Journal of Medicinal Plants Research Vol. 4(25), pp. 2778-2785, 29 December Special Review, 2010
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875 ©2010 Academic Journals

Review

Potential role of natural molecules in health and disease: Importance of boswellic acid

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Accepted 7 December, 2010

The therapeutic use of natural products was perhaps the oldest medical practices. Interestingly, 64% of total population of the world utilizes plants as drugs mainly in the developing countries. There are more than 85,000 plant species that have been documented for medical use globally. So, plant derived natural products hold great promise for discovery and development of new pharmaceuticals in diverse human ailments. The WHO estimates that almost 75% of the world's population had therapeutic experience with herbal remedies. There are many anticancer drugs under development that target signalling as well as epigenetic pathways that can cause cancer. *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, that include immunostimulation, antimicrobial, anti-inflammatory, anti-cancer and antiviral properties. This interest is substantiated by recent clinical trials demonstrating beneficial effects of *Boswellia* sp. preparations in several disease forms such as inflammatory bowel diseases and some cancer forms.

Key words: Natural products, boswellic acid, signaling, drugs.

NATURAL PRODUCTS AND THEIR ROLE IN HEALTH

Valued for their aromatic, savory, or medicinal characteristics, herbs come from plants or various parts of plants and possess certain chemical substances that have effects on the body. 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 (Madhuri et al., 2009). Additionally, 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. For example, tetramethylpyrazine (TMP), extracted from one of the most common Chinese herbal medicines has been suggested to be neuroprotective in the CNS as well as the peripheral nerve network (Tan et al., 2009). Overall, more than 2000 plants have been listed in the traditional (Herbal/Alternative) systems of medicine and some of these were providing comprehensive relief to the people suffering from cancer (Mahmood et al., 2010). However, to ensure common health protection, the quality and safety of herbal plants, particularly those used for treatment, are to be determined. To date, toxicological data on the identification of genotoxic and tumorigenic ingredients in many raw herbs and of carcinogenic components in

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herbal plants is timely and important. Thus, the issues of quality control and safety evaluation of raw herbs and herbal dietary supplements is mandatory. Two examples of tumorigenesis and mechanism of tumor induction were reported that is aristolochic acid and ridgeline, both of which have been detected in Chinese herbal plants. Thereafter, it was proposed that an organized effort with international participation on cancer risk assessment should be actively pursued so that the safety of commercial herbal plants and herbal dietary supplements can be ensured (Chiang et al., 2009).

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. Interest in natural products research is attributed to several factors, including unmet therapeutic needs, the remarkable diversity of both chemical structures and biological activities of naturally occurring secondary metabolites, the utility of bioactive natural products as biochemical and molecular probes, the development of novel and sensitive techniques to detect biologically active natural products, improved techniques to isolate, purify, and structurally characterize these active constituents, and advances in solving the demand for supply of complex natural products. Opportunities for multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology to exploit the vast diversity of chemical structures and biological activities of natural products is of tremendous importance (Bhushan et al., 2004). Furthermore, ethno botanical knowledge involves the interaction between plants and people and foremost among these are the management of plant diversity by indigenous communities and the traditional use of medicinal plants. The distinctive geographic position and historic demological background of the area kept folk phytotherapy potential of medicinal herbs hitherto alive, which were used in various forms. Among these, some herbs were used as single remedy while others depict better curative effects in synergistic mode against various ailments. Importance of ethno botanical inventory constructed from sethnomedicinal uses and folklore phytonims of flora in perspectives of initiative for future phytochemical and pharmacological research on these taxa to develop and discovery of new drugs is mandatory (Toksikol et al., 2009). Biological contaminants (microbes and other organisms) and chemical contaminants (mycotoxins, toxic elements such as heavy metals, and pesticide residues) are the major common contaminants of medicinal herbs and herbal products. To prevent and screen for contamination and ensure safety and conformity to quality standards, medicinal herbs and herbal products should be included in appropriate regulatory framework (Toksikol et al., 2009). It has been observed that several Chinese raw herbs and some commercially available manufactured herbal products contain aristolochic acids commonly used for weight control, contained toxic Aristolochia species, which had been associated with severe nephropathy and urothelial cancer in humans and animals (Toksikol et al., 2009).

