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An updated review of the therapeutic anti-inflammatory effects of frankincense

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ABSTRACT

Inflammatory responses are the consequences of infection, injury, and tissue dysfunctions. In general, these responses associate with the inception of several diseases such as rheumatoid arthritis, diabetes, allergy, asthma, cancer, epilepsy, and Alzheimer's disease. To enhance such responses a number of synthetic drugs are widely used, including steroidal/non-steroidal components, antibodies, and cytokine inhibitors. However, prolonged use of these components may generate some side effects, including the malfunction of digestive tract, liver intoxication, kidney damage, and cardiovascular disorders. Therefore, alternative application of natural compounds, such as herbal components, against inflammatory responses might be safer and more effective. Frankincense is a gum resin with potential therapeutic effects on various diseases with signs of inflammation. Therefore, frankincense can decrease the indications of numerous illnesses with the least side effects. The identification of critical active constituents in frankincense may be useful for the development of new components with desired biological effects. In this review, the potential therapeutic effects of frankincense will be described based on its anti-inflammatory effects.

Keywords: Alzheimer's disease; Anti-inflammatory; Cancer; Diabetes mellitus; Frankincense; Rheumatoid arthritis

Review Article

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INTRODUCTION

Inflammation is the primitive response of a tissue to infection, injury, trauma, and swelling- induced damages to trigger either tissue repair or clear the damaged cells. Through this process, a complex network of signaling pathways would be activated and mediated by a cascade of proinflammatory factors, including nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), prostaglandins, cytokines, and interleukins [1]. Inflammatory responses could be associated with a variety of chronic diseases. In general, steroidal/non-steroidal anti-inflammatory drugs are broadly applied to treat inflammation, especially at acute phase [2]. However, their prolonged application is hazardous due to a variety of side effects including damage to tissues such as liver, kidney, cardiovascular system, skin, and gut [3]. Therefore, their prescription should be performed with special care. On the other hand, despite the efficacy of antagonists against proinflammatory cytokines such as TNF-α and interleukin-1β (IL-1β), high cost medication of such components restricts their application [4]. Therefore, alternative low-cost natural anti-inflammatory compounds could be considered as replacement of drugs above [5]. Frankincense (also termed as olibanum *or Salaiguggul*), is a gum resin derived from *Boswellia* species. *Boswellia* genus comprises four main species, including *Boswellia serrata* from India, *Boswellia carterii* from East Africa and China, *Boswellia frereana* from Northeast Africa (Somalia), and *Boswellia sacra* from the Middle-East (AαBA) [3].

Since ancient times, frankincense has been widely used in different regions of Africa, China, India, and Middle East to prevent the inflammatory hallmarks' progress. In traditional Chinese medication, frankincense of *Boswellia carterii* is usually prescribed as an efficient drug for improvement of blood circulation and pain relief. Recently, frankincense is used in developed countries against a variety of chronic inflammatory diseases [6]. This review paper intends to summarize the reported therapeutic properties of *Boswellia* resin with a further focus on its anti-inflammatory effects. The keywords used in Pubmed and Google scholar were frankincense,

boswellic acid, anti-inflammatory, cancer, diabetes mellitus, asthma, pain, rheumatoid arthritis, Alzheimer's disease (AD), and epilepsy. The majority of the available articles were included (Table 1).

Main components of frankincense

Studies have identified more than 200 compounds in frankincense [7]. Detailed information about these components is available in various published papers [8-10]. The main component of frankincense is oil (60%). It contains mono- (13%) and diterpenes (40%) as well as ethyl acetate (21.4%), octyl acetate (13.4%) and methylanisole (7.6%). Some of the resins major components were the diterpenes incensole, and isoincensole, their oxide or acetate derivatives, and the triterpene boswellic acids. Boswellic acids are the major triterpenic acid of the gum resin derived from *Boswellia* species, and responsible for the most of its pharmaceutical effects [11, 12]. To identify the active components in the resin, boswellic acids were examined for their anti-inflammatory effects [13-15]. Afterward, many reports attributed the anti-inflammatory and cytotoxic properties of *Boswellia* resin solely to boswellic acids and their derivatives, specifically acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid [16]. However, the diterpen incensole and its acetate have also shown anti-inflammatory activities [17]. For example, robust anti-inflammatory and neuroprotective effects were reported in mice following head trauma [18]. Therefore, it is believed that several different constituents modulate the anti-inflammatory activity of the resin. It is also important to note that different species of *Boswellia* contain a different mixture of active and non-active ingredients [19].

