

PHCOG REV.: Plant Review

Phytochemical Profile of *Boswellia serrata*: An overview

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ABSTRACT

Salai guggal, also known as Olibanum, is an oleo-gum-resin from *Boswellia serrata* containing essential oil, gum and resin, which is exceedingly valued for alleviating various human sufferings. Its essential oil is a mixture of mono-, di- and sesqui-terpenes revealed the presence of 33 essential components. The gum fraction essentially composed of arabinose, xylose and galactose sugar with some digestive enzymes. Resin is the most important fraction of salai guggal comprising mainly of pentacyclic triterpenic acids succumb β -boswellic acid, 3-O-acetyl- β -boswellic acid, 11-keto- β -boswellic acid and 3-O-acetyl-11-keto- β -boswellic acid. The therapeutic value of salai guggal predominantly resides in its oleo-resin portion, which possess anti-inflammatory, anti-arthritic, anti-rheumatic, anti-diarrhoeal, anti-hyperlipidemic, anti-asthmatic, anti-cancer, anti-microbial and analgesic activity. In addition it has hepatoprotective and immunomodulatory activity as well. The drug has been established effective in crohn's disease, autoimmune-encephalitis and as an alternative to corticosteroids in treating peritumoral edema. The non-phenolic fraction of oleo-gum-resin causes sedation, reduction in motor activity and ptosis in rats. The alcoholic extract of salai guggal inhibits inflammation induced rise of serum transaminase and leukocyte elastase level. Boswellic acids are novel, specific, non-redox inhibitor of 5-lipoxygenase, which is a significant enzyme engross in arachidonic acid metabolism where its hydrophilic group at C-4 was found essential for 5-LOX inhibition. This also reduces the activity of elastase enzyme, thus helping in the management of asthma and allergic manifestations. The anti-phlogistic activity of boswellic acids is also related to anti-elastase activity. Drug also shows inhibition of topoisomerase enzyme in malignant cell. This review focuses on the phytochemical profile of *Boswellia serrata*

KEY WORDS - Apoptosis; *Boswellia serrata*; Boswellic acids; Inflammation; Leukotriene synthesis; 5-lipoxygenase.

INTRODUCTION

Salai guggal, an oleo-gum-resin from *Boswellia serrata* authority (Family-Burseraceae) is also known as Frankincense in English and Olibanum in Arabian. This tree, abundantly growing in dry hilly tracts of India, yields oleo-gum-resin which has been used for variety of therapeutic purposes (1) such as cancer (2), inflammation (3), arthritis (4), asthma (5), psoriasis (6), Colitis (7), Crohn's diseases (8) and hyperlipidemia (9). Although the oleo-gum-resin which was a component of European Pharmacopoeia until the beginning of this century, fell into oblivion with the use of synthetic drugs, still it is widely used in regions from north Africa to China. In eighties the alcoholic extract of salai guggal (AESG) was reported to possess anti-inflammatory and anti-arthritic activities in animals (3,10) which was due to boswellic acids, an ursane type compound with pentacyclic triterpenes. Boswellic acids selectively inhibit leukotriene synthesis (11,12) by inhibiting 5-LOX in an enzyme directed. non-redox, non competitive mechanism via binding to pentacyclic triterpene selective binding site (13,14). Salai guggal contains 8-9 % essential oil, 20-23 % gum, and about 50 % resin (15-17). A non-phenolic fraction of *Boswellia serrata* shows analgesic and psychopharmacological effects (18) and according to al-

Awadi *et al* the drug also shows anti-diabetic activity in rats against Streptozocin induced diabetes (19).

Taxonomical Hierarchy of *Boswellia serrata*

Kingdom	Plantae-Plants
Division	Angiospermae
Class	Dicotyledoneae
Order	Geraniales
Family	Burseraceae
Genus	<i>Boswellia</i>
Species	<i>Serrata</i>

PHYTOCHEMISTRY (Oleo-gum-resin)

Salai guggal contains essential oil, gum and resin. Its essential oil is a mixture of monoterpenes, diterpenes and sesquiterpenes. In addition phenolic compounds and a diterpene alcohol (serratol) is also found in essential oil. Gum portion of the drug consist of pentose and hexose sugars with some oxidizing and digestive enzymes. Resin portion mainly composed of pentacyclic triterpene acid of which boswellic acid is the active moiety (20). A new lupane triterpene was isolated from fractionation of methanol extract of *B. serrata* resin together with Boswellic acids (21). The fraction on further purification with EtoAC- Hexane (1:1) yielded 3 α -

hydroxy- lup 20(29) ene-24-oic acid whose structure was confirmed by NMR and mass spectroscopy (22).

