Phcog Rev. Vol, 3, Issue 5, 206-215, 2009
Available Online : www.phcogrev.com

PHCOG REV. : Review Article

Phytochemical and Pharmacological investigations on *Boswellia serrata*

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ABSTRACT

Salai guggal is an oleo-gum-resin obtained from *Boswellia serrata*. Its essential oil is a mixture of mono, di and sesquiterpenes while gum fraction composed of pentose and hexose sugar with some digestive enzymes. Resin is the most important fraction of Salai guggal comprising mainly of pentacyclic triterpenic acids namely Boswellic acids. 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. Boswellic acids are novel, specific, non-redox inhibitor of 5-lipoxygenase, an enzyme involved in arachidonic acid metabolism. This review focuses on the current state of therapeutic potential and phytochemical profile of *Boswellia serrata*.

Key words: Apoptosis; *Boswellia serrata*; Boswellic acids; Inflammation; Leukotriene synthesis; 5-lipoxygenase.

Abbreviations

ABA, Acetyl-boswellic acid; AESG, Alcoholic Extract of Salai Guggul; AKBA, Acetyl-keto-boswellic acid; BA, Boswellic acid; BS, Boswellia serrata; BSA, Bovine Serum Albumin; BSE, Boswellia serrata Extract; CHP, Cumene hydroperoxide; EGR, Extract of Gum Resin; ESR, Erythrocyte Sedimentation Rate; GC, Gas Chromatography; HDL, High Density Lipoprotein; HPLC, High Performance Liquid Chromatography; ILs, Interleukins; KBA, Keto-boswellic acid; 5-LOX, 5-Lipoxygenase; LPs, Lipopolysaccharides; LTs, Leukotrienes; MAPK, Mitogen Activated Protein Kinase; MS, Mass Spectroscopy; PC, Pyruvate carboxylase; PEPCK, Phosphoenol Pyruvate Carboxy Kinase; PI3-K, Phosphatidyl Inositol-3-Kinase; PMNLs, Polymophonuclear Leukocytes; PTs, Pentacyclic Triterpenes; TNFα, Tumor Necrosis Factor α.

INTRODUCTION

Salai guggal is an oleo-gum-resin obtained from *Boswellia serrata* (Family Burseraceae). It is also known as Frankincense in English and Olibanum in Arabian. This tree abundantly growing in dry hilly tracts of India which has been used for variety of therapeutic purposes such as cancer, inflammation, arthritis, asthma, psoriasis, colitis, crohn's diseases and hyperlipidemia (1-8). Alcoholic extract of Salai guggal (AESG) was reported to possess anti-inflammatory and anti-arthritic activities in animals which were due to boswellic acids, an ursane type compound with pentacyclic triterpenes (9). Boswellic acids selectively inhibit leukotriene synthesis by inhibiting 5-LOX in an enzyme directed, non-redox, non-competitive mechanism (10-13). Salai guggal contains 8-9 % essential oil, 20-23 % gum, and about 50 % resin (14-16).

PHYTOCHEMICAL PROFILE OF *BOSWELLIA SERRATA*

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 (17-20).

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 3α-hydroxy- lup 20(29) ene-24-oic acid whose structure was confirmed by NMR and mass spectroscopy (22).

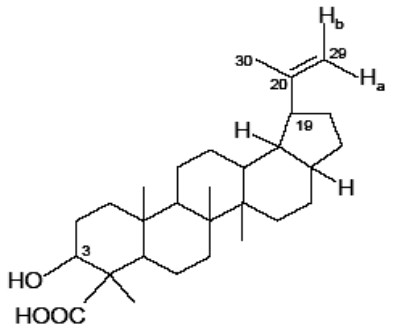


Fig. 1: 3α-hydroxy-lup-20(29)-en-24 oic acid

HPLC analysis of Indian and African samples of *B. serrata* gum resin yielded 12 different pentacyclic triterpene acids. This method provides differentiation and standardization of gum resin of different origin and gum resin phytopharmaceuticals (23-27). Kumar and Saxena carrying out TLC of essential oil from *B. serrata* leaves got pinene and cymene with Rf values 85 and 33 respectively whereas GLC studies 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 (16). This was shown in Table 1 and 2. Essential oil fraction from steam distillation of n-hexane extract of Salai guggal revealed 33 components containing esters (62.1%), alcohol (15.4%), monoterpenes (9.9%) and diterpenes (7.1%) (28). A highly sensitive reverse phase HPLC method for the detection and analysis of Boswellic acids in *B. serrata* was developed (29).