STATUS OF HERBAL MEDICINE IN DIFFERENT COUNTRIES

Traditional medicine is an important part of human health care in many developing countries and also in developed countries, increasing their commercial value and the demand for herbal medicines has grown dramatically in recent years with the world market for such medicines has reached US $60 billion (Toksikol et al., 2009) with annual growth rates of between 5 and 15%. Thus, the patent applications in the field of natural products, traditional herbal medicine and herbal medicinal products and related plant products are important targets of patent claims. Advances in molecular biology have led to discovery of potential cancer targets and a rich pipeline of anti cancer drugs (Kartal et al., 2007). A recent survey shows that more than 60% of cancer patients use vitamins or herbs as therapy (Pors et al., 2009). Of the 119 plant-derived pharmaceutical drugs, as many as 74% are used in the same ways the plants were used by natives. It is estimated that 27 million South Africans use herbal medicines from more than 1020 plant species. It is because of this fact that plants gathered from locations such as the rain forests are being studied for their possible medicinal values by various pharmaceutical companies.

Conditions such as high blood pressure, asthma, pain, and heart disease are often treated today with commercial medicines containing plant-based substances. For example, Ephedrine is derived from a herb called ephedra and is used in commercial medicines to relieve respiratory and asthma symptoms (Meadows et al., 2003). The native herb ephedra has been used for over two thousand years in Traditional Chinese Medicine to treat the similar symptoms (Borchers et al., 2008). Herbs have been considered natural and valuable sources for anticancer drug discovery. Herbal medicine has been prescribed in many countries over centuries for treating various diseases including infectious and malignant diseases. Complementary medicine is a formal method of health care in most countries of the ancient world. It is expected to become more widely integrated into the modern medical system, including the medical curriculum. Despite the perception of modern medicine as more efficacious, traditional medicine continues to be practiced. More than 70% of the developing world's population still depends primarily on the complementary

and alternative systems of medicine (CAM). In rural areas, cultural beliefs and practices often lead to self-care, home remedies or consultation with traditional healers. Herbal medicine can be broadly classified into four basic systems as follows: Traditional Chinese Herbalism, Ayurvedic Herbalism, Western Herbalism, which originally came from Greece and Rome to Europe and then spread to North and South America and Traditional Arabic and Islamic Medicine (TAIM) (Azaizeh et al., 2008). There is no doubt that today the concept of arabic traditional herbal medicine is a part of modern life in the Middle East and it is acquiring worldwide respect, with growing interest among traditional herbalists and the scientific community. TAIM therapies have shown remarkable success in healing acute as well as chronic diseases and have been utilized by people in most countries of the mediterranean who have faith in spiritual healers. TAIM is the first choice for many people in dealing with ailments such as infertility, epilepsy, psychosomatic troubles and depression. However, issues of efficacy and safety of complementary medicine have become increasingly important and supervision of the techniques and procedures used is required for commercial as well as traditional uses. More research is therefore needed to understand it and ensure its safe usage. Thus, the present status of traditional Arab medicine includes the efficacy and toxicity of specific medicinal preparations, with an emphasis on the modern *in vitro* and *in vivo* techniques.

