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Boswellia serrata-frankincense (A Jesus Gifted Herb); An Updated Pharmacological Profile

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ABSTRACT

Traditionally, herbal plants are widely and frequently used as medicines for curing and anticipating of various diseases and ailments. Plants belonging to family Burseraceae are very important and widely used as therapeutic agents. From ancient times, *Boswellia serrata* (BS), belonging to family Burseraceae is well known as frankincense (Jesus gifted herb). Resins are main constituents of Burseraceae family, β-boswellic acid, acteyl-β-boswellic acid, 11-keto-β-boswellic acid, acetyl-11-keto-β-boswellic acid, α-boswellic acid, acetyl-α-boswellic acid are few among several medicinally important constituents of BS generally used for curing various ailments such as rheumatism, skin diseases, cough, diarrhea, constipation, flatulence, stomachic, carminative, diuretic and neurodegenerative. Bench work has revealed numerous pharmacological activities of BS viz., anti-inflammatory, anti-oxidant, anti-ulcer, anti-arthritic, anti-asthmatic, anti-artherosclerotic, anti-cancer, anti-diarrhoeal, hepatoprotective, anti-microbial, anti-hyperglycemic, wound healing, diuretic and analgesic. However, few activities like wound healing, hypoglycemic property need intense and focused research for confirmed results. In this review, we have widely discussed chemical constituents and medicinal potential of BS.

Key words: *Boswellia serrata,* anti-inflammatory, anti-arthritic, anti cancer

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INTRODUCTION

Historically plants have been placed at top among the sources of novel drugs. As traditional medicines based on plants and plant extracts have made considerable contributions to human health and well-being. The medicinal plants are widely used by the traditional medicinal practitioners for curing and prevention of various diseases in their day to day practice. Among the plants known for medicinal value, the plants of family Burseraceae are very important for their therapeutic potential. Burseraceae is represented in plant kingdom with 17 genera and 600 species, where species of this family produce commercially valuable resin as raw material[1]. Frankincense, also known as olibanum, is the resin obtained from the trees of the *Boswellia*, native to Arabia and India. Frank ("pure") incense was the finest and scarcest, produced only in a small area of the Arabian Peninsula, Somalia and Ethiopia. The word frankincense derived from the old French word *frank-encens* means the true, authentic, pure, or "free lighting" incense. The word olibanum derived from the Arabic *al-luban* means the milk or authentic incense. Ancient civilizations used incense in their rituals and prayers to god Hindus, Babylonians, Assyrians, Persians, Romans, Chinese and Greeks burned these resins as they believe that burning *Boswellia* resins during scarification ceremonies or in their daily rituals prevent the influence of bad spirits and also please their Gods on their souls[1]. Gajabhakshya suggests that since antiquity *Boswellia* species was found to be one of ingredient of elephant's diet[2].

The resin is popularly used in Indian Systems of Medicine (Unani, Ayurvedic and Sidha) for the last several centuries in curing various ailments especially rheumatism, skin diseases, cough, diarrhoea, constipation, flatulence, stomachic, carminative, diuretic, central nervous diseases and others. Beyond that, there are medical evidences that frankincense was important for wound healing, dysentery, dyspepsia, lung diseases, hemorrhoids, urinary disorders and corneal ulcers[3]. It has made important contribution to the field of science from ancient times to modern research due to its large number of medicinal effects like anti-inflammatory[4], anti-oxidant[5], anti-ulcer[6], anti-arthritic[7], anti-asthmatic[8], anti-artherosclerotic[9], anti-cancer[10], anti-diarrhoeal[11], hepatoprotective[12], anti-microbial[13], anti-hyperglycemic[14], wound healing[15], diuretic[16] and analgesic[17]. In light of

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above an attempt has been made to review the pharmacognostical and pharmacological aspects of BS.

DESCRIPTION

BS is a moderate to large sized, branching and deciduous tree of genus *Boswellia* with thin, greenish grey, yellow or reddish and finally turning to ash colored papery bark (Table 1).

