A Systematic Review on Frankincense (Boswellia species)

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Abstract- **Frankincense (also termed as Olibanum) obtained from Boswellia trees, belonging to family Burseraceae, is an aromatic oleo gum resin traditionally used as a fumigant, a medicine, in aromatherapy and various cosmetic formulations in several countries. Its appearance is colorless-yellow liquid having a balsamic, citrusy and spicy odor. The commercial oil referred as frankincense is produced from this plant which has a spicy, woody and haunting smell. These oleo-gum-resins have been utilized as a significant constituent in Chinese and Ayurvedic medicine for treating several health-related problems. The main components of Frankincense oil are α-pinene, α-thujene, β-pinene. Essential oils and chemical extracts prepared from oleo-gum-resin of Boswellia species, both possess anti-neoplastic activity, and also have been determined as potential anti-cancer expedients. Frankincense oil shows different pharmacological properties like Anti-bacterial, Anti-inflammatory, Anti-microbial, Hepatoprotective and Therapeutic properties. This review is aimed to deliver an overview of current knowledge of volatile constituents, boswellic acids, and extracts of several Boswellia species.**

Index Terms- Frankincense, Boswellic Acids, Boswellia Spp., Olibanum Oil, Gum resin.

I. INTRODUCTION

The old biblical story of the "Three Wise Men" in which God delivered Gold, Frankincense, and Myrrh as gifts for the baby Jesus narrates the importance and application of Frankincense [1]. In the previous testament and ancient texts, also frequently referred have thereafter led to the expansive use of Frankincense in many religious rituals and currently, the oils are being used as a significant constituent in incense formulations, which are then burned in Roman Catholic, Jewish and Greek Orthodox ceremonies. Being an essential ingredient in the process of embalming, ancient Egyptians used *Boswellia* gum resin as a fumigant in the embalming process. The Frankincense obtained from various species of *Boswellia* is being used from decades in medicine worldwide [2]. *Boswellia* genus consists of almost 25 distinct species; some of the crucial species include *Boswellia sacra* or *Boswellia carterii*, *Boswellia serrata*, *Boswellia papyrifera*, and *Boswellia frereana* [3], [4].

Geographically, this tree is found in gulf countries: East Africa, South Asia, and in India it abundantly resides in dry, hilly areas of Gujarat, Rajasthan, Madhya Pradesh, Bihar and Maharashtra [5]. The Frankincense oil is commonly known as olibanum or al-Luban which means white paste [6]. Ayurveda literature documented Luban to treat some inflammatory diseases of skin, gums, and eye, and also asthma and bronchitis [7]. Traditionally, sesame oil or water soaked olibanum gum was used as a topical analgesic. On the international market, Frankincense oils can be obtained from several sources and are distributed by multiple companies. Oil extracted from several *Boswellia* species are sold by the name "Frankincense oil".

The *Boswellia* trees are flowering plants which have a papery brown, pale bark with a thick brownish inner gummy layer [8]. After making a notch into the bark of old aged trees, resinous exudates are collected. After some time, this gum resin hardens into an orange-brown gum, now termed as Salai guggal which is a mixture of essential oil (5-15) %, gum (6-30) % (mixture of polysaccharides), and 60–85% resins (mixture of terpenes) [9]. The Frankincense oil having a spicy, woody and haunting smell is usually obtained after steam distillation of air-dried olibanum gum resin. Although soxhlet extraction, solvent extraction is also routinely used for oil extraction, but these techniques are not cost effective so in these days supercritical fluid extraction (SFE), an environmentally friendly procedure which is a substitute for old methods concerning less extraction time, higher quality of products and extraction rate is used. In SFE, one of the most commonly used supercritical solvent is carbon dioxide, which being non-corrosive, non-toxic, non-inflammable and inert prevents degradation of labile thermal components if used at suitable temperature and pressure thus adding another feather to the oil quality [10].

The chemical composition of essential oil is dependent on the climatic, harvesting and geographical conditions [11]. Chemically monoterpenes, diterpenes, sesquiterpenes, phenolic compound and a diterpene alcohol serratol constitute the significant part of Frankincense oil. The compound analysis of oil showed that more than three hundred volatiles had been identified till date, out of which some common compounds are α-pinene, 1-octanol, linalool, limonene, octylacetate, α-thujene, and (E)-β-ocimene [12]. Also, polysaccharides mixture of gum contains some digestive and oxidizing enzymes. The two most stiff anti-inflammatory boswellic acids of Boswellia are acetyl-11-keto-beta-boswellic acid (AKBA) and 11-keto-beta-boswellic acid (KBA) [13].