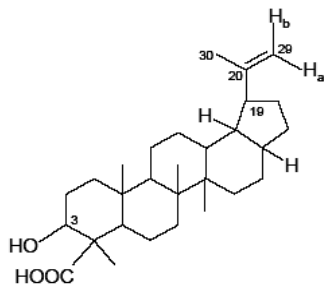


Fig. 1 : 3 α -hydroxy-lup-20(29)-en-24 oic acid (22)

HPLC analysis of Indian and African samples of *B. serrata* gum-resin yielded, 12 different pentacyclic triterpene acids (5,16,23-25). This method provides differentiation and standardization of gum-resin of different origin and gum-resin phytopharmaceuticals (26). Kumar and Saxena carrying out TLC of essential oil from *B. serrata* leaves using silica gel and vanillin-sulphuric acid spraying reagents got pinene and cymene with R_f values 85 and 33 respectively. Whereas GLC studies with OV-17 and SE-30 at 69-200°C yielded thirteen components including d- α -thujene (32%) as major and α -pinene, p-cymene and d-limonene as minor constituents in lower boiling fraction where as high boiling fraction yielded α -terpineol, methyl chavicol and four unidentified compounds (17). A highly sensitive reverse phase HPLC method for the detection and analysis of Boswellic acids in *Boswellia serrata* was developed by Ganzera *et al* (2001) using acidic mobile phase at 60°C at 210 and 254 nm (27).

Essential oil fraction from steam distillation of n-hexane extract of Salai guggal on GC-MS analysis revealed 33 components (28,29) containing esters (62.1%), alcohol (15.4%), monoterpenes (9.9%) and diterpenes (7.1%). This essential oil was found comprise of α -thujene, α -pinene, camphene, sabinene, β -pinene, myrcene, o-methylanisole, α -terpinene, hexyl acetate, p-cymene, 1-8-cineole, limonene, cis- β -ocimene, trans- β -ocimene, γ -terpinene, 1-octanol, terpinolene, linalool, 1-decanol, terpinen-4-ol, α -terpineol, 1-octylacetate, bornyl acetate, citronellyl acetate, neryl acetate, geranyl acetate, hexyl hexanoate, 1-decyl acetate, hexyl octanoate, isocembrene, cembrene, iso-incensole and incensole (30).

Table 2 : GLC profile of essential oil from *Boswellia serrata* (17)

Compound detected	Temperature °C
Bornyl acetate	137
p-Cymene	71
d-Limonene	129
Methyl chavicol	190
α -Phellandrene	200
α -Pinene	69
α -Terpineol	190
α -Terpinolene	178
d- α -Thujene	115

TLC of essential oil of *Boswellia serrata* leaves yielded nine components of different R_f values with their characteristic colour in five different solvent systems. In addition GLC yielded four more compounds which could not identified.

Boswellia serrata resin has been found to contain both pentacyclic as well as tetracyclic triterpenes. *Boswellia serrata* resin upon exhaustive successive extraction with n-hexane and chloroform followed by crystallization and subsequent studies on IR, NMR, Mass, melting point and specific rotation (16) parameters gave the presence of four pentacyclic triterpene acid i.e. B-Boswellic acid, 11-Keto- B-boswellic acid, Acetyl- B-boswellic acid and Acetyl-11-keto-B-boswellic acid.

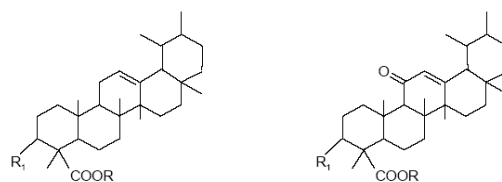


Fig. 2 : Pentacyclic triterpene acids A, B, C and D(16)

Tetracyclic triterpene acids E, F, G and H from resin of *Boswellia serrata* were obtained from acidic fraction of n-hexane extract by column chromatography using silica gel-G with n-hexane and ethyl acetate as eluent with following structures as determined by IR, NMR and Mass studies (26).