The anti-inflammatory effects of *Boswellia* resin and its active constituents, are mediated via several critical pathways involved in inflammation, including the nuclear factor-κB pathway [20], cytokines downstream of Nf-kB activation [18], interaction with lipoxygenases [21, 22], inhibition of cyclooxygenase [23], modulation of the mitogen-activated protein kinases (MAPKs) [24, 25], and production of reactive oxygen species (ROS) [26].

Analgesic effect of frankincense

Pain is an unpleasant sensation, mediated by prime sensory neurons (nociceptors) in response to a diversity of mechanical, thermal, and chemical signals, often linked with inflammatory responses [27]. Pain might be spontaneous or intermittent or persistent. Chronic pain could relate with chronic inflammation in many conditions, including osteoarthritis, rheumatoid arthritis, low back pain, fibromyalgia, pelvic and abdominal pain, neuropathic pain, migraine, and cancer [28]. Cytokines are the main important intermediaries of inflammatory pain, which could be induced by nociceptor sensitization indirectly via mediators or directly activating neurons by their specific receptors on the neuronal cells [29]. Inflammation-induced cyclooxygenase-2 (Cox-2) triggers localized pain hypersensitivity due to the release of prostanoids sensitizing peripheral nociceptor terminals. Furthermore, peripheral inflammation could generate pain hypersensitivity in neighboring undamaged tissue (secondary hyperalgesia), because of increased neuronal excitability of spinal cord (central sensitization), and a syndrome containing diffuse muscle and joint pain, fever, lethargy, and anorexia [30]. Immune cytokines, such as TNF-α, IL-1β, and IL-6, are important players for the activation of pain generation [29]. Acetyl-α-boswellic acid and acetyl-11-keto-β-boswellic acid are crucial constituents of frankincense that can prevent nuclear factor kappaB (NF-ƙB) signaling and consequent down-regulation of TNF-α expression in activated human monocytes [31]. Li et al. showed that frankincense oil and water extracts (FOE, FWE) could treat inflammation and pain. Of note, FOE is more-enriched with α-pinene, linalool, and 1-octanol than FEW. Therefore it has a greater and faster lessening effect for swelling and pain [32]. Water extract of frankincense alleviated neuropathic pain in mice via modulation of transient receptor potential vanilloid 1 (TRPV1) [33]. LI13019F1, a new composition of *Boswellia serrata* gum resin extracts, reduced pain, and protected articular cartilage from the damaging action of monoiodoacetate in a rat model [34]. A combined water extract of frankincense and Myrrh alleviated chronic constriction injury-induced mechanical allodynia and thermal hypersensitivity

by increasing TRPV1 expression at both the mRNA and protein levels in predominantly small-to-medium neurons [33]. Crude extracts and fractions of Omani frankincense obtained from *Boswellia sacra* indicated analgesic effect against muscle, stomach, and arthritis pain in animal models [35]. *Boswellia serrata* significantly increased the pain threshold and pain tolerance force and time in healthy volunteers in the mechanical pain model [36]. Oral administration of *Boswellia serrata* reduced the intensity and frequency of headaches in patients with chronic cluster headache [37]. Extract of *Boswellia elongata* produced significant anti-inflammatory and antinociceptive effects in carrageenan-induced rat paw edema, cotton pellet granuloma in rats, acetic acid-induced abdominal writhing, and hot-plate test model in mice [38].

