. Anti-inflammatory properties of acetylcholinesterase inhibitors administered in Alzheimers disease. *Antiinflamm Antiallergy Agents Med Chem*. 2009;8(1):85-100. doi:10.2174/187152309787580810
54. Tabet N. Acetylcholinesterase inhibitors for Alzheimer's disease: Anti-inflammatories in acetylcholine clothing! *Age Ageing*. 2006;35(4):336-8. doi:10.1093/ageing/af027
55. Beheshti S, Aghaie R. Therapeutic effect of frankincense in a rat model of Alzheimer's disease. *Avicenna J Phytomed*. 2016;6(4):468-75.
56. Inestrosa N, Alvarez A, Godoy J, Reyes A, De Ferrari G. Acetylcholinesterase-amyloid- β -peptide interaction and wnt signaling involvement in a β neurotoxicity. *Acta Neurol Scand Suppl*. 2000;102:53-9. doi:10.1034/j.1600-0404.2000.00308.x
57. Viayna E, Sabate R, Muñoz-Torrero D. Dual inhibitors of β -amyloid aggregation and acetylcholinesterase as multi-target anti-Alzheimer drug candidates. *Curr Top Med Chem*. 2013;13(15):1820-42. doi:10.2174/15680266113139990139
58. Boutajangout A, Sigurdsson EM, Krishnamurthy PK. Tau as a therapeutic target for Alzheimer's disease. *Curr Alzheimer Res*. 2011;8(6):666. doi:10.2174/156720511796717195
59. Neve RL, Harris P, Kosik KS, Kurnit DM, Donlon TA. Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. *Mol Brain Res*. 1986;1(3):271-80. doi:10.1016/0169-328X(86)90033-1
60. Avila J, Jiménez JS, Sayas CL, Bolós M, Zabala JC,

- Rivas G, et al. Tau structures. *Front Aging Neurosci.* 2016;8:262. doi:10.3389/fnagi.2016.00262
61. Wang Y, Mandelkow E. Tau in physiology and pathology. *Nat Rev Neurosci.* 2016;17(1):22. doi:10.1038/nrn.2015.1
62. Mandelkow E-M, Mandelkow E. Biochemistry and cell biology of tau protein in neurofibrillary degeneration. *Cold Spring Harb Perspect Med.* 2012;2(7):a006247. doi:10.1101/cshperspect.a006247
63. Alavi Naini SM, Soussi-Yanicostas N. Tau hyperphosphorylation and oxidative stress, a critical vicious circle in neurodegenerative tauopathies? *Oxid Med Cell Longev.* 2015;2015:151979. doi:10.1155/2015/151979
64. Kapitein LC, Hoogenraad CC. Building the neuronal microtubule cytoskeleton. *Neuron.* 2015;87(3):492-506. doi:10.1016/j.neuron.2015.05.046
65. Brandt R, Bakota L. Microtubule dynamics and the neurodegenerative triad of Alzheimer's disease: The hidden connection. *J Neurochem.* 2017;143(4):409-17. doi:10.1111/jnc.14011
66. Ramachandran G, Udgaonkar JB. Mechanistic studies unravel the complexity inherent in tau aggregation leading to Alzheimer's disease and the tauopathies. *Biochemistry.* 2013;52(24):4107-26. doi:10.1021/bi400209z
67. Haubrich J, Machado A, Boos FZ, Crestani AP, Sierra RO, de Oliveira Alvares L, et al. Enhancement of extinction memory by pharmacological and behavioral interventions targeted to its reactivation. *Sci Rep.* 2017;7(1):10960. doi:10.1038/s41598-017-11261-6
68. Morley JE, Farr SA. The role of amyloid-beta in the regulation of memory. *Biochem Pharmacol.* 2014;88(4):479-85. doi:10.1016/j.bcp.2013.12.018
69. Golde TE, Petrucelli L, Lewis J. Targeting $\alpha\beta$ and tau in Alzheimer's disease, an early interim report. *Exp Neurol.* 2010;223(2):252-66. doi:10.1016/j.expneurol.2009.07.035
70. Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid- β oligomers. *Nature.* 2009;457(7233):1128. doi:10.1038/nature07761
71. Giacobini E, Gold G. Alzheimer disease therapy—moving from amyloid- β to tau. *Nat Rev Neurol.* 2013;9(12):677. doi:10.1038/nrneurol.2013.223
72. Wobst HJ, Sharma A, Diamond MI, Wanker EE, Bieschke J. The green tea polyphenol (-)-epigallocatechin gallate prevents the aggregation of tau protein into toxic oligomers at substoichiometric ratios. *FEBS Letters.* 2015;589(1):77-83. doi:10.1016/j.febslet.2014.11.026
73. Peterson DW, George RC, Scaramozzino F, LaPointe NE, Anderson RA, Graves DJ, et al. Cinnamon extract inhibits tau aggregation associated with Alzheimer's disease in vitro. *J Alzheimers Dis.* 2009;17(3):585-97. doi:10.3233/JAD-2009-1083
74. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. *Neurobiol Aging.* 2000;21(3):383-21. doi:10.1016/S0197-4580(00)00124-X
75. Aisen PS. Inflammation and Alzheimer's disease: Mechanisms and therapeutic strategies. *Gerontology.* 1997;43(1-2):143-9. doi:10.1159/000213842
76. Joshi YB, Praticò D. The 5-lipoxygenase pathway: Oxidative and inflammatory contributions to the Alzheimer's disease phenotype. *Front Cell Neurosci.* 2015;8:436. doi:10.3389/fncel.2014.00436
77. Chu J, Praticò D. The 5-lipoxygenase as modulator of Alzheimer's γ -secretase and therapeutic target. *Brain Res Bull.* 2016;126(Pt 2):207-12. doi:10.1016/j.brainresbull.2016.03.010
78. Czapski GA, Czubowicz K, Strosznajder JB, Strosznajder RP. The lipoxygenases: Their regulation and implication in Alzheimer's disease. *Neurochem Res.* 2016;41(1-2):243-57. doi:10.1007/s11064-015-1776-x
79. Akitake Y, Nakatani Y, Kamei D, Hosokawa M, Akatsu H, Uematsu S, et al. Microsomal prostaglandin e synthase-1 is induced in Alzheimer's disease and its deletion mitigates Alzheimer's disease-like pathology in a mouse model. *J Neurosci Res.* 2013;91(7):909-19. doi:10.1002/jnr.23217
80. Chaudhry U, Zhuang H, Doré S. Microsomal prostaglandin E synthase-2: Cellular distribution and expression in Alzheimer's disease. *Exp Neurol.* 2010;223(2):359-65. doi:10.1016/j.expneurol.2009.07.027
81. Ikeda Matsuo Y. The role of mpeg-1 in inflammatory brain diseases. *Biol Pharm Bull.* 2017;40(5):557-63. doi:10.1248/bpb.b16-01026
82. Lee Y J, Han SB, Nam S-Y, Oh K-W, Hong JT. Inflammation and Alzheimer's disease. *Arch Pharmacol Res.* 2010;33(10):1539-56. doi:10.1007/s12272-010-1006-7
83. Feng Y, Wang X. Antioxidant therapies for Alzheimer's disease. *Oxid Med Cell Longev.* 2012;2012:472932. doi:10.1155/2012/472932
84. Wojsiat J, Zoltowska KM, Laskowska-Kaszub K, Wojda U. Oxidant/antioxidant imbalance in Alzheimer's disease: Therapeutic and diagnostic prospects. *Oxid Med Cell Longev.* 2018;2018:6435861. doi:10.1155/2018/6435861
85. Rosler M, Retz W, Thome J, Riederer P. Free radicals in Alzheimer's dementia: Currently available therapeutic strategies. *J Neural Transm Suppl.* 1998;54:211-9. doi:10.1007/978-3-7091-7508-8_21
86. Jeandel C, Nicolas MB, Dubois F, Nabet-Belleville F, Penin F, Cuny G. Lipid peroxidation and free radical scavengers in Alzheimer's disease. *Gerontology.* 1989;35(5-6):275-82. doi:10.1159/000213037