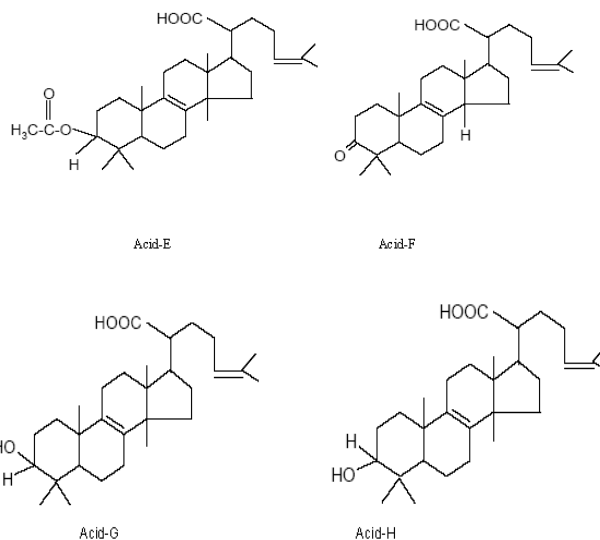


Fig. 3 : Tetracyclic triterpene Acids E, F, G and H(26)

A neutral fraction obtained from n-hexane extraction of *B. serrata* resin on further treatment with methanolic KOH yielded a pure compound following alumina column chromatography with n-hexane and ethylacetate as eluent.

This compound on IR, NMR and MASS spectroscopy was found to be serratol, a new diterpene cembranoid alcohol (31).

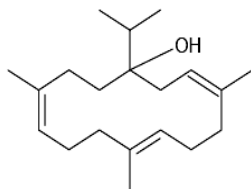


Fig. 4 : Serratol(31)

Optimization of solid phase microextraction for gas chromatography/mass spectroscopy for volatility and polarity of terpenoids in *Boswellia serrata* oleoresin has been successful in trapping cembrane and incensole as characteristic diterpenes. In addition, gas chromatography (40°C) using poly-dimethylsiloxane /divinylbenzene fibre yielded 50 monoterpenes with about 15 in more than 1% yield (32-35).

GC-MS study of samples of methanolic extract of *Boswellia serrata* oleo-resin (44) after trimethylation yielded 15 triterpenes i.e. α -boswellic acid, β -boswellic acid, 3-acetyl- α -boswellic acid, 3-acetyl- β -boswellic acid, α -amyrin, β -amyrin, 3-epi- α -amyrin, 3-epi- β -amyrin, lupeol, 3-epi-lupeol, α -amyrenone, β -amyrenone, lupenone, 3 α -hydroxy lup-20(29)en-24 oic acid and 3-O-acetyl hydroxy lup-20(29) en-24 oic acid on GC-MS studies (36).

Apart, three characteristics degradation products- 24-noroleana-3,12-diene (a), 24-norursa-3,12-diene (b) and 24-norlupa-3,20(29)-diene (c) were also found (37). Following HPTLC analysis of anti-inflammatory triterpene fraction of *B. serrata* boswellic acid was separated and isolated on silica gel 60F-254 plates with spot visualization and scanning at 250 nm (32).

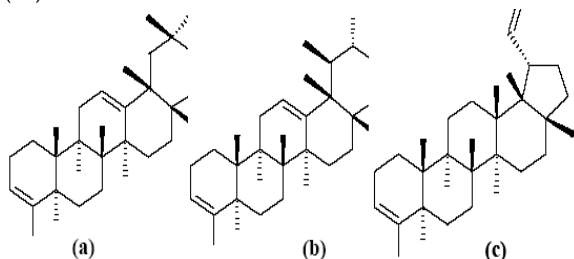


Fig. 5: Degradation products of Olibanum(37)

Capillary electrochromatography (CEC) was utilized for the analysis of boswellic acids by using Hypersil ODS material, and a mobile phase comprising of acetonitrile and aqueous 20 mM ammonium formate solution (pH 6.5) in the ratio of 9 : 1 (v : v). This technique was successfully used for the quantitative determination of boswellic acids.

PHARMACOLOGY

Anticancer Activity

Tsukada *et al* on examining the alcoholic extract of salai guggal (AESG) for anti-carcinogenicity in mice with ehrlich ascites carcinoma and S-180 tumor, found inhibition of tumor growth by inhibiting cell proliferation and cell growth due to

the interference with biosynthesis of DNA, RNA and proteins(38). BA, KBA and AKBA showed anti-proliferative and apoptotic effect HT-29 on colon cancer cell and caspase-8 activation pathway leading to apoptosis (39-42). Although both KBA and AKBA increased the amount of cytoplasmic DNA histone complex in a dose dependent manner, the formation of this complex was high due to BA.