The leaves are alternate, imparipinnate, 30-45 cm long, ex-stipulate and crowded at the end of the branches. The flowers are bisexual, small and white in axillary racemes or panicles at the tip of the branches. BS tree, on injury, exudates an oleo-gum-resin known as Salai Guggal, Indian Frankincense or Kundur (Table 2).

It is fragrant, transparent, golden yellow and after solidification it turns into brownish yellow tears or drops and crusts. Oleo-gum-resin mainly contains oils, terpenoids and gums (Table 3)[18].

Table 1: Scientific classification of *Boswellia serrata*

Kingdom	Plantae	Over-class	Rutanae
Division	Spermatophyta	Class	Anacardiales
Subdivision	Angiospermae	Family	Burseraceae
Tribe	Rosopsida	Genus	Boswellia
Sub-tribe	Rosidae S. lat.		

Table 2: Synonyms of *Boswellia serrata*

Language	Names
Bengali	Luban, Salai, Kundur
Gujrati	Gugali, Saleda, Dhup
Hindi	Madi, Salai, Saler, Salga, Salhe, Kundur, Luban, Sallai guggul
Sanskrit	Sallaki, Kundru, Gajabhakshya, Kundara, Ashvamutri
Kannada	Chitta, Guguladhup
Malayalam	Parangi, Saambraani
Telugu	Phirangi, Saambrani
Tamil	Parangisambrani, Parangi, Kungli, Kundrikam, Gugulu, Morada, Kunthreekan
English	Indian frankincense tree, Indian olibanum tree
Chinese	Fan Hun Hsiang
French	Baswellie-den telee
German	Salaibaum, Weihrauch, Gummiresina, Kirchenharz
Nepalese	Gobhar shalla
Arabic	Kuurdur, Zarw
Bemba	Kundur
Sinhalese	Kundirikkam
Unani	Luban

Table 3: Chemical composition of *Boswellia serrata*[18, 19, 20]

	Chemical constituent
Oil	α-thujene, p-cymene, Phellandrene, Cadinene, Camphene, d-borneol, Verbenone, Verbenol, α –pinene, d-limonene, Geraniol, Elemol, Cadinene, d-emonene, Linalool, Terpinol
Terpenoids	α-boswellic acid, β-boswellic acid, Acetyl-α-boswellic acid, Acetyl-β-boswellic acid, 11-keto- β -boswellic acid (KBA), Acetyl-11-keto-β-boswellic acid (AKBA), 3-α-cetoxytirucall-8, 24-dien-2l-oic acid, 3-ketotirucall-8,24-ien-21-oic acid, 3-α- hydroxytirucall-8,24-dien-21-oic acid, 3-β-hydroxytirucall-8,24-dien-21-oic acid, 3-α- hydroxyl-urs-9,12-diene-24-oic acid.
Gum	Moisture, Volatile oil, Resin, Gum, Diastase, Oxidase, Arabinose, Xylose, Galactose, 4-O-methyl-lucuroarabinogalactan

PHARMACOLOGICAL ACTIVITIES

Anti-inflammatory activity: Boswellic acids are specific non-redox inhibitors of leukotrienes interacting directly with 5-lipoxygenase (5-LOX) including inflammatory mediators such as 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB-4) in various animal models, ultimately leads to bronchoconstriction, chemotaxis and increased vascular permeability[21]. Methanolic extract of BS exhibits anti-inflammatory property by inhibiting cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β), nitric oxide and mitogen activated protein kinases (MAPK) in human peripheral blood mononuclesar cells and in mouse macrophages[4]. Boswellic acid extracts, boswellic acid and its biologically active pentacyclic triterpenes block leukotriene biosynthesis and exerts anti-inflammatory effect[3].

