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Boswellic Acid- Potential tumors suppressant terpenoid -Photochemistry, Extraction and Isolation Methods -A comprehensive review study

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Abstract

Natural products had served as a major source of drugs for centuries and about half of the pharmaceuticals used today are derived from natural products. Medicinal plants are of important therapeutic aid for various ailments Herbal constituents continue to influence the medicines of today and up to 25% of all prescription drugs in the United States have at least one active ingredient that comes from plant extracts or synthesized plant compounds. Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. Tumor metastases to distant sites generally have a greater effect than the primary tumors on the frequency of complications and the patient's quality of life and mortality. The gum resin of *Boswellia serrata*, frankincense, has a number of components including oils, [α -Thujene], terpenols, monosaccharide's and most importantly terpenes. 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.

Keywords: Cancer, Herbal plants, Chemotherapy, Anticancer activity

Introduction

The chemical diversity of the compounds found in nature makes plant, animal and marine materials important potential sources of new drugs, novel lead compounds and stereo specific structures for the synthesis of existing drugs. The most commonly used natural sources are plants and microorganisms, both land and marine. Selection of the plant or microorganism to be investigated may be based on ethnopharmacology or the current interest of the investigators. Herbal medicine continues to influence the medicines of today and up to 25% of all prescription drugs in the United States have at least one active ingredient that comes from plant extracts or synthesized plant compounds. According to the WHO as many as 4 billion people or 80% of the earth's population are estimated to use some form of herbal medicine in their health care given the advantages of being stable in the ambient environment, being permeable to the blood-brain and/or blood-eye barriers and convenient for administration, naturopathic compounds are increasingly growing and becoming promising therapeutic candidates for neural protection [1-3].

Cancer, as a major cause of death in the world, has posed a great challenge to the fields of medicine and immunology of worldwide concern. Cancer is one of the leading causes of death in both developed and developing countries [4]. Cancer is a disease of striking significance in the world today. It represents the second leading cause of human mortality after cardiovascular diseases. According to the WHO, cancer accounted for 7.8 million deaths [around 12% of all deaths] in 2007, with 38% in developed countries and 62% in developing countries. By 2030, nearly 21.4 million new cancer cases and more than 13.2 million deaths are projected to occur in the world [5-8]. Chemotherapy has been widely employed for various cancer treatments. The toxicity and resistance of traditional chemo therapeutic drugs make it urgent to develop new targets and novel drugs for the cancer therapy. Kinases are well-known targets for a variety of diseases and disorder [8-10]. Chemotherapy, hyperthermia, radiation and immune therapy is known to be much more effective, if the number of tumour cells is low. The biological and chemical diversity encountered in nature provide opportunities to discover new classes of chemical compounds. Identification of new drugs from plants has a long and successful history and certain anticancer components have been used in traditional medicine system for thousands of years. [11-17].

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Plant-derived compounds have been an important source of several useful anti-cancer agents in clinical practice such as vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, which are isolated or derived from *Catharanthus roseus* G. Don. [Apocynaceae], *Camptotheca acuminata* Decne [Nyssaceae], *Podophyllum peltatum* Linnaeus [Podophyllaceae] and *Taxus brevifolia* Nutt. [Taxaceae] [18-19]. In recent years, it has been seen that the traditional medicine such as Chinese medicine, Kampo medicine, Ayurveda and so on, are popular treatment for cancer in Asian countries, and these approaches are also accepted increasingly as complementary and alternative therapies for cancer in the rest of the world [20-21].

The search for novel herbal anticancer drug is paradoxically producing excellent scientific information on many previously unresearched herbal remedies. In the present perspective, there is a need to develop new medicines with effective components to meet new opportunities and challenges in cancer and other diverse pathologies. 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 [22-24].