B. serrata extract containing 60% BAs inhibited tumor and inflammation in mice. Topical application of Boswellin (1.2-3.6 mg) with 5 nmol TPA twice daily for 16 weeks to mice previously treated with dimethylbenz-anthracene, caused 87-99% inhibition in the number of tumor/mice (43).

As per Shao *et al* (2000) AESG inhibit the synthesis of DNA, RNA and protein in HL-60 cells. Out of boswellic acids, AKBA was most potent inhibitor and its inhibitory effect on DNA synthesis was irreversible (44).

According to Hoernlein *et al* (2000) AKBA caused reduction in thymidine incorporation and cell count in HL-60 and CCRF-CEM cells. This effect was pronounced when AKBA was cross-linked with CD-95 receptor. Flow cytometric analysis of propidium iodide stained cells indicated apoptosis which was confirmed by G₁ peak in AKBA treated cells and by DNA laddering in DNA relaxation assay, AKBA inhibited topoisomerase-1 from calf thymus at low concentration which in-turn induced apoptosis in HL-60 and CCRF-CEM cell. Boswellic acid treatment to female wistar rats inoculated with C-6 tumour cells not only showed significant reduction in brain tumour volume but also enhanced the survival time of animals in dose dependent manner (45-48).

Boswellic acids induce concentration dependent inhibition of glioma cell proliferation and show anti-edema effect in glioblastoma patients (49). It was also revealed that BAs induced apoptosis is protein synthesis dependent and not associated with free radical scavenging activity. AKBA causes rapid inhibition of phosphorylation of ERK pathways, impairing the motility of meningioma cells by impaired signal transduction and tumorigenesis thus causing cytotoxicity against meningioma cells (50).

Anti-inflammatory Activity

Studies on alcoholic extract of salai guggal (AESG) revealed anti-inflammatory activity in carrageenan induced paw edema in rat and mice; Dextran induced edema in rats and also in adrenalectomised rats (51-54). In another study AESG has shown anti-arthritis activity against formaldehyde induced arthritis (55). The alcoholic extract also inhibited inflammation induced increase in serum transaminase level and leukocyte count; however antipyretic and analgesic effect was not exhibited. Shrivastava *et al* (2003) ascertained that the BAs exert their action by inhibiting the synthesis of 5-LOX products. They also inhibit topoisomerase, elase and C-3 convertase enzymes (56).

Anti-arthritis

In an anti-arthritis study it was revealed that oral administration of BAs at a dose of 25,50 and 100 mg/kg/day to bovine serum albumin (BSA) induced arthritic rabbits reduces the population of leucocytes in BSA injected knee and changed the electrophoretic pattern of synovial fluid protein. The local injection of BAs (5, 10 and 20 mg) into the knee 15

min prior to BSA, reduces the infiltration of leukocytes into knee joint and pleural cavity and inhibited the migration of polymorphonuclear leukocytes (PMNLs) *in vitro* (57).

Muscle Relaxant activity

The doses of 2×10^{-5} to 2×10^{-4} gm/ml essential oil of oleo-gum-resin of *B. serrata* on muscles revealed stimulatory effect on skeletal muscles and spasmogenic effect on smooth muscle of guinea pig ileum. According to an earlier report the essential oil of *B. serrata* has selective action on biological tissues and its activity was not due to non specific action on cell membrane (58).

Hypolipidemic activity

Water soluble fraction of *B. serrata* extract decreased total cholesterol (38-48%) and increased HDL (22-30%) in rats fed on atherogenic diet, thus proving its hypolipidemic potential. The same fraction *in vitro* inhibited LPS induced nitric oxide production in rat macrophages (9,100,101). According to Zutshi *et al.* (1986) feeding of 100mg/kg of salai guggal reduced cholesterol level in wistar rats which were due to significant decrease in cholesterol synthesis (59).

Hepatoprotective Activity

Hagmann *et al* (1982) and Wendel *et al* (1986) revealed that alcoholic extract of salai guggal (AESG) causes hepatoprotection in galactosamine/endotoxin induced liver damage in mice which was reflected by reduced titre of SGOT, SGPT, aminotransferase and serum enzymes. According to Safayhi *et al* (1991). The hepatoprotection was most probably through inhibition of 5-LOX activity (60).

