Hygeia.J.D.Med. October 2015 –March 2016 ISSN 2229 3590
Hygeia:: journal for drugs and medicines
October 2015
Open Access www.hygeiajournal.com
Research article section: Medicinal Natural Products
A Half Yearly Scientific, International, Open Access Journal for Drugs and Medicines
DOI:10.15254/H.J.D.Med.7.2015.147 Review Article

ANTI-CANCER POTENTIAL OF BOSWELLIC ACID: A MINI REVIEW

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Key words
Anticancer, Boswellic acid

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Received: 10 April 2015,
Revised: 20 May 2015,
Accepted: 5 July 2015,
Available online: 8 October 2015

ABSTRACT

Plan: *Anticancer potential of Boswellic acid*
Preface*: Boswellia serrata has been the most investigated of all the species, with some photochemical studies, as well as bioactivity-related investigations. The presence of boswellic acids in almost all the species of Boswellia is a characteristic of this genus. The triterpenoids present in Boswellia are synthesized through isopentenyl pyrophosphate route (IPP) from a squalene intermediate and their role is yet to be fully understood, though they are certainly involved in defense mechanisms, as many of them have been reported to possess diverse biological activities.*
Outcome*: In the present review we discussed the anticancer potential of boswellic acid. It may help the researchers for further investigation.*

1. INTRODUCTION

Boswellic acids [BAs] are pentacyclic triterpenoids belonging to ursane group, which are the major constituents of the gum derived from the plant *Boswellia serrata* Roxb. Ex Colebr. [Family Burseraceae, Syn. B. glabra] commonly known by the names Salai guggal, white guggal, Indian olibanum. *Boswellia serrata* is middle-sized tree broadly spread in the India and Africa. B. Serrata has highly medicinal as well as economical potential. Currently it is extensively used in various formulations for the treatment of inflammation related disorders[1].

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Hygeia journal for drugs and medicines, 2229 3590
Researcher id: J-7191-2015

Boswellia serrata, or Frankincense resins are harvested from deep incisions made into the tree trunk of *Boswellia* species and this process causes the tree to 'bleed' a milky white substance that cure the wound to prevent infection [Fig-1]. The gum resin of Boswellia serrata, frankincense, has a number of components including oils, [α-Thujene], terpenols, monosaccharides and most importantly terpenes. Major research has centered on the components belonging to the pentacyclic triterpene group of compounds considered to be most bio-active. PT‟s are mostly synthesized in higher plants, due to their highly complex need for their synthesis. They exhibit a variety of profound effects such as being anti-inflammatory, anti-nociceptive, anti-oxidant, anti- bacterial, cancer drug sensitizing, cardio-protective and insulin resistance lowering [2-6.]

Fig -1 Boswellia serrata, frankincense tree incision and tears

Medicinal plants have an extensive record of utilization in remedial measures throughout the world and become a significant part of traditional remedy. Importantly, medicinal plants and herbal products must be safe for the patient. Natural sources have been used as a most important resource of drugs for centuries and most of products are formed in the pharmaceuticals is derived from natural products. Interest in natural products research is attributed to several factors likes the amazing assortment of both chemical structures and biological potentials of naturally occurring secondary metabolites and the efficacy of bioactive natural products as biochemical and molecular probes, the development of novel and sensitive techniques to identify biologically active natural products, superior techniques to purify, isolate and structurally characterized these complex natural products [7].

Cancer is the worldwide health problem and the most frightening disease of human and it's become the second leading cause of human mortality after cardiovascular diseases. According to WHO, cancer accounted for 7.8 million deaths in 2007, with 38% in developed countries and 62% in developing countries. Cancer is one of the leading causes of death in both developed and developing countries and is consequently, has posed an immense challenge in front of medicinal chemist[8].

Anticancer drugs discovered from herbal medicines have a long history and these are used in clinical practice, such as vincristine, vinblastine and the camptothecene derivatives, topotecan and irinotecan, etoposide, which are derived from *Catharanthus roseus* G. Don. [Apocynaceae]. *Camptotheca acuminata* Decne [Nyssaceae]. *Podophyllum peltatum* Linnaeus [Podophyllaceae] and *Taxus brevifolia* Nutt. [Taxaceae][9].