Anti-rheumatoid arthritis effect of frankincense

Rheumatoid arthritis (RA) is an enduring inflammatory progressive and disabling autoimmune disease. It causes inflammation, swelling, and pain in and around the joints and other body organs, determined by wide synovitis resulting in erosions of articular cartilage and marginal bone that lead to joint destruction [39]. A sophisticated, interactive network of cells and cytokines, including: TNF-α, IL-1β, IL-6, IL-17, and IL-8, are involved in the pathogenesis of RA [40, 41]. Both the autoreactive T and B cells play crucial roles in such autoimmune responses. Etzel et al. showed that H15, anexclusive extract of the gum resin of *Boswellia serrata* is useful in the treatment of RA [42]. Bioactive components of frankincense, including 3-hydroxylanosta-8, 24-dien-21-oic-acid, elemonic acid, acetyl elemolic acid decreased the edema volume of arthritis patients, significantly. The medication of frankincense for these patients resulted in a significant decrease in blood cytokines [4]. *Boswellia serrata* extract at dose 180 mg/kg showed statistically significant improvement inbody weight, and decreased ankle diameter and arthritic index in complete Freund's adjuvant-induced animal model of RA. Histopathological results exhibited a reduction in inflammatory parameters [43]. Oral administration of *Boswellia serrata* gum resin extract resulted in

reduced levels of inflammatory mediators (IL-1β, IL-6, TNF-α, IFN-γ, and PGE2), and increased level of IL-10. Its protective effects against rheumatoid arthritis were also evident from the decrease in arthritis scoring and bone histology [44].

Anti-diabetic effect of frankincense

Diabetes mellitus is a metabolic disease that causes hyper glycemia and is one of the most prevalent chronic disorders with a significant increase in developing countries. This disease is coupled with impaired insulin secretion from the pancreatic β-cells (type 1), and is characterized by insulin resistance in skeletal muscle, liver, and adipose tissue (type 2) [45]. Inflammation is critically involved in the pathogenesis and progression of diabetes [46]. Excessive consumption of energy, high rich carbohydrates, and saturated fats diets coinciding with low intake of healthy fats and antioxidants are responsible for the pathogenesis of diabetes [47]. The presence of advanced glycation end products and free fatty acids promotes inflammatory responses downstream of NF-κB signaling. Once activated, NF-κB triggers the synthesis and secretion of chemokines, such as monocyte chemotactic protein-1 (MCP1) (also known as CCL2), in adipocytes, which leads to infiltration of pro-inflammatory macrophages [47, 48]. In a randomized clinical trial study, frankincense lowered the blood glucose levels, hemoglobin A1c (HbA1c), insulin, total cholesterol, and triglycerides in type 2 diabetic patients without any adverse effects [49]. *Boswellia* extracts and 11-keto-β-boswellic acids prevented type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines [50]. Administration of *Boswellia serrata* gum resin for eight weeks considerably reduced fasting blood sugar, glycosylated hemoglobin, and triglyceride in type 2 diabetic patients [51]. A mixed herbal formulation, including *Boswellia serrata* gum resin, reduced the mean serum fasting blood glucose, glycosylated hemoglobin, and triglyceride in type 2 diabetic patients [52]. Supplementation of *Boswellia serrata* gum resin increased blood high-density lipoprotein (HDL) levels and decreased cholesterol, low-density lipoprotein (LDL), and fructosamine in type 2 diabetic patients [53]. Extracts from

the gum resin of *Boswellia serrata* prevented pancreatic islet destruction and consequent hyperglycemia in the multiple low-dose streptozotocin treatment as an animal model of type 1 diabetes probably by inhibition of the production/action of cytokines related to the induction of islet inflammation in an autoimmune process [54]. Extract from *Boswellia serrata* gum resin decreased glutamate decarboxylase 65 (GAD65) autoantibodies in a patient with latent autoimmune diabetes in adults (LADA) [55]. A single oral administration of *Boswellia glabra* leaf and root extract decreased the blood glucose level in alloxan-induced diabetic rats. The continued use of leaf and root extract for 28 days produced significant hypoglycemic effects; there was also a decrease in serum glucose, cholesterol, triglyceride, urea and creatinine levels and enzyme activities (alkaline phosphatase and glucose-6-phosphatase) [56].