Tumour suppressant terpenoid-Boswellic acid

Boswellic acid: (*B. Serrata*) is deciduous middle-sized tree widely distributed in the Indian subcontinent and Africa and is documented to be of high medicinal as well as economic importance. Currently it is extensively used in various formulations for the treatment of inflammation related disorders. 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. The other species of genus *Boswellia* include *B. ovalifoliolata* Bal. & Henry [India], *B. carterii* Birdw. [Somalia], *B. sacra* Fluckiger [Oman and Yemen] [17,18], *B. serrata* is the most investigated of all the species, while some phytochemical studies as well as bioactivity-related investigations have been reported for *B. carterii*, *B. ovalifoliolata* and *B. papyrifera* [25-30]. *Boswellia serrata*, frankincense resins are harvested from the deep incisions made into the tree trunk of *Boswellia* species. This wounding process causes the tree to 'bleed' a milky white

substance that seals and heals the wound to prevent infection [Fig-1].

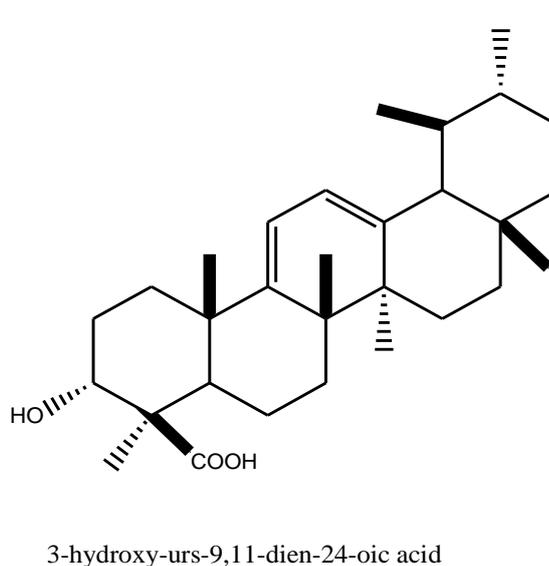
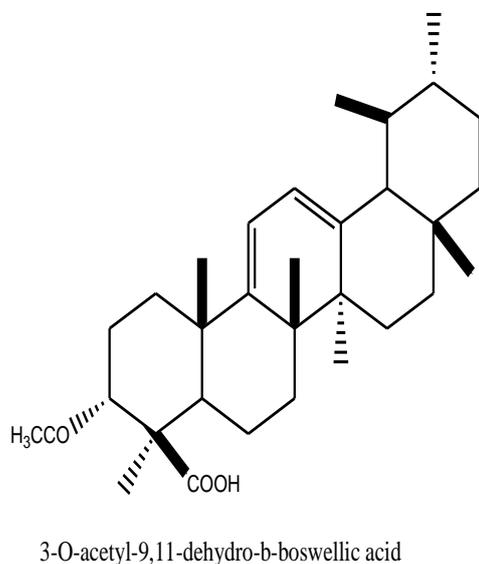
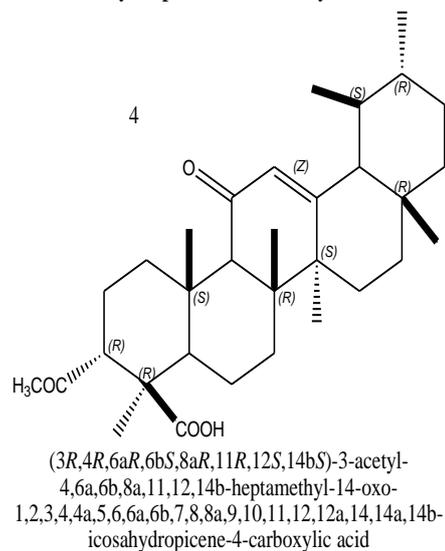
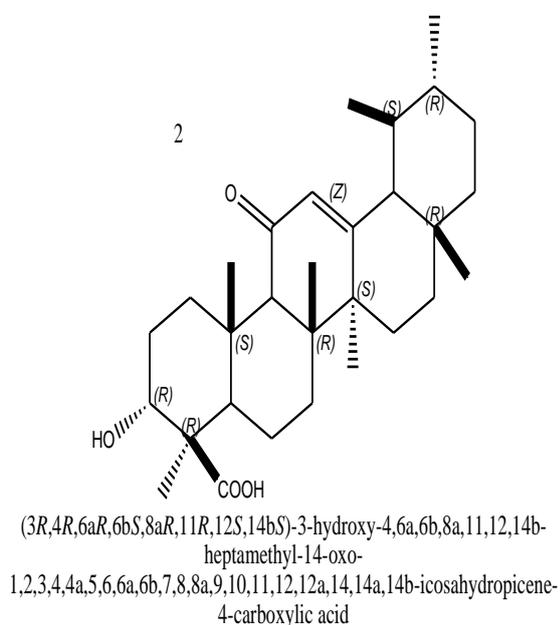
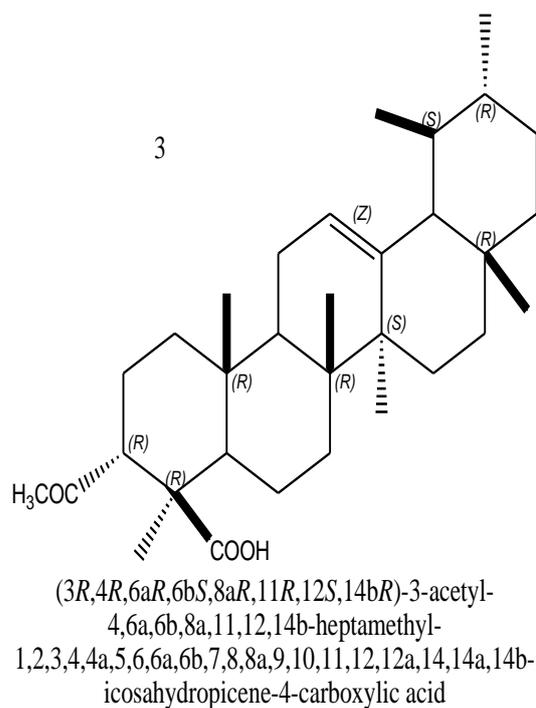
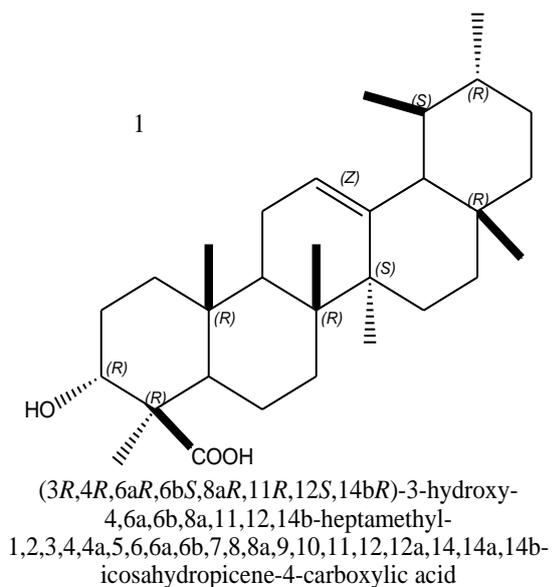