In the current scenario, there is a real need to develop the novel anticancer drugs which is safe or coast effective with effective mechanism. The new mode of developing combined components from effective traditional formulas and from single standard ingredient under traditional medicine theory, unlike the conventional way of clinic experience based drug development should be focused. This new mode will promote the academic research and the industry development of traditional medicines [10-11].

2. Chemistry of boswellic acid

The β-boswellic acid is lipophilic in nature and comprises of only one a-hydroxyl and a carboxyl function which belongs to ursane group of triterpenic acids, Therefore, to modulate their weakly acidic character and solubility, it was envisaged to modify their structure through the replacement of carboxyl by an amino function, making it weakly basic. The higher terpenoids constitute one of the major components [25–35%] of the gum resin, comprising mainly b-boswellic acid [BA, 1] as the main triterpenic acid along with 11-keto-b-boswellic acid [KBA, 2] and corresponding acetates ABA [12] and AKBA [13].

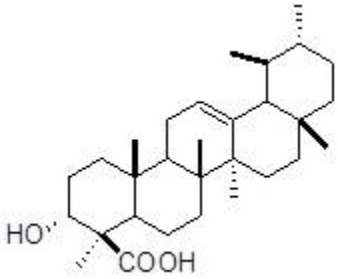


Fig.1.
(3R, 4R, 6aR, 6bS, 8aR, 11R, 12S, 14bR)-3-hydroxy-4, 6a, 6b, 8a, 11, 12, 14bheptamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicene-4-carboxylic acid

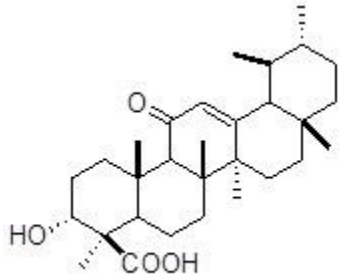


Fig.2
(3R, 4R, 6aR, 6bS, 8aR, 11R, 12S, 14bS)-3-hydroxy-4, 6a, 6b, 8a, 11, 12, 14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12, 12a,14,14a, 14b-icosahydropicene-4-carboxylic acid

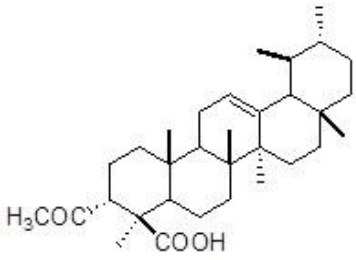


Fig.3
(3R, 4R, 6aR, 6bS, 8aR, 11R, 12S, 14bR)-3-acetyl-4, 6a, 6b, 8a, 11, 12, 14b-heptamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a, 14b-icosahydropicene-4-carboxylic acid

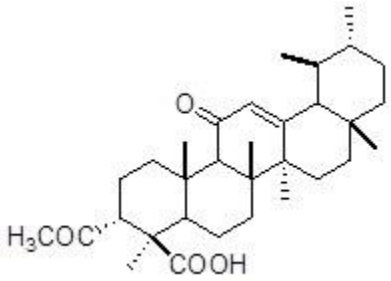
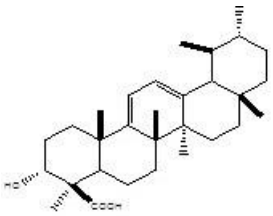


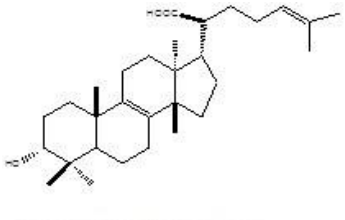
Fig.4
(3R, 4R, 6aR, 6bS, 8aR, 11R, 12S, 14bS)-3-acetyl-4, 6a, 6b, 8a, 11, 12, 14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a, 14b-icosahydropicene-4-carboxylic acid
Preeti Garg