Anti-tumor effect of frankincense

Cancer is the second foremost cause of death worldwide after myocardial infarction [57]. Chronic inflammation predisposes individuals to various types of cancer [58]; therefore, cellular mediators of inflammation are important elements of tumors' local environment. In general, inflammatory conditions are required for the generation of malignancy [59]. Conversely, an oncogenic change may induce inflammatory conditions for development of tumors [60]. To generate cancer-related inflammation, key intrinsic factors, including NF-κB and signal transducer and activator of transcription 3 (STAT3), are required as well as proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [61-63]. Moreover, deregulation in MAPK signaling plays a critical step in the progression of cancer [64]. The conventional used chemotherapeutic agents are often associated with several side effects. To overcome such problems, a shift to the natural compounds with fewer side effects is essential [65]. The anti-cancer potential of boswellic acid, one of the components of frankincense is well evidenced [65]. Syrovets et al. and Kunnumakkara et al. have shown that acetyl-boswellic acid [55] and acetyl-11-keto-β-boswellic acid can inhibit NF-κB [31] and STAT3 signaling pathways, respectively [66]. 3-O-acetyl-

11-keto-β-boswellic acid exerted anti-tumor effects in glioblastoma by arresting cell cycle at G2/M phase [67]. Extracts of the oleogum resins exhibited cytotoxicity against treatment-resistant metastatic human breast cancer cell line MDA-MB-231. The cytotoxic value against the cancer cells correlated positively with the contents of pentacyclic triterpenic acids in *Boswellia* extracts [68]. The essential oil of frankincense suppressed melanoma cancer through downregulation of Bcl-2/Bax cascade signaling and ameliorated hepatotoxicity via phase I and II drug-metabolizing enzymes [69]. Frankincense essential oil prepared from hydrodistillation of *Boswellia sacra* gum resins induced human pancreatic cancer cell death in cultures and a xenograft murine model [70]. Acetyl-11-keto-β-boswellic acid enhanced the cisplatin sensitivity of non-small cell lung cancer cells through cell cycle arrest, apoptosis induction, and autophagy suppression via p21-dependent signaling pathway [71]. Boswelic acid derived from *Boswellia Serrata* significantly increased the anticancer activities of Temozolomide and Afatinib. These effects were related to anti-inflammatory and antioxidant effects, based on the inhibition of growth factors and proinflammatory interleukins [72]. *Boswellia frereana* extract suppressed the influence of hepatocyte growth factor (HGF) in breast cancer cell motility and invasion in vitro, by reducing HGF/c-Met signaling events. The authors concluded that *Boswellia frereana* extract could play a novel role in the treatment of breast cancer [73]. 3-O-acetyl-11-keto-β-boswellic acid, the principal active ingredient of the gum resin from *Boswellia serrata* and *Boswellia carteri* inhibited cell proliferation, decreased DNA synthesis, and inhibited the migration, invasion, and colony formation of U251 and U87-MG human glioblastoma cell lines, and was proposed as a promising chemotherapy drug in the treatment of glioblastoma [67]. Methanolic extract of *Boswellia serrata* inhibited proliferation, angiogenesis, and migration and induced apoptosis in HT-29 human colon cancer cells by inhibiting microsomal prostaglandin E synthase-1 and decreasing the prostaglandin E2 level and its downstream targets [57].