Anti-oxidant activity: Essential oils (monoterpenes, sesquiterpenes and phenolic compounds) from BS can be an important source of natural anti-oxidants. Various findings have indicated that these essential oils might be helpful in preventing the progression of many diseases induced by oxidative stress[5]. *In-vitro* study on methanolic and aqueous extract of BS has revealed that it contains high amount of total flavanoids and total phenolics compound significantly inhibit the nitrite formation, superoxide free radical generation, scavenge DPPH and spare glutathione[22].

Anti-ulcer activity: The petroleum ether and aqueous extracts of BS at the dose of 250 mg kg^{-1} significantly show anti-ulcer activity, as indicated by the reduction of ulcer index in peptic ulcer rats[23]. Evaluation of anti-ulcer activity of boswellic acids in universally accepted animal models viz., pyloric ligation, ethanol/HCl, acetyl salicylic acid, indomethacin and cold restrained stress-induced ulceration in rats revealed that boswellic acids possess a dose dependent antiulcer activity exhibiting different degree of inhibition of the ulcer score towards different ulcerogenic agents[6] (Fig. 1).

Anti-arthritic activity: The gum resin of BS normally contains boswellic acids which helps to preserve the structural of joint cartilage and maintain a healthy immune mediator cascade at a cellular level. Boswellic acids are active against pain and inflammation by inhibiting leukotriene synthesis[7]. BS inhibit the enzymatic activity of 5-lipoxgenase (5-LOX), an inflammation marker in osteoarthritis[24,25] (Fig. 1). Oral and intraperitoneally, administrated BS extract inhibited carrageenan-induced rat hind paw oedema by 39.75% and 65-73%, respectively.

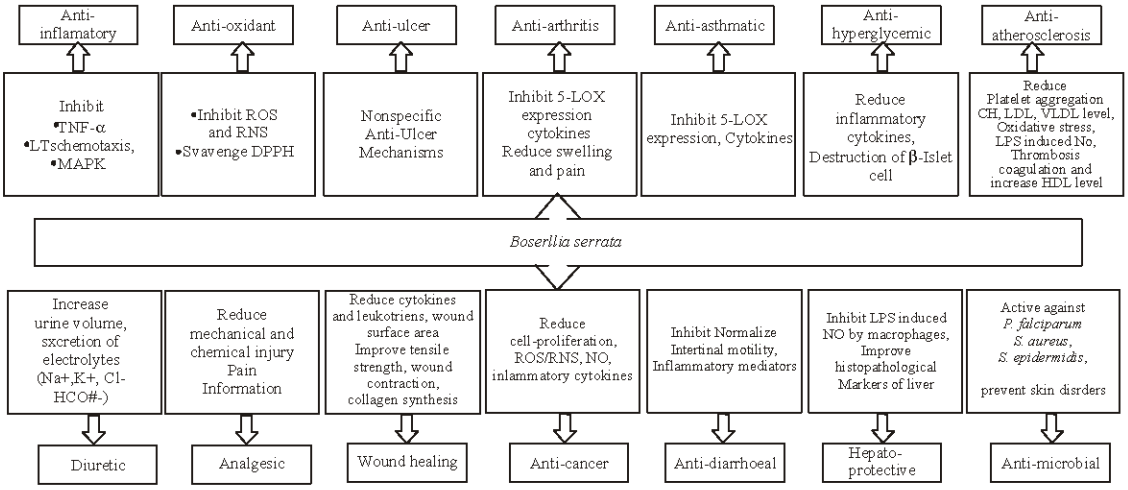

Fig. 1: *Boswellia serrata*: Pharmacological Profile. (Abbreviations: TNF-α: tumour necrosis factor-α; ROS: reactive oxygen species; LTs: leukotrienes; MAPK: mitogen-activated protein kinases;RNS: reactive nitrogen species; DPPH: di(phenyl)-(2,4,6-trinitrophenyl)iminoazanium; 5-LOX: lipo-oxygenase; LTC4: leukotrienes.-c4; NO: nitric oxide; CH: cholesterol; LDL: low density lipoprotein; VLDL: very low density lipoprotein; HDL: high density lipoprotein; LPS: Lipopolysaccharide)