A large volume of original research has accumulated on the chemistry of higher terpenoids ever since the first isolation of BA was reported in 1898 and HPLC procedures have revealed above fifteen specific PT derivatives in Boswellia species, such as α - and β-boswellic acid, 3-O-acetyl-β-boswellic acid, 3-O-acetyl-11-keto-β-boswellic acid, α-amyrin, β-amyrin, lupeol, 3-epi-α-amyrin, 3-epi-β-amyrin, 3-epi-lupeol, α-amyrenone, β-amyrenone, lupenone, lupeolic acid and 3-O-acetyl-lupeolic acid, tirucallic acid, and others Since then number of chemists have worked on its structure elucidation. By disclosing the stereo-identity of functional groups, BA is generally accompanied with a diene derivative, namely 3-O-acetyl-9, 11-dehydro-beta-boswellic acid which is believed to originate from 3-O-11-hydroxy-b-boswellic acid via dehydration. The diene derivative may be isolated by repeated crystallization of the methyl ester of BA. The structures of all the major pentacyclic triterpenes, which include BAs and the diene derivative, have been established by NMR spectroscopy. The structures of ABA and the methyl ester of BA have also been confirmed by X-ray crystallographic studies. In addition, a-amyrin and 3-hydroxy-urs-9, 11-dien-24-oic acid have also been isolated from the gum resin. Several tetracyclic terpenoid include 3a-hydroxy-tirucall-8, 24-dien-21-oic acid, 3a-acetoxy-tirucall-8, 24-dien-21-oic acid, 3b-hydroxytirucall-8, 24-dien-21-oic acid and 3-keto-tirucall-8, 24-dien- 21-oic acid. structure elucidation of two new triterpenoids from acidic and neutral fractions of the gum extract,2,3-dihydroxy-urs-12-ene-24-oic acid and urs-12-ene-3a,24-diol .The presence of another isomeric diol, viz. urs-12-ene-3b,24-diol [14-16]. The general composition of the dry Boswellia serrata extract of the gum resin shows around 50-60% various α -and β-boswellic acids, of which roughly 1-3% of the total are the most bio-active AKBA fraction [17-18].

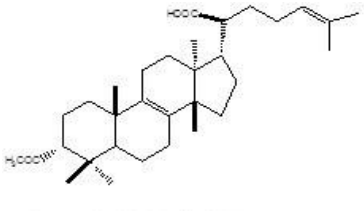
Boswellic acids present in Boswellia extracts, is a pentacyclic terpenoid, which has been shown to have antitumor effects in different types of tumor cells including colon, prostate, leukocytes, liver and brain. The inhibitory effects of AKBA on the nuclear factor kappa B, NFκB. and the signal transducer and activator of transcription-3 [STAT-3].-related pathways, which potentiate apoptosis and inhibit angiogenesis in neoplastic cells [19-25.]



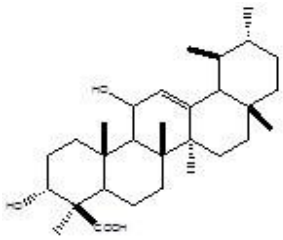
3-hydroxy-urs-9, 11-dien-24-oic acid



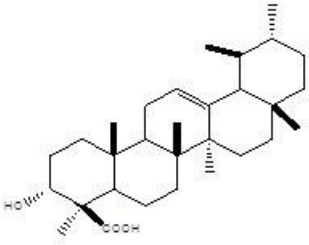
3 alpha-hydroxy-tirucall-8, 24-dien-21-oic acid



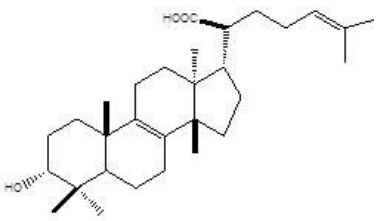
3 alpha-acetoxy-tirucall-8, 24-dien-21-oic acid