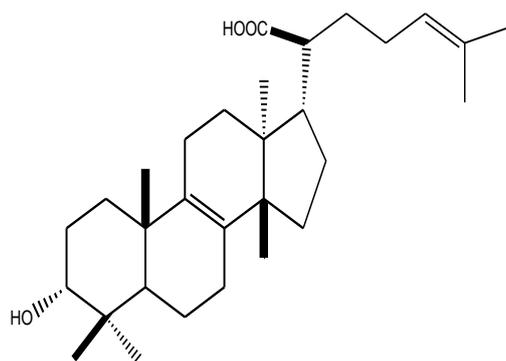
Fig 1: *Boswellia serrata*, tree incision and tears

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 centred on the components belonging to the pentacyclic triterpene group of compounds considered to be the most bio- active. Pentacyclic triterpenes are mainly synthesized in higher plants and having pharmacological action such as anti-inflammatory, anti-nociceptive, antioxidant, antibacterial, cancer drug sensitizing, cardio-protective and insulin resistance lowering [31-35].

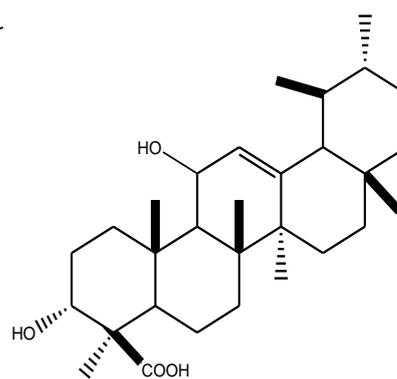
Phytochemistry of Boswellic acid

The β -boswellic acid, which belongs to ursane group of triterpenic acids, is lipophilic in nature and comprises only one α -hydroxyl and a carboxyl function. The higher terpenoids constitute one of the major components (25–35%) of the gum resin, comprising mainly β -boswellic acid (BA, 1) as the main triterpenic acid along with 11-keto- β -boswellic acid (KBA, 2) and corresponding acetates ABA (3) and AKBA (4).

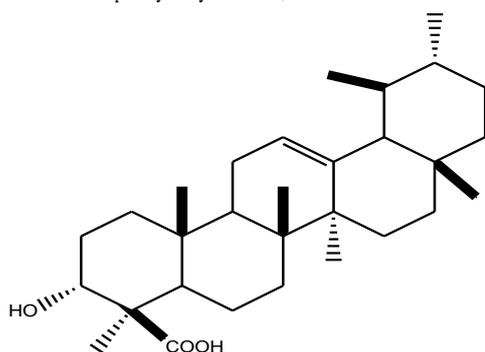




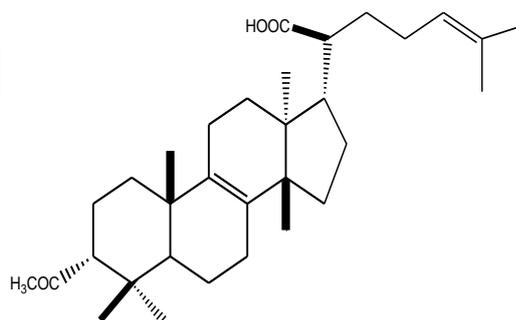
3 alpha-hydroxy-tirucall-8,24-dien-21-oic acid



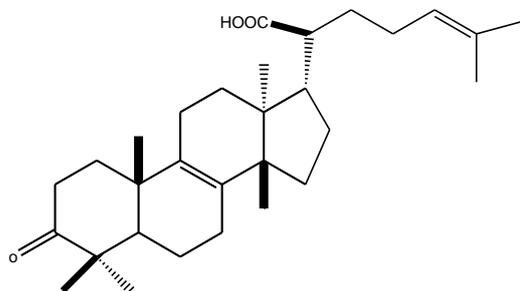
3-O-11-hydroxy-beta-boswellic acid



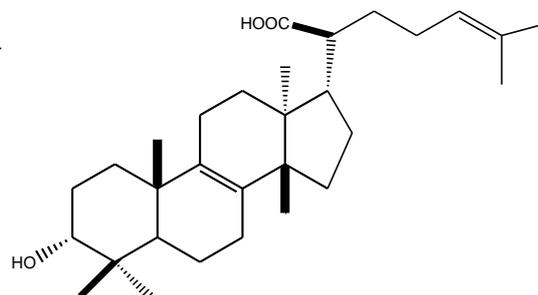
alpha-amyrin



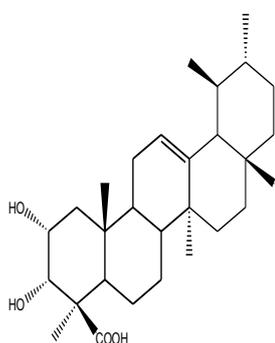
3a-acetoxy-tirucall-8,24-dien-21-oic acid