Moreover, the key bioactive compounds and the role of medicinal plants in Ayurvedic systems of medicine in India has been an increase in demand for the phytopharmaceutical products of Ayurveda in western countries, because of the fact that the allopathic drugs have more side effects. Different types of plant parts are used for the Ayurvedic formulation; overall out line of those herbal scenario and its future prospects for the scientific evaluation of medicinal plants is being used by traditional healers. As much as possible importance is also given for the taxonomic literature (Samy et al., 2008). Although, many drugs have been developed by pharmaceutical companies, there are many diseases which cannot be cured with these drugs. In order to overcome this problem, the combination of Western and Eastern medicine has been proposed. In the present scenario, the possible applications of Ayurveda in drug development takes into account the herbs used in Ayurveda contain many unknown active components, and new therapeutic approaches provided by the Ayurveda. Harmonization of the market for herbal medicines is a fundamental requirement for European industries and health professionals and it will be also useful for consumers (Juan et al., 2008). Herbal medicines are generally sold as food supplements, but a common regulatory status in the various European countries does not exist. As a consequence, information on clinical indications for use, efficacy and safety were influenced by different opinions, according to the clinical or traditional experience of various folk medicines available in each European country. However, with the introduction of the European herbal legislation for the harmonization of the market of herbal medicines, important regulations will contribute to safer use of herbal substances if adopted by the whole of the European community. In the European Union (EU) herbal medicinal products have become increasingly important (Vlietinck et al., 2009). This is, underlined by the recent introduction of a simplified procedure in the Member States of the EU allowing the registration of herbal medicinal products which fulfills the criteria of a traditional herbal medicinal product, that is sufficient evidence of its medicinal use throughout a period of at least 30 years for products in the EU and at least 15 years within the EU and 15 years elsewhere for products outside the EU. In addition, the standards put forward in the monographs of European pharmacopeias must allow us not only to define the quality of these products, but also to eliminate dangerous, substandard, adulterated and contaminated herbal medicinal products. Thus, the usefulness of the monographs to implement the criteria on quality and specifications put forward for these products in the different guidelines of the European Medicines Agency (EMEA). With the wide usage of traditional Chinese medicine (TCM) and the diversity of its dosage-forms, the reports about adverse reaction (ADR) caused by TCM have gradually increased. In order to circumvent this problem, the key point of TCM ADR monitoring is made clear by analyzing the current situation and the problems presented in TCM ADR monitoring in China. TCM injection has become one of the hotspots in the new TCM research and development. It is very urgent to monitor the post-marketing safety of TCM injections thus elucidating the pharmacovigilance's necessity in the post-marketing safety monitoring. Also, it introduced the rapid signal detection method of spontaneous reporting system database by data mining technology. In the western world, medicinal herbs are becoming increasingly popular and important in the public and scientific communities. In contrast to their regulated status in China and other countries, the herbal medicine is regarded as dietary supplements in the US. Accordingly, research must continue worldwide to identify and improve the efficacy of the active principals of herbs both singly and in combination from active ingredients, active fractions, and active herbal formulations. While western medicine currently employs pure, single compounds, either natural or synthetic, CM had long used multiple combinations of compounds in the form of processed natural products, primarily medicinal herbs, to treat and relieve the symptoms of many different human diseases. However, research using modern analytical and chemical techniques is needed to ensure efficacy and safety, to provide qualitative and quantitative analyses for dietary supplements and to develop new, effective and safe

world-class drugs from traditional herbs. Bioactivity-directed fractionation and isolation to identify active natural compounds from single herbs or formulations should be the primary focus. These lead structures can be chemically modified and improved through knowledge of structure--activity relationship, mechanism of action, drug metabolism, molecular modeling and combinatorial chemistry studies. Finally, efficacy and toxicity determination as well as clinical trials can contribute to the generation of new drugs from traditional system of medicine in 21st century. Fortunately, that significant advances have been made in herbal medicine during the past 20 to 25 years since the official policy of China was established that encouraged a blend of Western and Chinese traditional medicine. Scientific studies in China and the United States, as well as other countries, are being directed at collecting and cataloguing a great variety of the herbs listed in the folk pharmacopeias (Lambert et al., 2006). One of the most significant single agents identified recently is isodamine, an alkaloid isolated from the solancea plant. Its formula, pharmacological action, and clinical effects are very similar to those of atropine. On the basis of experimental and clinical studies, Chinese scientists report that anisodamine is a better spasmolytic agent than atropine by virtue of its milder activity on the salivary glands, the pupils and the central nervous system. Several herbal drugs have recently been developed and subjected to successful clinical trials. One of the reasons given for past failures of western investigators to identify the medicinal properties of Chinese and other traditional medications is that the research usually began with the isolation of individual chemical compounds. Recent studies new studies in the U.S. are focusing on single ingredients, entire herbal concoctions, and the use of herbal medicines in conjunction with Western drug products. These studies, taken together up to now, has led to interesting knowledge on the mode, mechanism, specificity of binding and correlation between structural aspects and energetics enabling a complete set of guidelines for design of new drugs. In contemporary research, several derivatives of these natural alkaloids are being prepared and investigated in several laboratories for ultimate discovery of new compounds that can be used as effective therapeutic agents. Herbal medicine, acupuncture and moxibustion, and massage are the three major constituent parts of TCM (Ben et al., 2010).