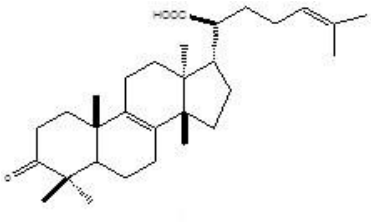
3-O-11-hydroxy-beta-boswellic acid



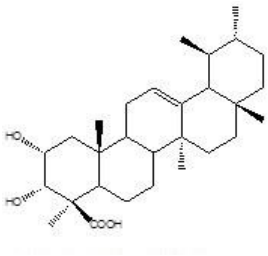
α-amyrin



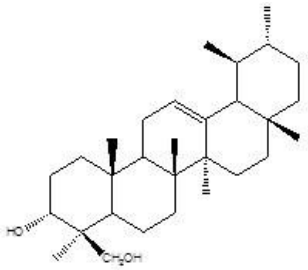
3-beta-hydroxytirucall- 8, 24-dien-21-oic acid



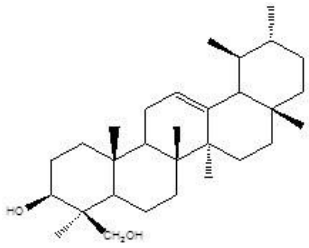
3-keto-tirucall-8, 24-dien-21-oic acid



2, 3-dihydroxy-urs-12-ene-24-oic acid



urs-12-ene-3 beta, 24-diol



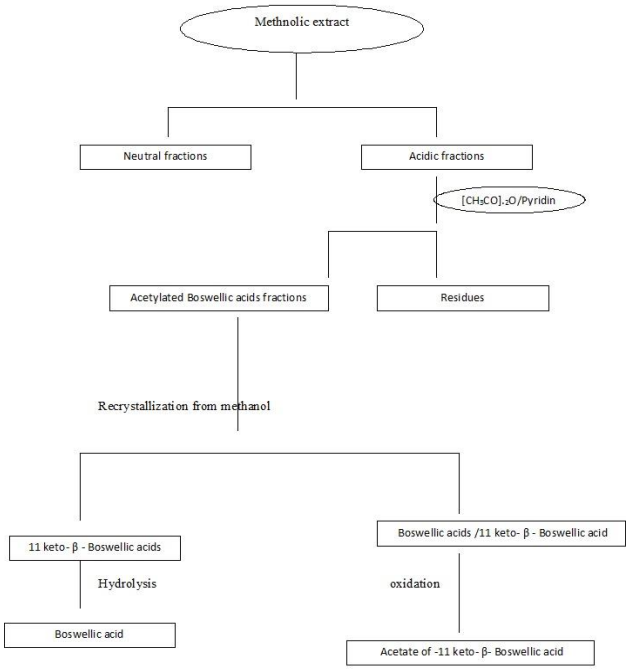
urs-12-ene-3 alpha, 24-diol

3. Anticancer profile of Boswellic acid:

Cancer is clearly a disease directly associated with the genes, and risk of cancer rises in the final decades of life. Since the dawn of molecular therapeutics, there has been an associated revolution in the development of anti-cancer drugs. BSE is reported to moderate the breast cancer and the brain tumor metastases. It is a known inducer of apoptosis and the ethanolic preparation tested for cytostatic, cytotoxic and apoptotic potential against leukemia and brain tumor cells has shown to induce apoptosis and to act as a potent anti-proliferative agent. BSE containing 60% BAs have apparently repressed tumors and inflammation in mice. BSE has also been reported for anti-carcinogenicity in mice with Ehrlic ascites carcinoma and S-180 tumor by inhibiting the cell proliferation and growth inhibition due to the interference with biosynthesis of DNA, RNA and proteins. It reduced the tumor cell proliferation and induced apoptosis in several in vitro experiments with animals. The efficacy of BSE against peri-tumoural edema can be increased by enhancing the bioavailability of AKBA. A composition of B. carterii has been shown to induce the cell differentiation in HL-60 cells at significantly low concentrations. B. carterii extract has also been reported for pro-apoptotic effects in HL-60 cells[1].