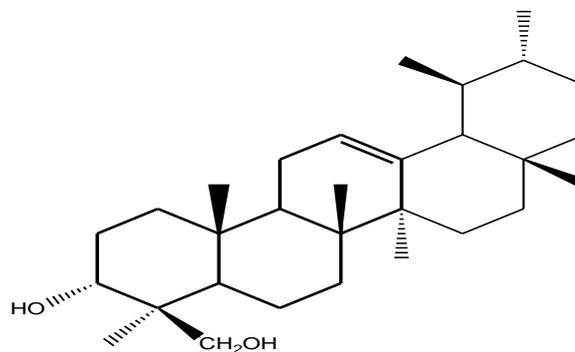
3-keto-tirucall-8,24-dien-21-oic acid



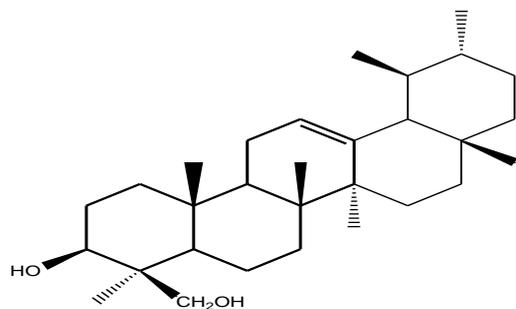
3beta-hydroxytirucall-8,24-dien-21-oic acid