Tetracyclic triterpene acids E, F, G and H from resin of *B. 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 (30).

A neutral fraction obtained from n-hexane extraction of *B. serrata* resin give serratol, a new diterpene cembranoid alcohol (30).

Optimization of solid phase microextraction for gas chromatography/mass spectroscopy for volatility and polarity of terpenoids in *B. serrata* oleo-resin has been successful in trapping cembrane and incensole as characteristic diterpenes (31-34). Monoterpenes in *B. serrata* oleo resin were shown in Table 3. GC-MS study of samples of methanolic extract of *B. serrata* after trimethylation yielded 15 triterpenes acid on GC-MS studies (35). 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 (36).

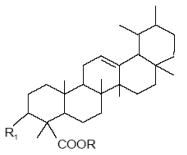
Table 1: TLC Profile of essential oil from Boswellia serrata leaves

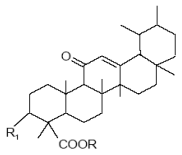
Compound	Colour	Mean % Rf values in different systems				
		I	II	III	IV	V
P-Cymene	Light blue	33	38	60	65	
d-Limonene	Light blue	42	55	51	58	
Terpinolene	Blue	68	69	62	62	
Bornyl acetate	Brown blue	68	69	62	62	
α-Pinene	Light blue	85	87	88	92	
α-Thujene	Violet	71	89	89	80	
α-Phellandrene	Dark violet	52	56	63	94	
Methyl chavicol	Brown blue	-	-	-	-	60
α-Terpineol	Greenish blue	-	-	-	-	60

Solvent systems: I: n-Hexane, II: Cyclohexane, III: Methylcyclohexane, IV: 2, 2-Dimethyl butane, V: Benzene.

Table 2: GLC profile of essential oil from Boswellia serrata leaves

Peak no.	Corresponding authentic	Temperature	Relative percentage
1.	α-Pinene	69	2.5
2.	p-Cymene	71	2.2
3.	d-Limonene	70	3.9
4.	Un-identified	109	5.0
5.	d-α-Thujene	115	32.0
6.	α-Terpineol	129	13.6
7.	Bornyl acetate	137	20.0
8.	α-Terpinolene	178	1.9
9.	Un-indentified	186	5.0
10.	Methyl chavicol	190	4.0
11.	Un-identified	196	5.3
12.	α-Phellandrene	200	1.5
13.	Un-identified	,	,