87. Zhao Y, Zhao B. Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxid Med Cell Longev.* 2013;2013:316523. doi:10.1155/2013/316523

88. Smith DG, Cappai R, Barnham KJ. The redox chemistry of the Alzheimer's disease amyloid β peptide. *Biochim Biophys Acta*. 2007;1768(8):1976-90. doi:10.1016/j.bbamem.2007.02.002
89. Zambrano CA, Egaña JT, Núñez MT, Maccioni RB, González-Billault C. Oxidative stress promotes τ dephosphorylation in neuronal cells: The roles of cdk5 and pp1. *Free Radic Biol Med*. 2004;36(11):1393-402. doi:10.1016/j.freeradbiomed.2004.03.007
90. Association As. 2018 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2018;14(3):367-429. doi:10.1016/j.jalz.2018.02.001
91. Gomaa AA, Makboul RM, Al-Mokhtar MA, Nicola MA. Polyphenol-rich *Boswellia serrata* gum prevents cognitive impairment and insulin resistance of diabetic rats through inhibition of gsk3 β activity, oxidative stress and pro-inflammatory cytokines. *Biomed Pharmacother*. 2019;109:281-92. doi:10.1016/j.biopha.2018.10.056
92. Overman MJ, Pendleton N, O'Neill TW, Bartfai G, Casanueva FF, Forti G, et al. Glycemia but not the metabolic syndrome is associated with cognitive decline: Findings from the european male ageing study. *Am J Geriatr Psychiatry*. 2017;25(6):662-71. doi:10.1016/j.jagp.2017.02.004
93. Lee HJ, Seo HI, Cha HY, Yang YJ, Kwon SH, Yang SJ. Diabetes and Alzheimer's disease: Mechanisms and nutritional aspects. *Clin Nutr Res*. 2018;7(4):229-40. doi:10.7762/cnr.2018.7.4.229
94. Yang Y, Wu Y, Zhang S, Song W. High glucose promotes abeta production by inhibiting app degradation. *PLoS One*. 2013;8(7):e69824. doi:10.1371/journal.pone.0069824
95. Freiherr J, Hallschmid M, Frey II WH, Brünner YF, Chapman CD, Hölscher C, et al. Intranasal insulin as a treatment for Alzheimer's disease: A review of basic research and clinical evidence. *CNS Drugs*. 2013;27(7):505-14. doi:10.1007/s40263-013-0076-8
96. Tumminia A, Vinciguerra F, Parisi M, Frittitta L. Type 2 diabetes mellitus and Alzheimer's disease: Role of insulin signalling and therapeutic implications. *Int J Mol Sci*. 2018;19(11):3306. doi:10.3390/ijms19113306
97. Avgerinos KI, Kalaitzidis G, Malli A, Kalaitzoglou D, Myserlis PG, Lioutas VA. Intranasal insulin in Alzheimer's dementia or mild cognitive impairment: A systematic review. *J Neurol*. 2018;265(7):1497-510. doi:10.1007/s00415-018-8768-0
98. Logie L, Ruiz Alcaraz AJ, Keane M, Woods YL, Bain J, Marquez R, et al. Characterization of a protein kinase B inhibitor in vitro and in insulin-treated liver cells. *Diabetes*. 2007;56(9):2218. doi:10.2337/db07-0343
99. Rad SK, Arya A, Karimian H, Madhavan P, Rizwan F, Koshy S, et al. Mechanism involved in insulin resistance via accumulation of β -amyloid and neurofibrillary tangles: Link between type 2 diabetes and Alzheimer's disease. *Drug Des Devel Ther*. 2018;12:3999-4021. doi:10.2147/DDDT.S173970
100. Naeini FB, Esmaeili S, Dadras A, Modaresi SMS, Nezhati MN, Afrasiabi A, et al. Synthesis and the inhibitory effects of amino acid derivatives of 3-o-acetyl-11-keto-beta-boswellic acid on acetylcholinesterase. *Int J Pharm Sci Rev Res*. 2014;28(1):200-6.