II. CLASSIFICATION OF MAJOR VARIETIES OF BOSWELLIA SPECIES

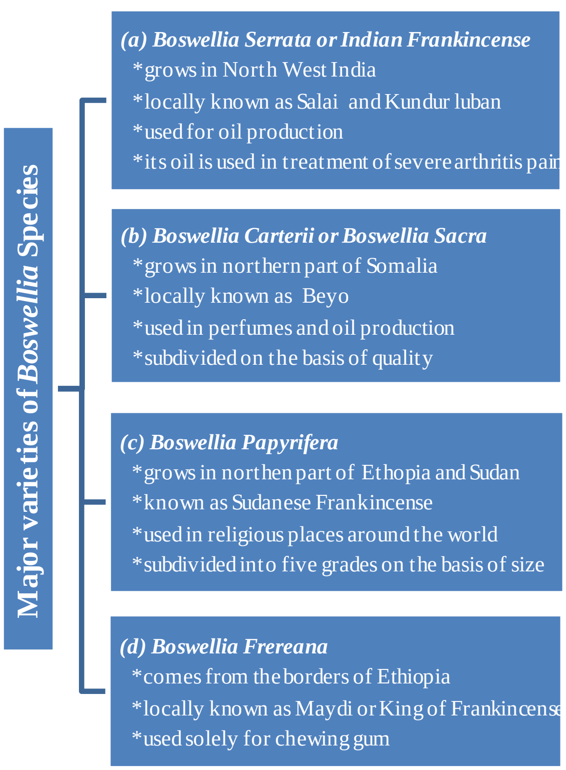

Fig. 1 Flowchart of significant varieties of *Boswellia* species

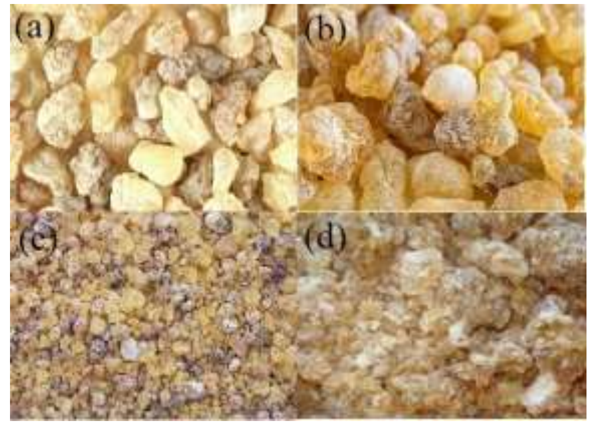

Fig. 2 Major varieties of Boswellia species: (a) *Boswellia Serrata*, (b) *Boswellia Carterii*, (c) *Boswellia Papyrifera*, (d) *Boswellia Frereana*

III. PHYTOCHEMISTRY OF *BOSWELLIA* SPECIES

The composition of *Boswellia spp*. gum resin differs from species to species, thus depending on resin quality and geographical conditions. *Boswellia spp*. is mainly considered for its pharmacological effects consisting of about 200 phytochemicals including essential oil and mucus [14]. The Boswellic acids define the chemical feature of all *Boswellia* species. The Boswellic Acids are present in Boswellia in different quantities, in which major ones are: α-Boswellic Acid, β-Boswellic Acid, Acetylated α-Boswellic Acid, Acetylated β-Boswellic Acid (ABA), 11-keto-β-Boswellic acid (KBA) and 3-O-acetyl-11-keto-β-Boswellic acid (AKBA) [15].

Amount of Boswellic acid in monetarily available *Boswellia* extracts differ within the ranges 37.5 to 65%. AKBA and KBA, the two Boswellic acids are the most active and promising anti-inflammatory agents in *Boswellia*. Frankincense oil mainly constitutes of monoterpenoids (in which α-Pinene (73.3%) is the primary component) and few diterpenes [16].

IV. INDIAN FRANKINCENSE SHOWING DIFFERENT PHARMACOLOGICAL ACTIVITIES

A. Anti-inflammatory activity

Studies found the potential of *Boswellia serrata* to exhibit anti-inflammatory activity [17]. Past review articles underlined biological actions of *Boswellia serrata* at a cellular level [18]. Therapeutically properties of Boswellic acids were determined for clinical trials on animals and their anti-inflammatory properties define obstruction of prostaglandin synthesis as a minor role [19]. Clinical trials of Indian Frankincense showed successful anti-inflammatory results in approx 88% of patients without any side effects [20]. Boswellic acids while oral management changes the cataphoretic pattern of tissue layer and reduce the counting of leukocytes; also it treats chronic polyarthritis [21]. *Boswellia serrata* resin extract inhibits the generation of 5-LO products in a dose-dependent manner in Poly-Morphonuclear Neutrophil Leukocytes (PMNL). As per reports, Boswellic acids produce anti-inflammatory activities in mouse macrophages and human peripheral blood mononuclear cells (PBMCs) [22]. In 2011, Khosravi et al. reported the ability of *Boswellia* extract to reduce inflammation of periodontium allied among plaque-induced gingivitis because of their anti-inflammatory actions produced by multiple mechanisms [23].