A. Boswellic acid R_1 = OH R = H
C. Acetyl-β-boswellic acid R_1 = OAc R = H

B. 11-Keto-β-boswellic acid R_1=OH R = H
D. Acetyl-11-keto-β-boswellic acid R_1 = OAc R = H

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

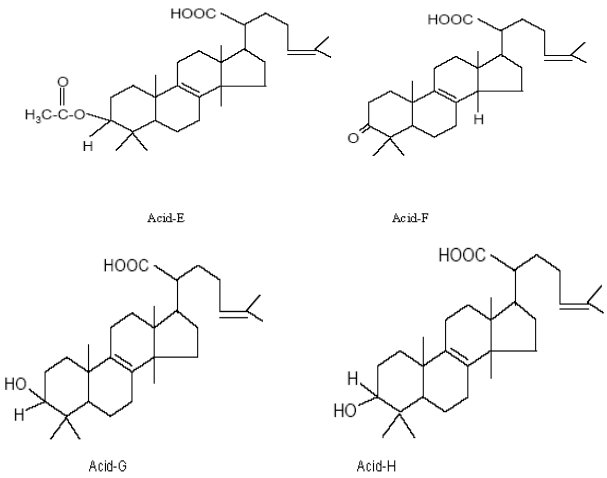


Fig. 3: Tetracyclic tritepenic Acids E, F, G and H

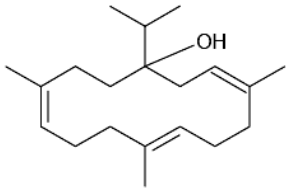


Fig. 4: Structure of Serratol

Table 3: Monoterpenes in B. serrata oleo-resin

Compound	Percentage	Compound	Percentage
β-Eudesmene	3.3	α-Phellandrene	0.5
γ-Murolene	3.0	Trans-Carveol	0.5
γ-Cadinene	2.9	β-Pinene	0.4
α-Copaene	2.8	Terpinyl acetate	0.4
α-Murolene	2.7	(-)-trans-Pinocarveol	0.4
α-Cubebene	1.9	(+)-α-Terpineol	0.4
δ-Cadinene	1.9	Aromadendrene	0.3
3,5-Dimethoxytoluene	1.6	Bornyl acetate	0.3
Germacrene D	1.4	Carvone	0.3
Allo-aromadendrene	1.3	δ-Guaiene	0.3
β-Caryophyllene	1.3	Sabinene	0.3
o-Methyl anisole	1.2	δ-Elemene	0.2
Linalool	1.0	α--Guaiene	0.2
β-Gurjunene	1.0	cis-Carveol	0.1
β-Bourbonene	0.9	Cumaldehyde	0.1
Camphene	0.9	Cuminol	0.1
Eucalyptol	0.9	cis-Verbenol	0.1
1-Hydroxy-1,7-dimethyl-4-isopropyl-2,7-cyclodecadiene	0.9	γ-Terpinene	0.1
Valencene	0.8	(-)-4-Terpineol	0.1
S-cis-Sabinol	0.6	α-Thujene	0.1
1,2,3,4,68a-Hexahydro-1-isopropyl-4,7-dimethyl-	0.6	Verbenone	0.1

naphthalene

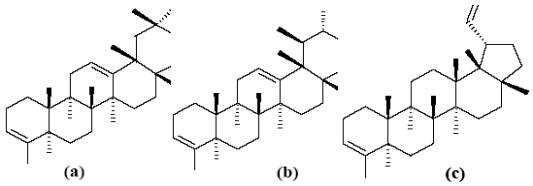


Fig. 5: Degradation products of Olibanum.

BIOMEDICAL APPLICATIONS OF *BOSWELLIA SERRATA*

Anticancer

Tsukada (37) found that anti-carcinogenic activity of alcoholic extract of Salai guggal (AESG) due to the interference with biosynthesis of DNA, RNA and proteins (37). BA, KBA and AKBA showed anti-proliferative and apoptopic effect on HT-29 colon cancer cell (38-39) and caspase-8 activation pathway leading to apoptosis (40-42). The effect of AKBA on cytoplasmic DNA histone complex and on caspase-3 activation was 3.7 and 3.4 times more respective to camptothecin (43). The apoptosis induced by AKBA was completely inhibited by caspase-8 or caspase-3 but it was partially inhibited by caspase-9 inhibitor (44-45). *B. serrata* extract containing 60% BAs inhibited tumor and inflammation in mice treated with dimethylbenz-anthracene, caused 87-99% inhibition in the number of tumor/mice (46). AESG inhibit the synthesis of DNA, RNA and protein in HL-60 cells which was irreversible (47).