101. Abbas G, Albroumi MA, Rehman NU, Hussain H, Al-Harrasi AS. Evaluation of essential oils from *Boswellia sacra* and *Teucrium mascatense* against acetyl cholinesterase enzyme and urease enzyme. *Indian J Pathol Microbiol*. 2017;8(4): 500-5. doi:10.5138/09750185.1901
102. Ota M, Houghton P. Boswellic acid with acetylcholinesterase inhibitory properties from frankincense. *Nat Prod Commun*. 2008;3(1):339;21-6. doi:10.1177%2F1934578X0800300105
103. Fathi E, Katouli FH, Riazi GH, Shasaltaneh MD, Parandavar E, Bayati S, et al. The effects of alpha boswellic acid on reelin expression and tau phosphorylation in human astrocytes. *Neuromolecular Med*. 2017;19(1):136-46. doi:10.1007/s12017-016-8437-3
104. Haghaei H, Aref Hosseini SR, Soltani S, Fathi F, Mokhtari F, Karima S, et al. Kinetic and thermodynamic study of beta-boswellic acid interaction with tau protein investigated by surface plasmon resonance and molecular modeling methods. *Bioimpacts*. 2019;231-9. doi:10.15171/bi.2020.03
105. Awasthi M, Upadhyay AK, Singh S, Pandey VP, Dwivedi UN. Terpenoids as promising therapeutic molecules against Alzheimer's disease: Amyloid beta- and acetylcholinesterase-directed pharmacokinetic and molecular docking analyses. *Mol Simul* 2018;44(1):1-11. doi:10.4172/2161-1459.C1.014
106. Manigandan V, Ramanathan T. In silico docking of mangrove derived ligands against Alzheimer's receptor proteins. *Curr Res Neurosci*. 2014;4(1):18-24. doi:10.3923/crn.2014.18.24
107. Sharma A, Upadhyay J, Jain A, Kharya MD, Namdeo A, Mahadik KR. Antioxidant activity of aqueous extract of *Boswellia serrata*. *J Chem Bio PhySci*. 2011;1:60-71.
108. Suhailah SAJ, Soheir NAER, Sahar KhA. Comparative study of antimicrobial and antioxidant activity of the oil of *Boswellia* (frankincense) and synthesized silver nanoparticles. *J Food Agric Environ*. 2018;16(1):20-5. doi:10.1234/4.2018.5477
109. Afsar V, Mohan Reddy Y, Saritha KV. In vitro antioxidant activity and anti-inflammatory activity of methanolic leaf extract of *Boswellia serrata*. *Int J LifeSc Bt & Pharm Res*. 2012;1(4):15-23.
110. Beghelli D, Isani G, Roncada P, Andreani G, Bistoni O, Bertocchi M, et al. Antioxidant and *ex vivo* immune system regulatory properties of *Boswellia serrata* extracts. *Oxid Med Cell Longev*. 2017;2017:7468064. doi:10.1155/2017/7468064
111. Calixto JB, Campos MM, Otuki MF, Santos AR. Anti-inflammatory compounds of plant origin. Part ii. Modulation of pro-inflammatory cytokines,

- chemokines and adhesion molecules. *Planta Med.* 2004;70(02):93-103. doi:10.1055/s-2004-815483.
112. Safayhi H, Rall B, Sailer E-R, Ammon HPT. Inhibition by boswellic acids of human leukocyte elastase. *J Pharmacol Exp Ther.* 1997;281(1):460-3.