Anti-allergy and asthma effect of frankincense

Asthma is one of the most widespread chronic diseases associated with narrow airways swell, and extra mucus production, which is highly prevelant in human societies. It is a multifactorial disease with genetic background and allergic responses to the environmental, infectious conditions, and nutritional components [74]. Inflammation of the airway in chronic asthma mediated by infiltration of activated mast cells, dendritic cells (DCs) and T helper type-2 (Th2) cells into the bronchial mucosa and subsequent releasing of pro-inflammatory mediators [75]. In a double-blind, placebo-controlled study, Gupta et al. have shown that 70% of patients who were suffering from bronchial asthma and treated with a gum resin, showed improvement of disease and disappearance of physical symptoms and signs such as dyspnea, rhonchi, number of attacks, as well as decreased in the eosinophilic count [76]. Neutrophils play central roles through releasing tissue-degenerative proteases, such as cathepsin G, and pro-inflammatory leukotriene's [77], especially leukotriene B4 (LTB4), which is a chemoattractant for leukocytes aggregation and adherence to vascular endothelium [78]. Boswellic acids, the pentacyclic triterpene acid compounds in the gum resin of frankincense, are capable of targeting cathepsin G, 5-lipooxygenase (5-LO) and LTB4 in neutrophils, and might be able to suppress the asthmatic hallmarks [77]. In a Sephadex LH-20 induced airway inflammation model of rats, LI13109F, a novel herbal composition containing the extracts of *Boswellia serrata* gum resin and *Aegle marmelos* fruit, reduced infiltrated granulocyte population in the bronco-alveolar lavage fluid and normalized Th1/Th2 cytokine balance. Further, a 56-day placebo-controlled and randomized, double-blind study on subjects with mild to moderate asthma evaluated the clinical efficacy of LI13109F [79]. In a double-blind, placebo-controlled studies, forty patients with bronchial asthma in the age range of 18-75 years were treated with a preparation of gum resin of 300 mg thrice daily for 6 weeks. 70% of patients showed improvement of the disease as evidenced by the disappearance of physical symptoms

and signs such as dyspnoea, rhonchi, number of attacks [80].

Anti-Alzheimer's disease effect of frankincense

Alzheimer's disease (AD) is a neurogenic syndrome and a type of dementia that causes complications with memory, thinking and behavior and cognitive decline, function, and determination [81]. The activation of the immune system, leads to a general inflammatory disease in the brain, as one of the main signs of AD. An inflammatory response is involved in the recruitment of environmental immune cells and the release of inflammatory mediators in the brain. Microglia and astrocytes are responsible for such phenomena in AD, which produce inflammatory cytokines. Prolonged inflammatory conditions contribute to the neurodegeneration and development of AD. C-reactive protein (CRP), TNF-α, IL-1α, IL-6, IL-10, and Cyclooxygenase-2 (COX-2) are examples of inflammatory cytokines in AD [82, 83], as well as activation of NF-κB [84]. Acetyl-11-keto-β-boswellic acid has shown potent anti-inflammatory effects. Acetyl-11-keto-β-boswellic acid could prohibit the phosphorylation of recombinant NF-κB [31] as well as inhibitor of NF-κB (IκB) [37]. Additionally, a single administration of frankincense extract had no significant effect on learning parameters, but long-term administration of frankincense improved the memory function [85].

Various studies have shown the beneficial effects of frankincense on animal models of AD. The hydro-alcoholic extract of frankincense improved memory retrieval in lipopolysaccharide (LPS) treated rats, via an anti-neuroinflammatory activity by reducing TNF-α levels in the hippocampus [86]. Long-term administration of frankincense improved dementia type of AD induced by intracerebroventricular (i.c.v) injection of streptozotocin in a time-dependent manner [87]. Meanwhile, the treatment of AD-induced rats with aqueous infusions of *Boswellia serrata* significantly ameliorated the neurodegenerative features of AD in rats [88]. Recently, it was shown that in high fat/high fructose diet/streptozotocin (STZ)- induced diabetic rats, *Boswellia serrata* gum showed a significant reduction in

amyloid-β (Aβ) deposits and p-tau positive cells, and reduced significantly the elevated hippocampal levels of TNF-α, IL-1β, and IL-6 [89]. Acetyl-11-keto-β-boswellic acid from *Boswellia serrata* improved learning and memory deficits, decreased cerebral Aβ levels and plaque burden, alleviated oxidative stress and inflammation, and reduced activated glial cells and synaptic defects in the APPswe/PS1dE9 mice. Furthermore, acetyl-11-keto-β-boswellic acid treatment remarkably suppressed amyloid precursor protein (APP) processing by inhibiting beta-site APP cleaving enzyme 1 (BACE1) protein expression to produce Aβ in the APPswe/PS1dE9 mice brains. Mechanistically, acetyl-11-keto-β-boswellic acid modulated antioxidant and anti-inflammatory pathways via increasing nuclear erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) expression, and via declining phosphorylation of IκBα and p65 [90]. The chloroform extract of *Boswellia socotrana* inhibited acetylcholinesterase activity [91].