Chinese herbal prescriptions enhance the clinical curative effect through the use of multi-composition formulas, and the combined use of several components from herbal extracts with an enhanced mode of formulae organization and compatibility. Overall, the study of combination components must establish the methodology of combining standard components, confirming the main components through trial design, removing the poisonous components and ascertaining dosage and ratios of all the components used. The mode of combination component has three forms: the one from the combined use of prepared medicinal herbs, the one from directly combined use of components and the one from the standard ingredient composition of single herb (Zhong et al., 2006). These three forms strictly follow the mechanisms of multi-component and multi-target medical intervention. The significance of using combined effective components is to ensure the accuracy and safety of clinical dosage, enhance the clinical effectiveness, reduce the use of medicinal herbs, decrease the side-effects, and to promote modern medicines that have clear ingredients and mechanisms. This is gaining importance, since modern medicine is faced with the problem of complicated disease spectra which suggest that the single-ingredient chemical drug may not be able to achieve satisfactory curative effect.

The search for novel anticancer drugs is paradoxically producing excellent scientific information on many previously unresearched herbal remedies. The goals for the success of chemoprevention include devising a tumor-specific risk model for identifying high-risk cohorts, increasing preclinical drug-testing models (that is gene targeting/knockout models), developing translational/mechanistic studies to develop novel chemo preventative agents, identifying surrogate endpoints using molecular alterations, and locating promising new targets of drug activity and further study of existing candidate surrogate-endpoint markers. In the present perspective, there is a need to develop new medicine 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.

BOSWELLIC ACID IN HEALTH AND DISEASE

The search for new anticancer drugs from plants would be a fruitful frontier in cancer treatment and chemoprevention (Table 1). The pentacyclic tripenes are found to be widely distributed among plants (Dolle et al., 2006). Pentacyclic triterpenes are produced by arrangement of squalene epoxide. At least 4000 known triterpenes has been reported. Many triterpenes occurs freely but others occur as glycosides (saponins) or in special combined forms. Importantly, pentacyclic triterpenes has a wide spectrum of biological activities and some of them may be useful in medicine. Betulinic acid, a very promising compound acts by inducing apoptosis in cancer cells. Due to the complex biosynthesis including cyclization of squalene as a key

Table 1. Summarized role of boswellic acids in health and disease.

Disease	Role
Cancer	(i) Anti-carcinogenicity in mice with ehrlic ascites carcinoma and sarcaoma-180, found inhibition of tumor growth. (ii) Anti-proliferative and apoptotic effect on colon cancer. Induced anti-edema effect in glioblastoma patients.
Arthritis	(i) Decreases infiltration of leukocytes into knee joint and pleural cavity and inhibits the migration of polymorph nuclear leukocytes. (ii) Decreases severity of pain and disability in osteoarthritic patients.
Inflammation	(i) Decreases galactosamine/endotoxin induced hepatitis in mice. (ii) Decreases inflammatory features in indomethacin-induced ileitis in rats. (iii) Decreases experimental murine colitis. (iv) Inhibits the synthesis of 5-LOX products. (v) Inhibits topoisomerase, elastase and C-3 convertase enzymes.
Hypolipidemia	(i) Decreases cholesterol and increases HDL in rats. (ii) Induced nitric oxide production in rat macrophages.
Asthma	Increases stimulation of mitogen activated protein kinase MAPK and mobilization of intracellular ca^{2+}
Immunomodulatory	Anti-anaphylactic and mast cell degranulation
Autoimmune encephalitis	(i) Inhibited ionophore stimulated release of leukotrienes from PMNL's. (ii) Decreases symptoms of AE.
Crohn's disease	Decreases activity index
Analgesic	Decreases motor activity and ptosis in rats

step, only higher plants are capable to carry out this catalysis, contain pentacyclic triterpenes (Venalainen et al., 2003). Until today, a plethora of pentacyclic tripenes with diverse bioactive properties has been identified and characterized. Due to its apparent specificity for melanoma cells, betulinic acid seems to be a more promising anti-cancer substance than drugs like taxol. The therapeutic potential of pentacyclic triterpenes–lupeol, betuline, betulinic acid has been reported but boswellic acid being the most potent source for bioactive pentacyclic triterpenes represents one of the most promising anticancer agent (Poeckel et al., 2006).