 113. Ammon H, Safayhi H, Mack T, Sabieraj J. Mechanism of antiinflammatory actions of curcumine and boswellic acids. *J Ethnopharmacol.* 1993;38(2-3):105-12. doi: 10.1016/0378-8741(93)90005-P
 114. Siemoneit U, Koeberle A, Rossi A, Dehm F, Verhoff M, Reckel S, et al. Inhibition of microsomal prostaglandin E2 synthase1 as a molecular basis for the anti-inflammatory actions of Boswellic acids from frankincense. *Br J Pharmacol.* 2011;162(1):147-62. doi:10.1111/j.1476-5381.2010.01020.x
 115. Koeberle A, Henkel A, Verhoff M, Tausch L, König S, Fischer D, et al. Triterpene acids from frankincense and semi-synthetic derivatives that inhibit 5-lipoxygenase and cathepsin G. *Molecules.* 2018;23(2):506. doi:10.3390/molecules23020506
 116. Rockenstein E, Torrance M, Adame A, Mante M, Bar-on P, Rose JB, et al. Neuroprotective effects of regulators of the glycogen synthase kinase-3beta signaling pathway in a transgenic model of Alzheimer's disease are associated with reduced amyloid precursor protein phosphorylation. *J Neurosci.* 2007;27(8):1981-91. doi:10.1523/jneurosci.4321-06.2007
 117. Umar S, Umar K, Sarwar AHMG, Khan A, Ahmad N, Ahmad S, et al. *Boswellia serrata* extract attenuates inflammatory mediators and oxidative stress in collagen induced arthritis. *Phytomedicine.* 2014;21(6):847-56. doi:10.1016/j.phymed.2014.02.001
 118. Ammon HPT. Boswellic extracts and 11-keto-Boswellic acids prevent type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines. *Phytomedicine.* 2019;63:153002. doi:10.1016/j.phymed.2019.153002
 119. Gerbeth K, Hüscher J, Fricker G, Werz O, Schubert-Zsilavecz M, Abdel-Tawab M. In vitro metabolism, permeation, and brain availability of six major Boswellic acids from *Boswellia serrata* gum resins. *Fitoterapia.* 2013;84:99-106. doi:10.1016/j.fitote.2012.10.009
 120. Sayed AS, El Sayed NSED. 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 antigitamatergic pathways. *J Mol Neurosci.* 2016;59(1):58-67. doi:10.1007/s12031-016-0734-7
 121. Beheshti S, Karimi B. Frankincense improves memory retrieval in rats treated with lipopolysaccharide. *J Herbmed Pharmacol.* 2016;5(1):12-16.
 122. Stoka V, Turk V, Turk B. Lysosomal cathepsins and their regulation in aging and neurodegeneration. *Ageing Res Rev.* 2016;32:22-37. doi:10.1016/j.arr.2016.04.010
 123. Rastegar S, Nouri A, Masoudi R, Tavakoli R. Role of cathepsins in Alzheimer's disease: A systematic review. *J Medical Biomed Sci.* 2018;7(1): 40-8
 124. Bernstein HG, Keilhoff G. Putative roles of cathepsin B in Alzheimer's disease pathology: The good, the bad, and the ugly in one? *Neural Regen Res.* 2018;13(12):2100-1. doi:10.4103/1673-5374.241457
 125. Chai YL, Chong JR, Weng J, Howlett D, Halsey A, Lee JH, et al. Lysosomal cathepsin d is upregulated in Alzheimer's disease neocortex and may be a marker for neurofibrillary degeneration. *Brain Pathology.* 2019;29(1):63-74. doi:10.1111/bpa.12631