Anti-arthritic studies of BS show effective results in both adjuvant and established arthritis. 5-Loxin, a novel BS extract enriched with AKBA, exert its beneficial anti-inflammatory effect by reducing proinflammatory cytokine mediators. 5-Loxin potentially improves pain, joint stiffness and physical function in osteoarthritis patients[26]. Another experimental study demonstrate that BS extract at the dose of 333 mg/capsule reduce the pain in the affected knee joints, decrease swelling and improve knee flexion, stairs climbing and walking distance in patients of osteoarthritis of knee[7]. BS extract has been claimed to decrease the glycosaminoglycan degradation which helps to keep the cartilage in good condition which might be responsible for the recovery of the patients in Osteoarthritis and stops the progression of this condition[27]. BS extract has an effect on production of antibodies and cell-mediated immunity and inhibits human leukocyte elastase (HLE), a marker of several diseases including rheumatoid arthritis[3] (Fig. 1). Thus, BS significantly improved patient's mobility.

Anti-asthmatic activity: In asthma, increased level of leukotrienes and various inflammatory mediators results in bronchoconstriction. BS extract exhibit a potential therapy for asthma as it has been evidenced from the results of studies that ethanolic extract of *BS* inhibited 5-lipoxygenase (5-LOX), an enzyme responsible for the synthesis of leukotrienes[28]. Clinical trial conducted by Gupta *et al*, (1998) on males and females in the age range of 18-75 years having dyspnoea, number of attacks, increase in forced expiratory volume, subset1, forced vital capacity and peak expiratory flow rate as well as decrease in eosinophilic count and erythrocyte sedimentation rate, symptoms of bronchial asthma significantly showed improvement of disease as evident by disappearance of these physical symptoms and signs when treated with a preparation of gum resin[8]. Furthermore, BS extract also significantly decrease the levels of leukotriene-C4 (LT-C4), nitric oxide (NO) and malondialdehyde (MDA) in plasma of 63 bronchial asthmatic patients[29]. In preclinical studies *BS* extract containing AKBA and with other active constituents like KBA, acetyl beta-boswellic acid and beta-boswellic acid showed anti-anaphylactic and mast cell stabilizing activity[30].

Anti-atherosclerotic activity: It has also been reported that aqueous and hydroalcoholic extracts of BS gum resin exhibits anti-thrombotic, anti-oxidant, anti-platelet and anti-coagulant activities which are beneficial in the prevention of thrombus formation and coronary atherosclerosis[31]. An *in-vivo* and *in vitro* study on hypocholesterolemic activity revealed that water-soluble fraction of the oleo-gum-resin of BS extract inhibits the lipopolysaccharide-induced nitric oxide (NO) production and an increase in serum HDL level in rat macrophages[9].

Anticancer activity: Triterpenic acids of BS including beta-boswellic acid, 3-O-acetyl-beta-boswellic acid 11-keto-beta-boswellic acid (KBA) and 3-O-acetyl-11-keto-beta-boswellic acid (AKBA) in a dose dependent