Boswellic acid acetate (BAA) induces differentiation and apoptosis in leukemia cell lines. *Boswellia carterii* (BC-4) induced differentiation of HL-60, U-937 and ML-1 cells proving that BC-4 was a potent inducer where 90% cell showed morphological changes and 80-90% cell showed NBT reduction. BC-4 like topoisomerase inhibitor, VP-16, induces leukemia differentiation at low and apoptosis at high concentration (48-52). Overall pentacyclic triterpene (BAs) having powerful growth inhibition, differentiation, induction and chemoprevention could be useful for cancer treatment. 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 (53-54). Boswellic acids induce concentration dependent inhibition of glioma cell proliferation and show anti-edema effect in glioblastoma patients. It was noticed that in contrast to steroids, boswellic acids synergize cytotoxic cytokines and CD-50 ligand in glioma cell apoptosis (55-57).

Anti-inflammatory

Shrivastava et al. (58) ascertained that the BAs exert their action by inhibiting the synthesis of 5-LOX products. They also inhibit topoisomerase, elastase and C-3 convertase enzymes. It has been found effective in the treatment of asthma, arthritis, cancer and ulcerative colitis (58-60). According to Kov et al. (61) TNFα expression of vascular cell adhesive molecule 1 is sensitive to BSE (61). Polyherbal formulation containing *Boswellia serrata, Commiphora mukul*, *Semicarpus anacardium*, *Strychnos nux-vomica* and *Terminalia arjuna* shows anti-inflammatory and anti-atherosclerotic properties (62). According to Weber et al. by modulating P-glycoprotein (P-gp) function, *B. serrata* extract can be used fore treating peritumoral oedema and chronic inflammatory disease (121).

Anti-arthritic

Oral administration of BAs reduces the population of leucocytes, inhibit the migration of polymorphonuclear leukocytes *in vitro* and changed the electrophoretic pattern of synovial fluid protein in bovine serum albumin (BSA) induced arthritis (63).

Hypolipidemic

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 (64-65). The same fraction *in vitro* inhibited LPS induced nitric oxide production in rat macrophages (66).

Immunomodulatory

BSE showed anti-anaphylactic and mast cell stabilizing or inhibiting mast cell degranulation activity in passive paws anaphylaxis and induced mast cell degranulation (67-68). Dalunen et al. found that BAs inhibit graft rejection to the same extent as with high dose of steroids (69).

Analgesic and Psychopharmacological activity

Menon and Kar found the non-phenolic fraction of BS showing sedative and analgesic effects. The fraction also potentiated secobarbitone induced hypnosis in rat while conditioned avoidance response was not significantly affected (70, 71).

Hepatoprotective

Hagmann et al. revealed that alcoholic extract of Salai guggal (AESG) causes hepatoprotection in galactosamine/endotoxin induced liver damage in mice. According to Safayhi et al hepatoprotection was most probably through the inhibition of 5-LOX activity (71-73).

Clastogenic

Clastogenic effect of aqueous extract of *B. serrata, Spirulina alga* and *Withania somnifera* used in stress relief, memory enhancement and memory boost (74).

Muscle Relaxant activity

Essential oil of oleo-gum-resin of *B. serrata* revealed stimulatory effect on skeletal muscles and spasmogenic effect on smooth muscle of guinea pig ileum (75). 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 (76).

Activity in Autoimmune Encephalitis

Acetyl-boswellic acid shows effectiveness in autoimmune encephalitis due to inhibition of ionophore stimulated release of leukotrienes from polymorphonuclear leukocytes (77).

Hypoglycemic

Herbal formulation containing *B. serrata* oleo-gum-resin has been reported to produce significant anti-diabetic activity on non-insulin dependent diabetes mellitus in streptozocin induced diabetic rat by affecting hepatic gluconeogenesis, pyruvate carboxylase and phosphoenol pyruvate carboxykinase (78).

Activity in Crohn's Disease

B. serrata extract was proved superior on efficacy and safety aspects compared to masalazine, a molecule commonly used in treating Crohn's disease (79-80).

Antidiarrhoeal

B. 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 (81).

Anti-asthmatic

Gupta et al. (1998) established anti-asthmatic potential of alcohol extract of Salai guggal (AESG) in patients with prolong history of asthma due to stimulation of MAPK and mobilization of intracellular Ca^{2+} (5).