 126. Wu Z, Ni J, Liu Y, Teeling JL, Takayama F, Collcutt A, et al. Cathepsin B plays a critical role in inducing Alzheimer's disease-like phenotypes following chronic systemic exposure to lipopolysaccharide from *Porphyromonas gingivalis* in mice. *Brain Behav Immun.* 2017;65:350-61. doi:10.1016/j.bbi.2017.06.002
 127. Savage MJ, Iqbal M, Loh T, Trusko SP, Scott R, Siman R. Cathepsin G: Localization in human cerebral cortex and generation of amyloidogenic fragments from the beta-amyloid precursor protein. *Neuroscience* 1994;60(3):607-19. doi:10.1016/0306-4522(94)90490-1
 128. Bhojak TJ, DeKosky ST, Ganguli M, Kamboh MI. Genetic polymorphism in the cathepsin g gene and the risk of Alzheimer's disease. *Neurosci Lett.* 2001;309(2):138-40. doi:10.1016/s0304-3940(01)02033-x
 129. Chopra A, Saluja M, Tillu G, Sarmukkaddam S, Venugopalan A, Narsimulu G, et al. Ayurvedic medicine offers a good alternative to glucosamine and celecoxib in the treatment of symptomatic knee osteoarthritis: A randomized, double-blind, controlled equivalence drug trial. *Rheumatology (Oxford).* 2013;52(8):1408-17. doi:10.1093/rheumatology/kes414
 130. Masoud A, Al-Ghazali M, Al-Futini F, Al-Mansori A, Al-Subahi A, Farhan A, et al. Antioxidant effect of frankincense extract in the brain cortex of diabetic rats. *J Assoc Arab Uni Basic App Sci.* 2017;24(1):95-100. doi:10.1016/j.jaubas.2016.10.003
 131. Ebrahimipour S, Fazeli M, Mehri S, Taherianfard M, Hosseinzadeh H. Boswellic acid improves cognitive function in a rat model through its antioxidant activity: -neuroprotective effect of Boswellic acid. *J Pharmacopuncture.* 2017;20(1):10-17. doi:10.3831/KPI.2017.20.001
 132. Hosseini Sh M, Kamali A R, Hosseini Sh 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(2):189-197.
 133. Farshchi A, Ghiasi G, Farshchi S, Malek Khatabi P. Effects of *Boswellia papyrifera* gum extract on learning and memory in mice and rats. *Iran J Basic Med Sci.* 2010;13(2):9-15. doi:10.22038/IJBMS.2010.5075
 134. Bawazir A. E, Aljarari RM. Protective effect of *Boswellia carteri* on aluminium chloride-induced Alzheimer's disease in male albino rat. *Int J Pharm. Phytopharmacological Res.* 2018;8:29-39.

135. Mahmoudi A, Hosseini-Sharifabad A, Monsef-Esfahani HR, Yazdinejad AR, Khanavi M, Roghani A, et al. Evaluation of systemic administration of *Boswellia papyrifera* extracts on spatial memory retention in male rats. *J Nat Med*. 2011;65(3-4):519–525. doi:10.1007/s11418-011-0533-y
136. Hosseini Sh M, Esfandiari E. Effect of *Boswellia serrata* gum resin on the morphology of hippocampal cal pyramidal cells in aged rat. *Anat Sci Int*. 2015;90(1):47–53. doi:10.1007/s12565-014-0228-z
137. Franceschi F, Togni S, Belcaro G, Dugall M, Luzzi R, Ledda A, et al. A novel lecithin based delivery form of Boswellic acids (casperome(r)) for the management of osteo-muscular pain: A registry study in young rugby players. *Eur Rev Med Pharmacol* 2016;20(19):4156–61.
138. Gupta I, Gupta V, Parihar A, Gupta S, Ludtke R, Safayhi H, et al. Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: Results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res*. 1998;3(11):511–4.