Saji Uthaman, et al. prepared boswellic acid nanoparticles formulation and evaluated its anticancer activity for the treatment of prostate cancer. Boswellic acid nanoparticles causes apoptosis DNA fragmentation, outcome of which leading that the nanoparticles causes fragmentation of DNA which cause hall mark of apoptosis[26]. Suhail et al. demonstrated that Boswellia sacra essential oil prepared from hydro distillation has tumor cell-specific cytotoxicity in multiple cancer cell types. Consistent with anti-proliferative, pro-apoptotic, and anti-invasive activities in cultured breast cancer cells, Boswellia sacra essential oil is shown to induce tumor cell cytotoxicity in a drug resistant and metastasized breast cancer case.

In addition to establishing standard procedures to produce essential oil with consistent chemical composition, safety and toxicity studies of the oil and pre-clinical validation of the in vitro results will be required. Moreover, formulation and standardization of clinical protocols to observe cancer progression following Boswellia sacra essential oil insertion are desirable instantly for prospective human clinical trials [27].



Extraction and isolation method of various Boswellic acid

Ahmed et al. investigate the efficacy of Boswellia serrata methylene chloride extract against colon cancer- induced in rats. Serum MMP-7, MMP-9 and EGF, plasma TGF-β and TNF-α levels were assayed using ELISA procedure. Immunohistochemical technique was used for estimation of colon COX-2 and cyclin D1 expression. Colon β-catenin, K-ras and c- myc gene expression was detected by RT-PCR. Also, histological investigation of colon tissue was done.

Colon cancer group showed considerable rise in the studied biochemical markers. In the contrary, the all treated groups showed considerable fall in these markers. Colon cancer group showed significant elevation in COX-2 and cyclin D1 expression in colon tissue. In contrast, all treated groups exhibited marked depletion in COX-2 and cyclin D1 expression.

Cancer group showed important up-regulation in the expression level of β-catenin K-ras and c-myc genes in colon tissue. While, all treated groups exhibited significant down-regulation in the expression levels of these genes. Histopathological investigation of colon tissue sections in cancer group showed dysplasia and anaplasis in the lining epithelial cells of the glandular structure. While, treatment with 5-fluorouracil or Boswellia serrata extract showed marked improvement in the histological feature of colon tissue.

This study indicated that Boswellia serrata methylene chloride extract has a promising therapeutic role against colon cancer induced in rats through its potential anti-inflammatory property, anti-proliferative capacity and apoptotic activity [28.]

Liu et al. showed that acetyl-keto-b-boswellic acid [AKBA] inhibited cellular growth in several colon cancer cell lines. Cell cycle analysis by flow cytometry showed that cells were arrested at the G1 phase after AKBA treatment and analysis showed that cyclin D1 and E, CDK 2 and 4 and phosphorylated Rb were decreased in AKBA-treated cells while p21 expression was increased. The growth inhibitory effect of AKBA was dependent on p21of the apoptotic effect of AKBA, suggested that p21 may have protected cells against apoptosis by inducing a G1 arrest. AKBA inhibited cellular growth in colon cancer cells [29].

Streffer et al. a clinical study with brain tumour patients has also been conducted, in which BSE was administered to 29 patients having gliomas in three groups with different doses prior to surgical intervention. After seven days of treatment, the reduction in size of perifocal oedema was found to be the largest in case of a group having highest intake of extract, to a lesser extent in the group receiving, with no effect being seen in the group receiving the smallest dose[30].

Sinha et al. also found that boswellic acid also inhibit basic fibroblast growth factor [bFGF] induced angiogenesis using an in vivo Matrigel Plug assay. Recent studies also demonstrated BAs can act as anti-angiogenic agents [31.]

Singh et al. study that BAs can even be considered as alternative drugs to corticosteroids, as they have been shown to reduce cerebral peri-tumoural oedema by modulating P-glycoprotein [PgP] function.Pgp has gained importance as the transporter, mainly for drug disposition and the resulting clinical response; BAs as well as BSE inhibited the transport activity of PgP in the micro-molecular range**.** In the normal cells ABA didn't shown apoptosis, ABA cause DNA fragmentation in melanoma and fibrosarcoma, ABA is a cytostatic rather than a cytotoxic agent, as it induces differentiation, apoptosis and cytostasis in various cell lines, and can be used in chemo-preventive intervention strategies, either to interrupt the occurrence of a primary tumour or to decrease the likelihood of metastasis. BAs have been shown to induce cell differentiation and inhibit topoisomerase I and II [32.]