Boswellic acids (BAs), belonging to ursane group, 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 or dhup (Havel et al., 2002). Gum resin of *Boswellia* species known as Indian frankincense has been used as an anti-inflammatory agent in Traditional Ayurvedic Medicine in India. Also, ancient Ayurvedic texts described its therapeutic use. Clinical trails performed by CSIR laboratories in India has shown fair to excellent results in 88% of the patients, with no adverse side effect (Kuo et al., 2009). A randomized, double blind, controlled clinical trials on patients with osteo-arthritis of knee exhibited statistically significant improvement in the pain, decreased swelling and increased knee flexion (Bhushan et al., 2000). The therapeutic effects shown by *B. serrata* extract are comparable to those exhibited by sulfasalazine and mesalazine in patients with ulcerative colitis (Lohmander et al., 1996). Here, the source of anti-inflammatory actions has been attributed to boswellic acids (Kiela et al., 2004) a group of triterpene acids isolated from the *Boswellia* resin (Jurjus et al., 2004). These compounds exert anti-inflammatory activity by inhibiting 5-lipoxygenase (5-LOX). The boswellic acids also gained prominence recently for their antiproliferative actions. Boswellic acids inhibited several leukemia cell lines *in vitro* and inhibited melanoma growth and induced apoptosis (Safayhi et al., 1992). The acetyl boswellic acids are found to be unique class of dual inhibitors of human topoisomerases I and II (Zhao et al., 2003). Immunomodulatory activity of boswellic acids has been reported by (Syrovets et al., 2000). A detailed study on the structural requirements for boswellic acids indicated

that of all the six acids, 3-O-acetyl-11-keto-β-boswellic acid (AKBA) shows most pronounced inhibitory activity against 5-LOX (Makare et al., 2000). AKBA acts by unique mechanism, in which it binds to 5-LOX in a calcium-dependent and reversible manner and acts as a non-redox-type, non-competitive inhibitor (Gokaraju et al., 2004). In addition, AKBA or a plant extract, or composition containing acids, is reported to be effective for topical application, as an agent to soften lines and/or relax the skin. AKBA has thus become the subject of intensive research for its potential for the treatment of chronic inflammatory disorders.