139. Majeed M, Majeed S, Narayanan NK, Nagabhusanam K. A pilot, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of a novel *Boswellia serrata* extract in the management of osteoarthritis of the knee. *Phytother Res*. 2019;33(5):1457–68. doi:10.1002/ptr.6338
140. Karimifar M, Soltani R, Hajhashemi V, Sarrafchi S. Evaluation of the effect of *Elaeagnus angustifolia* alone and combined with *Boswellia thurifera* compared with ibuprofen in patients with knee osteoarthritis: A randomized double-blind controlled clinical trial. *Clin Rheumatol* 2017;36(8):1849–53. doi:10.1007/s10067-017-3603-z
141. Karlapudi V, Prasad Mungara AVV, Sengupta K, Davis BA, Raychaudhuri SP. A placebo-controlled double-blind study demonstrates the clinical efficacy of a novel herbal formulation for relieving joint discomfort in human subjects with osteoarthritis of knee. *J Med Food*. 2018;21(5):511–20. doi:10.1089/jmf.2017.0065
142. Holtmeier W, Zeuzem S, Preiss J, Kruis W, Bohm S, Maaser C, et al. Randomized, placebo-controlled, double-blind trial of *Boswellia serrata* in maintaining remission of crohn's disease: Good safety profile but lack of efficacy. *Inflamm Bowel Dis*. 2011;17(2):573–82. doi:10.1002/ibd.21345
143. Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R. therapy of active crohn disease with *Boswellia serrata* extract. *Z Gastroenterol*. 2001;39(1):11–7. doi:10.1055/s-2001-10708
144. Madisch A, Miehlke S, Eichele O, Mrwa J, Bethke B, Kuhlisch E, et al. *Boswellia serrata* extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial. *Int. J. Colorectal Dis*. 2007;22(12):1445–51. doi:10.1007/s00384-007-0364-1
145. Gupta I, Parihar A, Malhotra P, Gupta S, Ludtke R, Safayhi H, et al. Effects of gum resin of *Boswellia serrata* in patients with chronic colitis. *Planta Medica*. 2001;67(5):391–5. doi:10.1055/s-2001-15802
146. Khosravi Samani M, Mahmoodian H, Moghadamnia A, Poorsattar Bejeh Mir A, Chitsazan M. The effect of frankincense in the treatment of moderate plaque-induced gingivitis: A double blinded randomized clinical trial. *Daru*. 2011;19(4):288–94.
147. Eshaghian R, Mazaheri M, Ghanadian M, Rouholamin S, Feizi A, Babaeian M. The effect of frankincense (*Boswellia serrata*, oleoresin) and ginger (*Zingiber officinale*, rhizoma) on heavy menstrual bleeding: A randomized, placebo-controlled, clinical trial. *Complement Ther Med*. 2019;42:42–7. doi:10.1016/j.ctim.2018.09.022.
148. Mehrzadi S, Tavakolifar B, Huseini HF, Mosavat SH, Heydari M. The effects of *Boswellia serrata* gum resin on the blood glucose and lipid profile of diabetic patients: A double-blind randomized placebo-controlled clinical trial. *J. Evid.-Based Integr. Med*. 2018;23:2515690x18772728. doi:10.1177/2515690x18772728.
149. Togni S, Maramaldi G, Bonetta A, Giacomelli L, Di Pierro F. Clinical evaluation of safety and efficacy of boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: A randomized placebo controlled trial. *Eur Rev Med Pharmacol*. 2015;19(8):1338–44.
150. Faizy TD, Broocks G, Thaler C, Rauch G, Gebert P, Sturmer KH, et al. Development of cortical lesion volumes on double inversion recovery mri in patients with relapse-onset multiple sclerosis. *Front Neurol*. 2019;10:133. doi:10.3389/fneur.2019.00133
151. Haroyan A, Mukuchyan V, Mkrtchyan N, Minasyan N, Gasparyan S, Sargsyan A, et al. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: A comparative, randomized, double-blind, placebo-controlled study. *BMC Complement Altern Med*. 2018;18(1):7. doi:10.1186/s12906-017-2062-z
152. Gerbeth K, Meins J, Kirste S, Momm F, Schubert-Zsilavec M, Abdel-Tawab M. Determination of major boswellic acids in plasma by high-pressure liquid chromatography/mass spectrometry. *J Pharm Biomed Anal*. 2011;56(5):998–1005. doi:10.1016/j.jpba.2011.07.026
153. Sedighi B, Pardakhty A, Kamali H, Shafiee K, Hasani BN. Effect of *Boswellia papyrifera* on cognitive impairment in multiple sclerosis. *Iran J Neurol*. 2014;13(3):149–53.