Pharmacodynamic Studies on *Boswellia serrata*

BA and its derivatives are the novel, non-redox, specific inhibitor of 5-Lipoxygenase enzyme, responsible for the formation of leukotrienes which causes vasoconstriction, bronchoconstriction, increased vascular permeability and chemotaxis (83-84). Human leukocyte elastase (HLE) plays a role in cystic fibrosis, glomerulonephritis, and pulmonary emphysema (85). The blockade of leukotriene formation and HLE by BAs might be rationale for antiphlogistic activity (85-87). Acetyl-keto-β-boswellic acid is an effective cytotoxic agent acting through the inhibition of topoisomerase I and IIα (88-99).

BAs inhibit *in vitro* immunohaemolysis of antibody coated sheep RBC by pooled guinea pig serum and the reduced immunohaemolysis was reported due to the inhibition of C-3 convertase enzyme (94-95). *B. serrata* extract activate mitogen activated protein kinase P-42^{MAPK} and P-38 ^{MAPK} in isolated human polymorphonuclear leukocytes (96). The KBA, ABA and AKBA gave substantial kinase activity whereas BA lacking in 11-keto group was less effective (Safayhi and Sailer, 1997). KBA stimulate mobilization of Ca^{2+} in PMNL (98-100). Phosphatidyl inositol 3-kinase involves in MAPK activation. MAPK activation by BAs is inhibited when Ca^{2+} is removed by chelation (101).

Pharmacokinetic studies on *Boswellia serrata*

Studies of 11-Keto-β-boswellic acid carried out on healthy, adult volunteers revealed its half life as 6 hrs. It was further revealed that the plasma concentration reaches to steady state after 30 hrs and the drug is safe and well tolerated while taken orally (101-102). The concentration of 11-Keto-boswellic acid in human plasma is determined by GC-MS (102). High fat meal leads to increased plasma concentration of Boswellic acids (103-104).

Miscellaneous studies on *Boswellia serrata*

The gum resin of *B. serrata* is extracted with MeOH. The methanolic extract washed with 2% aqueous KOH, then aqueous solution washed with n-hexane. Acidification of aqueous extract yield BAs (105-106). Ammon et al. (1991) compared the 5-LOX inhibitory activity of Acetyl-keto-boswellic acid (AKBA) with other natural pentacyclic triterpenes, which inhibit 5-LOX by specific, non-redox and non-competitive mechanism (11). Sailer et al. (1996) studied structure activity relationship of boswellic acid and established that 5-LOX inhibitory activity of AKBA was slightly diminished by deacetylation of acetoxy groups or reduction of carboxyl group to alcohol. β-boswellic acid lacking 11-keto group inhibit 5-LOX activity partially and incompletely whereas its corresponding alcohol had no 5-LOX inhibitory activity. The pentacyclic triterpene ring is crucial for binding to effector site whereas 11-keto group and hydrophilic group on C-4 of ring A are essential for 5-LOX inhibitory activity (13). BSE inhibit the transport activity of Pgp in lymphocytic leukemia cell line and porcine brain capillary endothelial cells. This effect was not associated with boswellic acid which has no keto group in their structure (107-112).

Photoaffinity analog-Azido I^{125}-KBA, which inhibits 5-LOX actively, is used to characterize AKBA effector site (109). The labeling of 5-LOX by azido I^{125} KBA depends on the presence of Ca^{2+} > 500 nm and ATP (112) and is abolished by heat denaturation. AKBA binds to site in presence of Ca^{2+} which is distinct from substrate binding site of 5-LOX. The AKBA binding site on 5-LOX is distinct from arachidonate substrate binding site (113). *B. serrata* affect 5-LOX product formation in calcium and ionophore stimulated neutrophils. The unique feature of *B. serrata* is that at low concentration (1-10 μg/ml) it potentiates 5-LOX product formation (5-HETE) (113) whereas at high concentration (10-15 μg/ml) it inhibits 5-HETE formation (114-115).