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



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

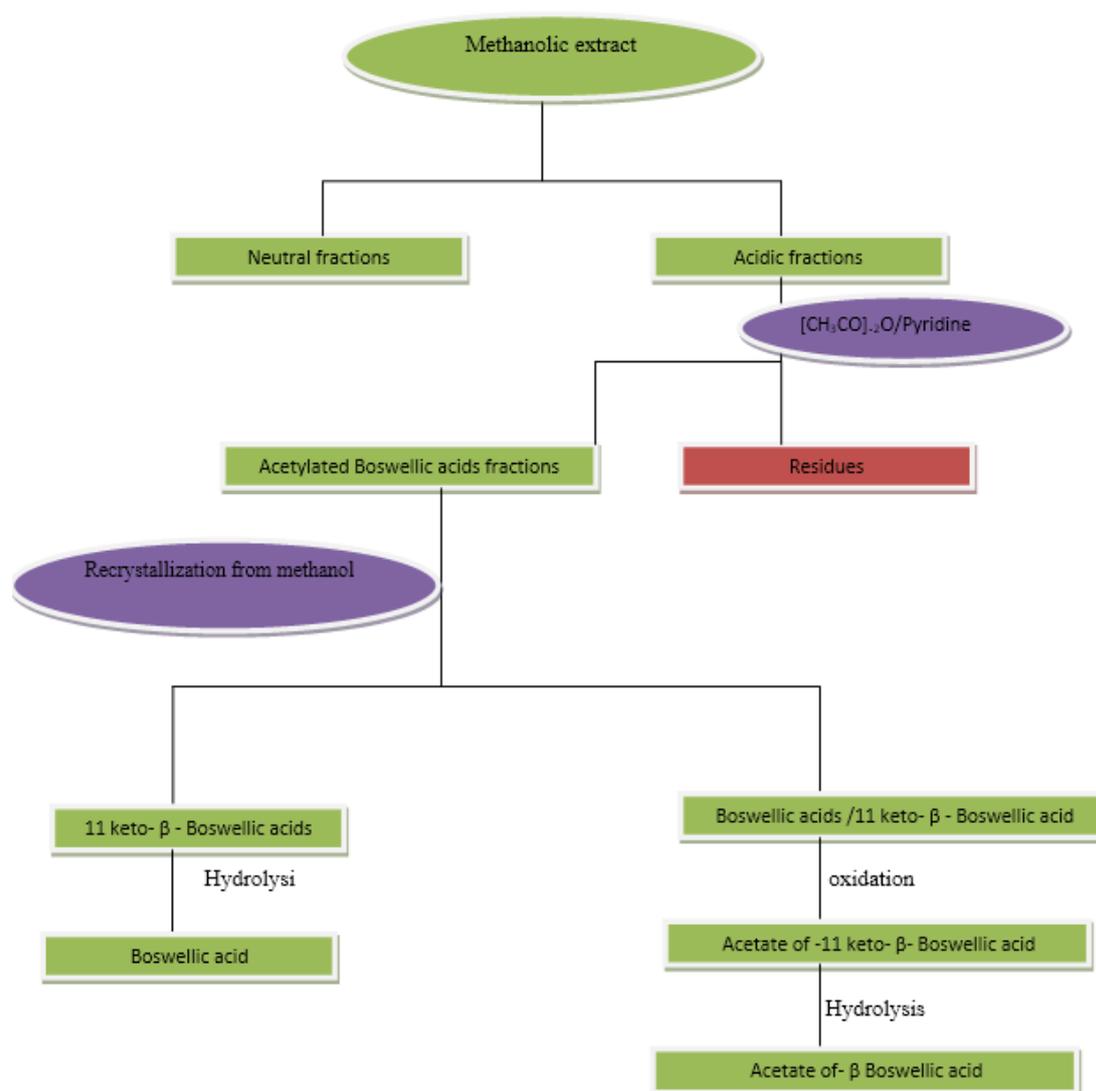


urs-12-ene-3 alpha, 24-diol

A large volume of the original research has been accumulated on the chemistry of higher terpenoids ever since the first isolation of BA was reported in 1898 and HPLC procedures have shown over fifteen specific PT compounds 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 a 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, α -amyrin and 3-hydroxy-urs-9, 11-dien-24-oic acid also has been isolated from the gum resin. Several tetracyclic terpenoic acids include 3-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. The 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) showed the presence of another isomeric diol, viz. urs-12-ene-3b,24-diol^[36-49]. The general composition of the dry *Boswellia serrata* extract of the gum resin shows approximately 50-60% various α - and β -boswellic acids, of which roughly 1-3% of the total are the most bio-active AKBA fraction^[50-51].

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, NF κ B and the signal transducer and activator of transcription-3 [STAT-3] related pathways potentiate apoptosis and inhibit angiogenesis in neoplastic cells^[52-60].



Extraction and isolation method of various Boswellic acids Anticancer activity

Cancer is clearly a disease directly associated with the genes and risk of cancer is more 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 tumour metastases. It is a known inducer of apoptosis and the ethanolic extract tested for cytotoxic, cytostatic and apoptotic activity against leukaemia and brain tumour cells has shown to induce apoptosis and to act as a potent anti-proliferative agent. BSE containing 60% BAs have reportedly inhibited tumours and inflammation in mice. BSE has also been reported for anti-carcinogenicity in mice with ehrlich ascites carcinoma and S-180 tumour by inhibiting the cell proliferation and growth inhibition due to the interference with biosynthesis of DNA, RNA and proteins. It reduced the tumour cell proliferation and induced apoptosis in several *in vitro* experiments with animals. The efficacy of BSE against peri-tumoural oedema 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 [61-68].

Xiufeng Pang and co-worker had reported that AKBA suppressed tumor growth in the human through inhibition of angiogenesis induced by VEGFR2 signalling pathways and proved their anticancer effect [69]. Byoungduck Park *et al* reported from their work that acetyl-11-keto-b-boswellic acid [AKBA] regulated the expression of COX-2, MMP-9, CXCR4 and VEGF in the tissues as anticancer biological property [70-71]. Saji Uthaman *et al* prepared boswellic acid nanoparticles formulation which is a promising anticancer agent in the treatment of prostate cancer. Boswellic acid nanoparticles cause apoptosis and DNA fragmentation [72-73]. Human pancreatic cancer cells were sensitive to Fractions III and IV [containing higher molecular weight compounds] treatment with suppressed cell viability and increased cell death. Essential oil activated the caspase-dependent apoptotic pathway, induced a rapid and transient activation of Akt and Erk1/2 and suppressed levels of cyclin D1 cdk4 expression in cultured pancreatic cancer cells. In addition, *Boswellia sacra* essential oil Fraction IV exhibited anti-proliferative and pro-apoptotic activities against pancreatic tumours [74].