154. Kazemian A, Toghiani A, Shafiei K, Afshar H, Rafiei R, Memari M, et al. Evaluating the efficacy of mixture of *Boswellia carterii*, *Zingiber officinale*, and *Achillea millefolium* on severity of symptoms, anxiety, and depression in irritable bowel syndrome patients. *J Res Med Sci*. 2017;22:120. doi:10.4103/jrms.JRMS_905_16.
155. Prabhavathi K, Chandra US, Soanker R, Rani PU. A randomized, double blind, placebo controlled, cross

- over study to evaluate the analgesic activity of *Boswellia serrata* in healthy volunteers using mechanical pain model. *Indian J Pharmacol.* 2014;46(5):475-9. doi:[10.4103/0253-7613.140570](https://doi.org/10.4103/0253-7613.140570)
156. Tajadini H, Saifadini R, Choopani R, Mehrabani M, Kamalinejad M, Haghdoost AA. Herbal medicine davaie loban in mild to moderate Alzheimer's disease: A 12-week randomized double-blind placebo-controlled clinical trial. *Complement. Ther. Med.* 2015;23(6):767-72. doi:[10.1016/j.ctim.2015.06.009](https://doi.org/10.1016/j.ctim.2015.06.009)
157. Etzel R. Use of incense in the treatment of Alzheimer's disease, US Patents.1998;US5720975A.
158. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement (N Y).* 2019;5:272-93. doi:[10.1016/j.trci.2019.05.008](https://doi.org/10.1016/j.trci.2019.05.008)
159. Davison EK, Brimble MA. Natural product derived privileged scaffolds in drug discovery. *Curr Opin Chem Biol.* 2019;52:1-8. doi:[10.1016/j.cbpa.2018.12.007](https://doi.org/10.1016/j.cbpa.2018.12.007)
160. Hughes RE, Nikolic K, Ramsay RR. One for all? Hitting multiple Alzheimer's disease targets with one drug. *Front Neurosci.* 2016;10:177. doi:[10.3389/fnins.2016.00177](https://doi.org/10.3389/fnins.2016.00177)
161. Deng YH, Wang NN, Zou ZX, Zhang L, Xu KP, Chen AF, et al. Multi-target screening and experimental validation of natural products from selaginella plants against Alzheimer's disease. *Front Pharmacol.* 2017;8:539. doi:[10.3389/fphar.2017.00539](https://doi.org/10.3389/fphar.2017.00539)
162. Ramsay RR, Popovic-Nikolic MR, Nikolic K, Uliassi E, Bolognesi ML. A perspective on multi-target drug discovery and design for complex diseases. *Clin Transl Med.* 2018;7(1):3. doi:[10.1186/s40169-017-0181-2](https://doi.org/10.1186/s40169-017-0181-2)
163. Liu Z, Zhang A, Sun H, Han Y, Kong L, Wang X. Two decades of new drug discovery and development for Alzheimer's disease. *RSC Advances.* 2017;7(10):6046-58. doi:[10.1039/C6RA26737H](https://doi.org/10.1039/C6RA26737H)
164. Dias KST, Viegas C. Multi-target directed drugs: A modern approach for design of new drugs for the treatment of Alzheimer's disease. *Curr Neuropharmacol.* 2014;12(3):239-55. doi:[10.2174/1570159X1203140511153200](https://doi.org/10.2174/1570159X1203140511153200)
165. Ibrahim MM, Gabr MT. Multitarget therapeutic strategies for Alzheimer's disease. *Neural Regen Res.* 2019;14(3):437-40. doi:[10.4103/1673-5374.245463](https://doi.org/10.4103/1673-5374.245463)