manner demonstrate *in-vitro* anti-carcinogenic effects by inhibiting the DNA, RNA and protein synthesis in human leukemia HL-60 cells. Among all, AKBA was the significant inhibition of cellular growth of HL-60 cells without affecting cell viability[32]. Triterpenediol (TPD) of boswellic acid constituting isomeric mixture of 3-α, 24-dihydroxyurs-12-ene and 3-α, 24-dihydroxyolean-12-ene exhibited potential apoptotic activity against cancer cells of human leukemia HL-60. Authors hypothesized that induction of oxidative stress in tumor cells and regulated activation of both intrinsic and extrinsic signaling pathways by ROS and NO may elicit cell death mechanisms by TPD[33] (Fig. 1). Further, it has also been evidenced that the ethanolic extract of *BS* gum resin containing a defined amount of boswellic acids exhibit potent anti-proliferative effect on five leukemia (HL-60, K562, U937, MOLT-4, THP-1) and two brain tumor (LN-18, LN-229) cell lines[34]. Moreover, it has been demonstrated that AKBA inhibit the phosphorylation of extracellular signal-regulated kinase 1 and 2 (Erk-1 and Erk-2) in meningioma cells and might be involved in the suppression of proliferation and apoptosis related tumor on the basis of above concerned mechanisms[35]. Pentacyclic TPD in human cervical cancer HeLa and SiHa cells by suppressing the expression of PI3K/pAkt, ERK1/2 and NF-kappaB/Akt in various signaling cascades effectively coordinates the survival of cancer cells[36].

Shah *et al.*[37] also highlight the fact that analogues prepared from β-boswellic acid and 11-keto-β-boswellic acid improved cytotoxic and apoptotic activity by inducing DNA fragmentation through various replacement reactions. Researchers have evaluated the efficacy of AKBA as a chemo protective agent against intestinal adenomatous polyposis coli multiple intestinal neoplasia [APC(Min/+)] mouse model. AKBA treatment reduces the numbers and size of colonic polyposis as well as number of dysplastic cells[38]. AKBA has also been found to be involved in the inhibition of the Wnt/β-catenin and NF-κB/cyclooxygenase-2 signaling cascades[39]. AKBA inhibited the growth of colorectal cancer (CRC) cells and implicated its anti-tumor effects through partial involvement in the up-regulation of specific mRNA pathways and modulation of DNA methylation of various tumor suppressor genes[40]. Furthermore, oral administration of acetyl-11-keto-beta-boswellic acid (AKBA) derived from the gum resin of the BS showed decrease in tumor volume as well as inhibited the enlargement and metastasis of human CRC tumors in orthotopically implanted tumors in nude mice. These findings revealed that AKBA, could effectively inhibited the enlargement and metastasis of human CRC *in vivo* through the suppression and down regulation of various cancer-associated biomarkers such as nuclear factor-κB (NF-κB), tumor survival (bcl-2, bcl-xL, inhibitor of apoptosis (IAP-1) and survivin), proliferative (cyclin D1), invasive (intercellular adhesion molecule 1 and matrix metalloproteinase-9) and angiogenic C-X-C (CXC) receptor 4 and vascular endothelial growth factor)[41]. Intriguingly, it has also been reported that AKBA can down regulate CXCR4 expression in pancreatic cancer cells[38].

Subsequently, in *in-vitro* techniques AKBA significantly suppress VEGF induced phosphorylation of VEGF receptor 2 kinase (KDR/Flk-1) factor responsible for tumour[42]. A clinical study on malignant brain tumor patients revealed that BS potentially reduces their cerebral edema[43].

Anti-diarrhoeal activity: Borrelli *et al.*[11], concluded that BS extract directly inhibits intestinal motility through a mechanism involvement of L-type calcium channels (Fig. 1). *Boswellia* extract prevents diarrhoea and normalizes intestinal motility in pathophysiological states without slowing the rate of transit in control animals as well as can reduce diarrhoea in patients associated with inflammatory bowel Disease[11]. However, treatment with this herbal drug is associated to improve a number of parameters related pathology including stool consistency and frequency[44,45].

Hepato-protective activity: Inhibition of the LPS induced NO production by water-soluble fraction of the oleo-resin gum of BS in the activated rat peritoneal macrophages is responsible mechanism for hepato-protective and reno-protective activity[9]. Y *et al.* reported that hexane extract of BS oleo gum resin showed effective hepato-protective activity with improved histopathological changes in liver at lower dose (Fig. 1). The results were comparable to standard silymarin, a well-known hepato-protective agent[12].