The anticancer related activity of compounds of *B. serrata* and its isolates has drawn attention of scientists working in this area and several patents and publications have appeared in last one and a half decade. Historically, the gum exudate or the resin obtained from the bark of the tree has been widely used by the practitioners of the Indian systems of medicine for various medical conditions such as arthritis, asthma, ulcers, and skin diseases; currently it is extensively used in various formulations for the treatment of inflammation related disorders (Gokaraju et al., 2004). *B. serrata*, a deciduous middle-sized tree widely distributed in the Indian subcontinent and Africa is documented to be of high medicinal as well as economic importance (Rao et al., 2003). *Boswellia* subspecies are trees in Asia and Africa and medicinal dry extracts of different *Boswellia* trees are traded as phytopharmaceutical for oral administration. Generally, *Boswellia* extracts are claimed to be inhibitors of inflammation processes, with efficacy against perifocal oedema in brain tumour patients and antitumor activity. With regard to occurrence of *B. serrata* in India, it is usually present occurs in the dry hilly forests of Rajasthan, Madhya Pradesh, Gujarat, Bihar etc. *B. serrata* gum resin is a complex mixture of terpenoids (pentacyclic as well as tetra cyclic) and sugars comprising more than 200 different substances (Ray et al., 1948) including polysaccharides, essential oils, proteins and inorganic compounds. Generally, *B. serrata* gum resin contains 8 to 12% essential oils, 45 to 60% polysaccharides and 25 to 35% higher terpenoids (Langenheim et al., 2009). *B. 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 shows the presence of four pentacyclic triterpene acid that is β- boswellic acid, 11-keto- β-boswellic acid, acetyl-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Tetra cyclic triter pine acids obtained from acidic fraction of n-hexane and ethyl acetate as eluent reveals different structures. The other species of genus *Boswellia* include *Boswellia ovalifoliolata* Bal. and Henry (India), *Boswellia carterii* Birdw. (Somalia), *Boswellia sacra* Fluckiger (Oman and Yemen), *Boswellia pirottae* Chiov. (Ethopia), *Boswellia dalzielii* Hutch. (West Africa), *Boswellia frereana* Birdw. (Somalia), *Boswellia neglecta* S. Moore (Kenya), *Boswellia papyrifera* (Del.) Hochst. (Ethopia), *Boswellia rivae* Engl. (Ethopia), *Boswellia hildebrandtii* Engl. (Somalia), *Boswellia ogadensis* Vollesen (Ethopia), *Boswellia popoviana* Hepper (Yemen), *Boswellia nana* Hepper (Yemen), *Boswellia bullata* Thul. and Gifri (Yemen), *Boswellia dioscorides* Thul. and Gifri (Yemen), *Boswellia elongata* Balf. f. (Yemen), *Boswellia ameero* Balf. f. (Yemen) (Gautam et al., 2010) and *Boswellia socotrana* Balf. f. (Yemen). The aroma from these resins is valued for its presumed healing properties and superior qualities for religious rituals since the time of the ancient Egyptians, and has been used in incense, fumigants, and as a fixative in perfumes (Dzubak et al., 2006). Moreover, *B. serrata* is the most investigated of all the species, with photochemical studies as well as bioactivity-related investigations. The presence of BAs in almost all the species of *Boswellia* feature is a characteristic feature of this genus. The triterpenoids 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 defence mechanisms, as many of them have been reported to possess diverse biological activities (Frank et al., 2009) that include immunostimulation Chen (2009), antimicrobial (Farid et al., 2003), anti-inflammatory Dzubak anti-cancer (Atal et al., 1985) and antiviral properties (Duan et al., 2002). The structures and bioactivities of BAs are well documented and nutraceutical preparations in diverse forms comprising of *Boswellia serrata* extract (BSE) in combination with other plant extracts or molecules have been in use for many years. Surprisingly, not much has been reported regarding chemical modifications or preparation of structural analogues of the key constituents. Salai guggal, also known as Olibanum/ frankincense, is an oleo-gum-resin from *B. 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 reveals 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. 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 shown to possess hepatoprotective and immunomodulatory activities 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 caused sedation, reduction in motor activity and ptosis in rats (Dzubak et al., 2006). The alcoholic extract of salai guggal inhibited inflammation induced rise

of serum transaminase and leukocyte elastase level. As mentioned earlier, boswellic acids are novel, specific, non-redox inhibitor of 5-lipoxygenase (5-LOX), which is a significant enzyme involved in arachidonic acid metabolism where its hydrophilic group at C-4 is found to be essential for 5-LOX inhibition. This also reduces the activity of elastase enzyme, thus helping in the management of asthma and allergic manifestations (Canuso et al., 1971). Frankincense oil, an extract prepared by steam distillation from frankincense gum resin, is one of the most commonly used oils in aroma therapy practices (Jose et al., 2000). There has been considerable work done on the composition of frankincense oil from different according to the species and commercial brands; and the constituents of frankincense oil differ climate, harvest conditions and geographical sources of frankincense resins. Due to the contribution of boswellic acids, it is possible that frankincense oil also holds anti-cancer and anti-neoplastic properties. Based on gene expression analysis, frankincense oil activates several anti-proliferative and pro-apoptotic pathways that might be responsible for frankincense oil-induced cell death in J82 bladder cancer cells.