McCarty et al. study that BAs have great attention as anticancer agents especially from the time when 5-LO inhibitors were also recognized as cancer chemo-preventive agents. Making these cellular signals part of the therapeutic targets, either alone or better in 12 combination with other modalities has been shown to slow tumor progression, reduce tumor cell invasiveness and tumor cell motility and decrease tumor angiogenesis. [88-90].Cigarette smoke is known to cause an inflammatory response in the colon that can lead to colon adeno-carcinoma. The mechanism is to up-regulation of 5-LO induced protein expression accompanied by up-regulation of mettaloproteinases-2 and vascular endothelial growth factor.

5-LO inhibitors reduced the incidence of adenomas, angiogenesis and MMP-2 activity and VEGF. The results showed that cigarette smoke induced 5-LO expression leading to colon adenoma formation can be reduced by 5-LO inhibitors [33].

5-LO and its metabolites have been found to have an increased expression in lung cancers and to inhibit apoptosis as well as contribute to cell proliferation. These advances in the understanding of the molecular biology of lung cancer has led to the conclusion that 5-LO pathway inhibitors should be part of the chemoprevention armamentarium in these illnesses study by Yn [34].

Bunn et al. study that in addition to natural isolates, semi-synthetic acyl analogues of BAs have displayed significant cytotoxicity against various human cancer cell lines in vitro, and markedly induced apoptosis in HL-60 cells. Most of the acyl analogues displayed improved cytotoxicity compared to their natural counterparts. A natural diol derivative of BA [also synthesized semi-synthetically] has also shown anti-cancer activity in in vivo models and also induced apoptosis. In an attempt to establish the mechanism of apoptosis by diol of BA, it was observed that the effect was mediated through an extrinsic pathway via activation of TNF family of proteins [TNF-R1, DR4], with the generation of NO and ROS leading to caspase-8 activation. Likewise, semisynthetic amino alcohol analogues have displayed improved cytotoxicity in vitro compared to the parent BAs against various human cancer cell lines [35].

Pathania et al. study that BA145 induced autophagy in PC-3 cancer cells and HUVECs significantly impeded its negative regulation on cell proliferation, migration, invasion and tube formation. These effects of BA145 induced autophagy were observed under both normoxic and hypoxic conditions. However, inhibition of autophagy using either pharmacological inhibitors or RNA interference enhanced the BA145 mediated death of these cells. Similar observations were noticed with sunitinib, the anti-angiogenic properties of which were significantly enhanced during combination treatments with autophagy inhibitors. In mouse tumor xenografts, co-treatment with chloroquinone and BA145 led to a considerable reduction in tumor burden and angiogenesis compared to BA145 alone. These studies reveal the essential role of BA145 triggered autophagy in the regulation of angiogenesis and cytoprotection. It also suggests that the combination of the autophagy inhibitors with chemotherapy or anti-angiogenic agents may be an effective therapeutic approach against cancer [36.]

4. CONCLUSION

Medicinal plants have a long history of use in therapy throughout the world and still make an important part of traditional medicine. Importantly, medicinal plants and herbal products must be safe for the patient. Natural products had served as a major source of drugs for centuries and about half of the pharmaceuticals in use today are derived from natural products. Boswellic acid consists of a series of pentacyclic triterpene molecules that are produced by the plant *Boswellia serrata*. The potential applications of Bowsellic acid for treatment of cancer have been focused here. In this review article we highlight the anticancer potential of boswellic acid. It may help the researchers for further investigation.

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Preeti Garg and Aakash Deep. Anti-Cancer Potential of Boswellic Acid: A Mini Review. *Hygeia.J.D.Med* **2015**; 7(2):18-27. Available from http://www.hygeiajournal.com / Article ID-Hygeia.J.D.Med/147/15.
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