-Oxotirucallic acid enhanced 5-LOX product (5-HETE) formation in ionophore stimulated polymorphonuclear cells, initiate Ca^{2+} mobilization MEK-1/2 phosphorylation, 5-LOX translocation and 5-LOX product formation in resting cells (116-117). The acetoxy derivative of 3-oxo-TA acted in same manner while 3-OH-TA barely stimulated MEK phosphorylation and inhibit 5-LOX product formation (115). While studying the effect of carboxyl group of boswellic acid on enzyme inhibition. It was observed that the C-4 alcohol derivative of KBA still exerted 5-LOX inhibitory activity whereas C-4 alcohol analog of β-BA, methyl ester analog of KBA and acetyl 11-keto amyrin shows no inhibitory activity upto 50 μm, showing that hydrophilic group at C-4 in boswellic acid is essential for 5-LOX inhibition (116-121). Structure of boswellic and its derivatives were shown in Table 4.

Commerce in Salai guggal - Salai guggal sample collected in

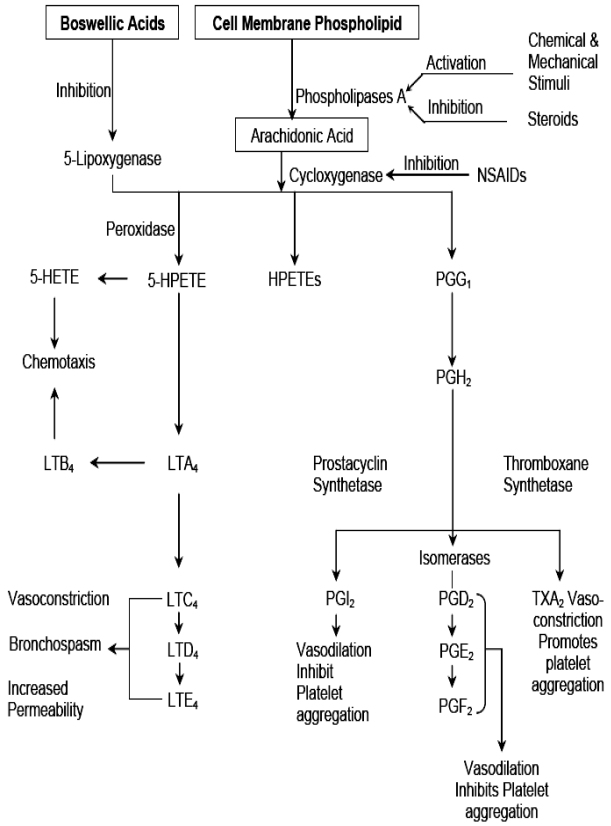


Fig. 6: Biosynthesis of prostaglandins and leukotrienes

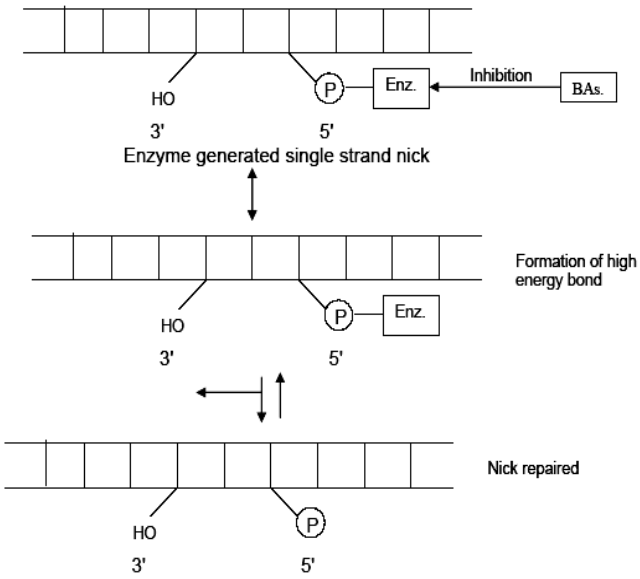


Fig. 7: Mechanism of action of BAs by inhibiting topoisomerase

June were graded on colour basis grade as blue green, greenish blue, yellowish green and light yellow revealed that there was a gradual increase in essential oil and resin contents and reduction in gum content as we proceed from grade 1 to 4. Blue green sample yielded minimum (8.5%) essential oil, where as it was highest (13.3%) in light yellow sample. Similarly the resin percentage was also found less (54%) in blue green sample to high (57%) in light yellow samples (122). The People Republic of China is the largest market of *B. serrata* resins with import of Salai guggal or more than 1000 tonnes in 1984, while the import in Europe and Latin America was 500 tonnes in 1987. Somalia and Ethiopia is the biggest producer of resin. Somalia produces 800-900 tonnes in 1987, while Sudan and Ethiopia produces 2000 tonnes resin in 1987. In 1984 Somalia olibanum was priced at US $ 6/kg (123). Export of Salai guggal from India and destinations and Principle Producers of oleo-resin were shown in Table 5 and 6.