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. Treatment with *Boswellia serrata* extract in colon cancer induced in rats resulted in significant reduction in K-ras gene expression level in colon tissue. This finding could be attributed to the activity of the active constituents of *Boswellia serrata* [boswellic acid and its derivatives]. This explanation stems from the ability of *Boswellia* sp. essential oil to suppress Akt activation in human breast cancer cell lines. It is well known that Akt expression is increased in human colon tumors and chemically-induced colon tumor in rats and Akt is a downstream target of the K-ras pathway. Therefore, the suppression of Akt expression might be the proposed mechanism by which *Boswellia serrata* extract could suppress K-ras gene expression level in colon cancer induced in rats [75].

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 p21 of 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 [76]. BSE shows reduction in perifocal oedema which was observed when the herbal medication was administered to seven patients for treatment of glioblastoma and five patients for leucencephalopathy. Although no tumour response was seen in the patients, leucencephalopathy patients showed a clinical benefit [77].

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 [78-79]. BSE has also been used as a coating material in the drug delivery of 5-fluorouracil for the treatment of colorectal cancer [80-81].

AKBA was also found to 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 [82]. 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 [83]. In the normal cells ABA didn't show 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 [84-85].

AKBA exerted its growth inhibitory effect by inhibiting cell proliferation, evidenced by a decrease in 3H-thymidine incorporation in cells treated with AKBA, so that boswellic acid showed potential anticancer activity in colon cancer [86-87]. BAs has gained much 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 tumour progression, reduce tumour cell invasiveness and tumour cell motility and decrease tumour angiogenesis [88-90]. Cigarette smoke is known to cause an inflammatory response in the colon that can lead to colon adeno-carcinoma. The mechanism seems to be via an up-regulation of 5-LO induced protein expression accompanied by up-regulation of metalloproteinases-2 and vascular endothelial growth factor. 5-LO inhibitors reduced the incidence of adenomas, angiogenesis and MMP-2 activity and VEGF. The results strongly suggest that cigarette smoke induced 5-LO expression leading to colon adenoma formation can be reduced by 5-LO inhibitors [91-92]. 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. The 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^[93].

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^[94-95]. A natural diol derivative of BA [also synthesized semi-synthetically] has also shown anti-cancer activity in^[96] *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^[97].

BAs found to be a potent enhancer of antigen-specific Th1 and Th2 immune responses in comparison to alum with Th2 limitation, thus indicating the potential of the biopolymeric fraction of *B. serrata* as an adjuvant for vaccine applications. Similarly, the lymphocyte transformation of BAs and other purified compounds have shown more activity than the parent extract of *B. carterii*. A purified mixture of BAs from *B. carterii* has displayed *in vitro* carrier dependent immunomodulatory activities and the methanolic extract of *B. carterii* has been shown to have significant activity against the hepatitis C virus^[98-99].

BAs and their derivatives have been found to inhibit normal and increased leucocytic elastase or plasmin activity and can be subsequently used in the treatment of diseases such as pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis [mucoviscidosis], glomerulonephritis and rheumatoid arthritis caused by the increased activity of leucocytic elastase or plasmin^[100].

Conclusion:- This review is an attempt to address the vistas of antitumor activity of boswellic acid and their derivatives. A large volume of research has been carried out for development of new and effective anticancer derivatives. This review focuses some potential results of anticancer derivatives of Boswellic acid. Information provided in this review can be helpful for medicinal chemists and other researchers for further exploration of these potential tumors suppressant terpenoid.

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