Hypoglycemic Activity

Herbal formulation containing *B. serrata* oleo-gum-resin as one of the ingredient has been reported to produce significant anti-diabetic activity on non-insulin dependent diabetes mellitus in streptozocin induced diabetic rat model where reduction in blood-glucose level was comparable to that of phenformin. The formulation in question worked by effecting hepatic gluconeogenesis influencing pyruvate carboxylase and phosphoenol pyruvate carboxykinase systems (61).

Antidiarrhoeal

In a recent study *Boswellia serrata* extract (BSE) was found effective in treating diarrhoea in patient with inflammatory bowel syndrome without causing constipation. It was also found effective against acetylcholine and barium chloride induced diarrhoea by inhibiting contraction of intestinal smooth muscles. The extract also inhibited gastrointestinal transit in croton and castor oil induced diarrhoea in mice. However, intestinal motility remained unaffected in control mice by BSE (62).

Analgesic and Psychopharmacological Activity

Menon and Kar (1971) found the non-phenolic fraction of BS showing sedative and analgesic effects. It produced reduction in motor activity and ptosis in rats. The fraction also potentiated secobarbitone induced hypnosis in rat. As per the same study the secondary conditioned response was blocked while conditioned avoidance response was not significantly affected in trained rats by non-phenolic fraction of *B. serrata*. (63).

Clastogenic activity

Clastogenic effect of dietary supplements used in stress relief, memory enhancement and memory boost was demonstrated by Ghoshal *et al* (2001) using Swiss Albino mice. Aqueous extracts of *Spirulina alga*, *Boswellia serrata* and *Withania somnifera* were administered (per oral) and cyclophosphamide was administered i.p. After 16.5 h colchicine solution (0.041% kg) was administered i.p. After 1.5 h animals were killed, bone marrow cells were processed, following hypotonic treatment in KCl (0.05 M) and fixed in methanol:acetic acid (3:1), stained with giemsa. All cells have at least one aberration (64).

Anti-asthmatic activity

In a double blind placebo control clinical study with 300mg thrice daily dose for 6 weeks, Gupta *et al* (1998) established anti-asthmatic potential of alcohol extract of salai guggal (AESG) where 70% of the patients with prolong history of asthma showed improvement in physical symptom and sign of dyspnoea, bronchi, number of attacks, increase in stimulation of mitogen activated protein kinase MAPK and mobilization of intracellular Ca^{2+} (65).

Immunomodulatory Activity

BSE showed anti-anaphylactic and mast cell stabilizing or inhibiting mast cell degranulation activity in passive paw anaphylaxis and induced mast cell degranulation (66).

Activity in Autoimmune Encephalitis

Crude Acetyl-boswellic acid (ABA) inhibited ionophore stimulated release of leukotrienes from polymorphonuclear leukocytes (PMLNs). Here pure compound was found three times more potent and even the intraperitoneal administration of this compound reduced the symptoms of autoimmune encephalitis (67).

Activity in Crohn's Disease

In a comparative study on the management of Crohn's disease *B. serrata* extract was proved superior on efficacy and safety aspects compared to mesalazine, a molecule commonly used in treating Crohn's disease (68).

CONCLUSION

Boswellia serrata is a potent natural and safe alternative to conventional NSAIDs used in traditional and ayurvedic medicine to treat a variety of disorders. However there is a shortage of clinical trial regarding *in-vitro* and *in-vivo* studies. The gas chromatography of essential oil shows the presence of mono-, di- and sesquiterpenes and column chromatography is used for the separation of pentacyclic and tetracyclic triterpenic acid as well as diterpene alcohol (serratol). Mass spectroscopy and capillary electrochromatography is used for the determination of molecular weight, fragmentation pattern and quantitative analysis respectively. However there is a lack of phytochemical studies on gum portion of *Boswellia serrata*. There are insufficient data regarding different fractions of *B. serrata*, which leads to possible variation in therapeutic value based on the chemical profile of fractions used. Clinical trials of *B. serrata* are in process for cancer, alzheimer's disease, asthma, anaphylactic shock and high lipoprotein in blood. *Boswellia serrata* embibing a tremendous potential deserves a special attention of the scientific fraternity to emerge as a milestone for medical science of this millennium due to its safety profile.

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