Side Effects

No sign of toxicity and severe side effects have been observed for *B. serrata*, except rare side effects with very mild symptoms of diarrhoea, urticaria, nausea and skin rashes. Topical administration of *B. serrata* extract may cause contact dermatitis (114-117).

Conclusion

Boswellia serrata is a potent natural and safe alternative to conventional NSAIDs used in traditional and ayurvedic

Table 4: Structure of Boswellic acid and its derivatives

Substitution			5-LOX enzyme activity
R^1	**R^2**	**R^3**	
O	α-AcO	COOH	Inhibition
O	α-HO	COOH	Inhibition
O	α-HO	CH_2OH	Inhibition
2H	α-AcO	COOH	partial inhibition
2H	α-HO	COOH	partial inhibition
O	α-AcO	CH_2OAc	no inhibition
O	α-HO	$COOCH_3$	no inhibition
2H	α-HO	CH_2OH	no inhibition
O	β-AcO	CH_3	no inhibition
2H	β-HO	CH_3	no inhibition

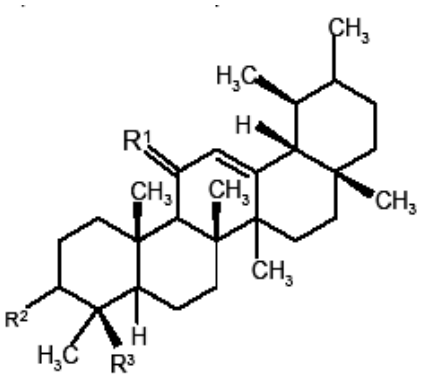


Fig. 8: Boswellic acid and its derivatives.

Table 5: Export of salai guggal from India and destinations 1987-1992 (tonnes) (123)

Country	*1987*	*1988*	*1989*	*1990*	*1991*	*1992*
Japan	10	-	-	-	-	54
Singapore	9	19	1	9	4	17
USA	25	8	2	15	4	15
Saudi Arabia	13	-	-	12	6	8
Malaysia	5	3	1	4	-	4
Trininad	8	6	6	15	7	3
Hongkong	13	13	-	1	-	2
Spain	3	6	-	4	-	2
UAE	30	5	-	-	23	-
France	10	5	2	7	-	-
Total	***167***	***81***	***19***	***75***	***70***	***113***

Table 6: Principal Producers – 1987 (123)

Boswellia serrata	Producing country	Production/Trade (in tonnes)
Eritrean type	Ethiopia, Sudan	2000
Maidi	Somalia	800
Beyo	Somalia	200
Indian type	India	200

Acknowledgement: The authors are thankful to Department of Biotechnology, Ministry of Science and Technology, New Delhi, for funding RGYI research project to Dr. Namdeo and Senior Research Fellowship to Mr. Ajay Sharma.

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