Anti-epileptic effects of frankincense

Epilepsy is an enduring disorder of the central nervous system, which is characterized by repeated seizures. It is the most prevalent neurological disease worldwide [92]. Evidence shows that inflammation might be a cause, and a consequence of epilepsy [93]. Several inflammatory mediators were detected in the brain tissue of epileptic patients [94]. There are some studies, which show that frankincense might be useful in the control of seizures. Frankincense reduced the severity of seizures induced by pilocarpine, which was attributed to its potent antioxidant and anti-inflammatory effects [95]. Incensole and β-boswellic acid extracted from *Boswellia sacra* showed significant *in vivo* anticonvulsant activity and decreased seizures induced by the gamma-aminobutyric acid receptor type A ($GABA_A$) antagonist, pentylenetetrazol in zebrafish larvae [96]. Meanwhile, boswellic acids isolated from the oleo-gum resin of *Boswellia serrata* showed dose-dependent anticonvulsant activity against electrically induced convulsions in experimental animals by decreasing the duration of hind limb tonic extension (HLTE) and by increasing the latency of HLTE, significantly [97].

Table 1: Therapeutic effects of frankincense and/or its ingredients on inflammatory diseases

Disease	Substance	Effectiveness	Reference
Rheumatoid arthritis	*Boswellia serrata* extract	Decrease in ankle diameter and arthritic index in complete Freund's adjuvant-induced animal model of RA	Kumar et al., 2019
	Bioactive components of frankincense including 3-hydroxylanosta-8, 24-dien-21-oic-acid, elemonic acid, acetyl elemolic acid	Decrease in the edema volume of arthritis patients	Su et al., 2015
	H15, an exclusive extract of the gum resin of *Boswelliaserrata*	Treatment of rheumatoid arthritis	Etzel et al., 1996
	Boswellia serrata gum resin	Attenuation of inflammatory mediators and oxidative stress in collagen-induced arthritis	Umar t al., 2014
Diabetes mellitus	11-keto-β-boswellic acids	Prevention of type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines	Ammon., 2019
	Frankincense	Anti-hyperglycemic effect in type 2 diabetic patients	Azadmehr et al., 2014
	Boswellia serrata gum resin	Prevention of pancreatic islet destruction and consequent hyperglycemia in an animal model of type 1 diabetes by inhibition of the	Shehata et al., 2011

		production/action of cytokines related to the induction of islet inflammation in an autoimmune process	
	Boswellia serrata gum resin		Franic et al., 2020
		Reduction of glutamate decarboxylase 65 (GAD65) autoantibodies in a patient with latent autoimmune diabetes in adults (LADA)	
	Boswellia serrata gum resin		Mehrzadi et al., 2018
		Reduction of fasting blood sugar, glycosylated hemoglobin, and triglyceride in type 2 diabetic patients	
Cancer	Frankincense	Suppression of melanoma cancer through downregulation of Bcl-2/Bax cascade signaling	Hakkim et al., 2019
	Frankincense	Cytotoxicity against the human, treatment-resistant, metastatic breast cancer cell line MDA-MB-231	Schmiech et al., 2019
	3-O-acetyl-11-keto-β-boswellic acid	Anti-tumor effects in glioblastoma by arresting cell cycle at G2/M phase	Li et al., 2018
	Boswellic acid	Antagonism of signal transducers and activators of transcription 3 signaling, proliferation, and survival of multiple myeloma via the protein tyrosine phosphatase shp-1	Kunnumakkara et al., 2009