Anti-microbial activity: It was established very first time in *in-vitro* studies by Schmidt *et al.*[46] that *Boswellia* diterpenes exhibit anti-protozoal activity against Plasmodium falciparum[46]. BS (dry extracts) when used in combination with other herbal species like *Usnea barbata*, *Rosmarinus officinalis* and *Salvia* officinalis showed antimicrobial activity which might be used for the topical treatment of skin disorders like acne vulgaris and seborrhoic eczema[47] (Fig. 1). AKBA showed concentration dependent potential anti-microbial effect against *Staphylococcus aureus*. Moreover, it has also been observed that AKBA inhibited the formation of biofilms generated by *S. aureus* and *Staphylococcus* epidermidis and causes disruption of microbial membrane[48].

Wound healing activity: Previously, there were no studies carried for wound healing activity of the oleo-gum- resins obtained from BS. In 2010, Mallik *et al.*[15] formulated a cream using oleo-gum-resins of BS and

applied the cream topically on the excision wound surface as single dose at different percentages. Results of this formulation indicated that BS influencing the various phases of wound healing like fibroplasias, collagen synthesis and wound contraction, decrease surface area and increase the tensile strength of the wound resulting in faster healing[15] (Fig. 1).

Diuretic activity: Oleo-gum-resin of BS significantly shows diuretic effect[27]. Phytochemical screening of BS confirmed the presence of saponins and flavonoids. Furosemide induced significant diuresis and electrolytes (Na^+ and K^+) excretion while plant extracts increased urinary output and electrolytes excretion in a dose-dependent manner. Furthermore, aqueous BS oleo gum extracts administered particularly at the dose of 50 mg kg^{-1} significantly induced water and electrolyte excretion without any signs of toxicity[49] (Fig. 1).

Diuretic activity of the plant extract has been evaluated by increase in urine volume and increased excretion of electrolytes such as sodium (Na^+), potassium (K^+), chloride (Cl^-) and bicarbonate (HCO^{3-}). Whereas, blood urea nitrogen (BUN) levels significantly increased due to dehydration by diuretic effect of the *BS*, but creatinine level found to be with in the normal value. This study shows that extracts did not show any toxic effect on kidney[16].

Analgesic activity: BS non-phenolic fraction obtained from the gum resin has been found to exhibit marked sedative and analgesic effects. A significant analgesic effect observed as evaluated by both hot-wire and mechanical pressure methods. Gum resin OSF BS produced a marked reduction in the spontaneous motor activity and caused apoptosis in rats[50]. Significant reduction of painful sensation due to tail immersion in warm water and with hot plate method was observed with BS. Further, pain induced using acetic acid, formalin were also abolished by different fractions of BS. Acetic acid induced abdominal constriction and tail immersion methods elucidated peripheral and central activity respectively, while the formalin test investigated both. The hot plate method elucidates peripheral mediated effects of BS[17].

Anti-hyperglycemic activity: In an experimental study, it has been revealed that BE could prevent hyperglycemia and inflammation of pancreatic islets in BK+/+ wild type mice treated with 40 mg kg^{-1} STZ i.p. Authors found that extracts from the gum resin of *BS* significantly prevented the islet destruction and subsequently hyperglycemia in an animal model of type 1 diabetes. Inhibition of the production of cytokines related might be the underlying mechanisms[14] (Fig. 1).

CONCLUSION AND FUTURE PROSPECTIVE

Jesus gifted herb, *BS* from last decades had experimentally showed various therapeutic effects. It is an important medicinal plant for the treatment of inflammation, ulcer, arthritis, asthma, atherosclerosis, diarrhea, infections, hyperglycemia, wound healing and pain. BS has significantly showed a wide range of medicinal properties and may be used as a promising therapeutic agent for various diseases and serious ailments like cancer. Recent researches have confirmed that BS could play efficient and capable role in eradicating various tumors. This opens a new vista for research for the treatment of diseases which need focus and are at their initial stage of development.

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