BAs have attracted considerable attention as anticancer agents in the recent past (Singh et al., 2008) especially from the time when 5-LOX inhibitors are also recognized as cancer chemo-preventive agents (Barton et al., 2009; Neuzil et al., 2007). BSE is reported to modulate the breast cancer and the brain tumour metastases (Doucas et al., 2006). It is a known inducer of apoptosis (Tsangaris et al., 2000) and the ethanolic extract tested for cytotoxic, cytostatic and apoptotic activity against leukemia and brain tumour cells has shown to induce apoptosis and to act as a potent anti-proliferative agent (Kuo et al., 2009). BSE containing 60% BAs have reportedly inhibited tumors and inflammation in mice (Tran, 2005). BSE has also been reported for anti-carcinogenicity in mice with Ehrlich Ascites Carcinoma (EAC) and S-180 tumour by inhibiting the cell proliferation and growth inhibition due to the interference with biosynthesis of DNA, RNA and proteins (Scheck et al., 2006). Moreover, BSE has also been used as a coating material in the drug delivery of 5-fluorouracil for the treatment of colorectal cancer (Mercola et al., 2010). Both KBA and AKBA have also shows apoptotic and anti-proliferative effects on colon cancer (HT-29) cells (Salimath et al., 2004). Conner et al (2009) reported the cytotoxicity of BAs against human malignant glioma. 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 (Frank et al., 2009). Pgp has gained importance as the transporter, mainly for drug disposition and the resulting clinical response; BAs as well as BSE inhibits the transport activity of Pgp in the micro-molecular range. ABA gave excellent DNA fragmentation in melanoma and fibro sarcoma. In 2002, the EMEA designated *Boswellia* an orphan drug status for the treatment of peritumoral oedema. Importantly, pharmacokinetic studies yielded low plasma concentrations of the active ingredients 11-keto-β-boswellic acid (KBA) and 3-acetyl-11-keto-β-boswellic acid (AKBA). Neither KBA nor AKBA could be identified as substrates of P-glycoprotein. However, both KBA and AKBA modulated the activity of Organic Anion Transfer (OAT) P1B3 and MRP2, indicating that therapeutic relevant interactions with other anionic drugs may be expected. Taken together, 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, (Conner et al., 2009) and AKBA has been described as a catalytic inhibitor of topoisomerase I and IIa (Weber et al., 2006). Both ABA and AKBA inhibit NF-kB signalling, (Conner et al., 2009) and is a probable mechanism in the mechanism of action against cancer cells (Syrovets et al., 2000).

The constitutive activation of NF-kB has been shown to be responsible for both the chemo-resistance and a highly malignant phenotype of prostate cancer (Landvik et al., 2000). These compounds reportedly inhibits constitutively activated NF-kB signalling at a molecular level by intercepting the IkB kinase (IKK) activity since they have specificity for IKK inhibition. The topical application of water-soluble AKBA–cyclodextrin complex on PC-3 tumors xenografted onto chick chorioallantoic membranes induced concentration-dependent inhibition of proliferation as well as apoptosis (Castelli et al., 2000). Similarly, in nude mice carrying PC-3 tumors, the systemic application of AKBA– g-cyclodextrin inhibited the tumour growth and triggered apoptosis with no detectable systemic toxicity (Kapil, 2009). AKBA also causes a decrease of androgen receptor expression, crucial for the development and progression of the prostate cancer, at mRNA and protein levels (Jing et al., 2004). The apoptotic effects and the mechanisms of action of AKBA were also studied in LNCaP and PC-3 human prostate cancer cells. Results suggested that AKBA induces apoptosis in prostate cancer cells through DR5-mediated pathway. Importantly, 4-Amino analogues prepared from beta-boswellic acid and 11-keto-beta-boswellic acid, where in the carboxyl group in ursane nucleus is replaced by an amino function showed improved cytotoxicity than the parent molecules. In addition semi-synthetic acyl analogues of BAs have also displayed significant cytotoxicity against various human cancer cell lines *in vitro* and markedly induced apoptosis in HL-60 cells. It is because of this reason that *Boswellia* sp. gum extracts and their triterpenic constituents, especially boswellic acids, have drawn the attention of

medicinal chemists, biochemists and pharmacologists since the first report of their anti-inflammatory activity. Therefore, more effort in building diverse libraries based on its chemical scaffold and the generation of biological data, including target-based studies, is necessary.

It is apparent from the literature that all the patents and publications have reported the use of either the compounds comprising boswellic acids or individual natural boswellic acids for the cytotoxic and anticancer related activities. Not much has been reported on the bioactivity of semi-synthetic analogues of boswellic acids for modulating the cancer related disorders. Therefore, the use of the semi-synthetic analogues of boswellic acids for the induction of apoptosis and there of cytotoxicity will be an important study to understand the therapeutic potential of modified boswellic acid derivatives in cancer treatment.

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