Frankincense as a therapeutic anti-inflammatory compound

	Frankincence from *Boswellia sacra*	Induction of human pancreatic cancer cell death in cultures, and a xenograft murine model	Ni et al., 2012
	Acetyl-11-keto-β-boswellic acid	Enhance the cisplatin sensitivity of non-small cell lung cancer cells through cell cycle arrest, apoptosis induction, and autophagy suppression via p21-dependent signaling pathway	Lv et al., 2020
	Boswellic acid from *Boswellia serrata*	Increase the anticancer activities of Temozolomide and Afatinib by inhibition of growth factors and proinflammatory interleukins	Barbarisi et al., 2019
Allergy and asthma	Frankincense	Improvement of Asthma and disappearance of physical symptoms and signs such as dyspnea, rhonchi, number of attacks	Gupta et al., 1998
	LI13109F, a herbal composition containing the extracts of *Boswellia serrata* gum resin and *Aegle marmelos fruit*	Reduction of infiltrated granulocyte population in the bronco-alveolar lavage fluid and normalization of Th1/Th2 cytokine balance in an airway inflammation model of rats	Yugandhar et al., 2018
	Frankincense	Improvement of asthma by the disappearance of physical symptoms and signs such as dyspnoea, rhonchi, number of	Gupta et al., 1998

		attacks	
Alzheimer's disease	*Boswellia serrata* gum	Reduction in Aβ deposits and p-tau positive cells in diabetic rats	Gomaa et al., 2019
	Boswellia serrata gum	Amelioration of the neurodegenerative features of AD in rats	Yassin et al., 2013
	Frankincense	Improvement of dementia type of AD induced by i.c.v injection of streptozotocin	Beheshti and Aghaie., 2016
	The chloroform extract of *Boswellia socotrana*	Inhibition of acetylcholinesterase activity	Bakthira et al., 2011
	Acetyl-11-keto-β-boswellic acid from *Boswellia serrata*	Reduce cerebral amyloid-β (Aβ) levels, oxidative stress and inflammation, and activated glial cells and synaptic defects in the APPswe/PS1dE9 mice	Wei et al., 2020
Epilepsy	Frankincense	Reduction of the severity of pilocarpine-induced seizures	Brillatz et al., 2016
	Incensole and boswellic acids extracted from Boswellia sacra	Anticonvulsant activity in PTZ-induced seizures in zebrafish larvae	Hosny et al., 2020
	Boswellic acids isolated from *Boswellia serrata*	Anticonvulsant activity	Sengani et al., 2012

Conclusion

A variety of chronic diseases are associated with inflammation. Different drugs have been designated and studied for the treatment of inflammation, including antibodies, cytokine antagonists, and so on. However, their application was associated with numerous side effects including hepatotoxicity, renal disturbances, cardiovascular disease, and gastroenteritis [99-104]. Frankincense is an herbal product with powerful anti-inflammatory compositions [106-108]. In this paper, we reviewed several aspects of anti-inflammatory activities of this compound in various inflammatory diseases, including rheumatoid arthritis, diabetes mellitus, cancer, asthma, Alzheimer's disease, and epilepsy. These diseases' clinical or animal models revealed potent therapeutic activities of frankincense, mainly based on anti-inflammatory activities. Frankincense resulted in reduced levels of inflammatory mediators (IL-1β, IL-6, TNF-α, IFN-γ, and PGE2), and protected against rheumatoid arthritis. *Boswellia* extracts and 11-keto-β-boswellic acids prevented type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines. Boswellic acids increased the anticancer activity, related to its anti-inflammatory and antioxidant effects, based on the inhibition of growth factors and proinflammatory interleukins. Boswellic acids targeted cathepsin G, 5-lipooxygenase (5-LO) and leukotriene B4 in neutrophils, and suppressed the asthmatic hallmarks. AKβBA improved learning and memory deficits, decreased cerebral Aβ levels and plaque burden, alleviated oxidative stress and inflammation, and reduced activated glial cells and synaptic defects in a mice model of Alzheimer's disease. Accordingly, frankincense can serve as a therapeutic compound for the treatment of chronic inflammatory diseases.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest to disclose.

Authors' Contributions

Rasoul Zaker and Siamak Beheshti contributed to the drafting of the manuscript.

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