Researchers carried out molecular linkup simulation studies by radiometric binding assays by enrolling dexamethasone (DEX) as a functional control which found that Boswellic acids attach strongly to GR [24]. Also, in a random clinical trial, Notarnicola et al. assessed the efficacy of the combination of BA-Methylsulfonylmethane (MSM) to treat knee arthritis, rather than Glucosamine (GS) [25].

B. Anti-microbial activity

Anti-microbial activity of Boswellic acids opposite to microbial pathogens was defined by a study conducted on the oral cavity, which hindered effect of AKBA against tested pathogens (MIC of 2-4 mg/ml) and also, AKBA inhibited biofilms formed by S.mutans and Actinomyces viscous reducing assigned biofilms. This study depicted concentration dependent bactericidal activity thus preventing exposure of S.mutans. Therefore, AKBA is of great potential for mouthwash to prevent and treat oral diseases and as an anti-microbial agent against oral pathogens.

In another study, AKBA was proved the most promising anti-microbial agent among other Boswellic acids, when the anti-microbial activity of Boswellic acids against gram-positive and gram-negative pathogens group was tested. But, the anti-microbial spectrum was restricted to gram-positive only [26].

C. Anti-asthmatic activity

Traditionally, *Boswellia* has been referred as a universal remedy for the respiratory system to treat a catarrh, cough, asthma and bronchitis. Boswellic acids being higher terpenoids cause inhibition of leukotriene biosynthesis, which prevents inflammation in many chronic inflammatory diseases. Also, due to the simulation of MAPK, the transition of intracellular Ca^{2+} and inhibition of leukotriene biosynthesis, patients with the history of asthma were depicted with the anti-asthmatic activity of alcohol extract of *Boswellia serrata* in several studies [27]. Boswellic acids diminished the response of BL-induced injury in rats and resulted in the demolition of infiltrating cells, lung architecture and lung fibrosis [28].

In a vermin model of asthma, Liu et al. Found Boswellic acid treated animals could extinguish airway hyperresponsiveness (AHR), Th2 cytokines secretion and airway inflammation. Boswellic acid's healing effect in allergies makes it a promising medication for treating asthma, mechanism of which involves inhibition of signal transducer, the activator of transcription-6(STAT6) and GATA-3 expression [29].

D. Clastogenic activity

Traditionally, utilization of *Boswellia* species is presumed to improve performance, brain memory and cognitive skills in Chinese and Indian medicinal system also, its intake is advised to pregnant women for their progeny good health [30]. The clastogenic effect is produced by an aqueous extract of Spirulina alga, *Boswellia serrata* and Withania somnifera which is useful in stress consolation, mind intensification, and augmentation. A *Boswellia papyrifera* acid intensifies dimensional memory confinement in male rats after intrinsic management.

Due to the contact of Boswellic Acids and neurotransmitter signaling cascades in the brain, these results were found to be dose dependent [31]. Also, it was found that treatment by the combination of extracts of Melissa officinalis and *Boswellia serrata* could forbid inattention in rats treated with Pentothal and multiple mechanisms could be the reason for their defensive actions on damaged brain cells.

E. Hypolipidemic activity

Studies conducted in past decades reported Boswellia as an active hypolipidemic agent. As a hypolipidemic agent, *Boswellia serrata* extract reduces the level of cholesterol in experimental animals. Also, a study proposed anti-hyperlipidemic activity of *Boswellia* which balances triglycerides and cholesterol levels in animals further, fed to high cholesterol and saturated fat containing diet [32]. AKBA has anti-adiposity property by which it accelerates lipolysis in a mature human cell in adipose tissue and is also known to inhibit NF-kB activity in coronary artery disease called atherosclerosis. Apart from this, the physical process came with downregulation of PPAR-g2 expression and phenotypic markers [33].

F. Anti-cancer or anti-tumor activity

Frankincense is the highest source of anti-cancerous agent, and principal components of the methanolic extract of *Boswellia serrata,* i.e. Boswellin (BE) possess anti-carcinogenic, anti-tumor and anti-hyperlipidemic activities [34]. Researchers found that pentacyclic triterpenes of Olibanum are anticipating anti-cancer agents [35]. Boswellic acids by applying their cytotoxicity influence caspase-mediated cell death in human leukemia, colon, and in other cancer cell lines [36]. A chemoproteomic approach based on mass spectrometry exhibited that β-Boswellic acids contact with the ribosomal proteins and release protein synthesis and thus regulates cancer development [37]. The first Boswellic acids, when analyzed for their in vitro anti tumor activity, released RNA, DNA and protein synthesis in human leukemia HL-60 cells, effect of which was determined to be irreversible [38].

AKBA obtained from Indian Frankincense hindered the growth of a prostate tumor by inhibition of angiogenesis generated by activating VEGFR2 and mTOR signaling pathways. In a study of colorectal cancer cells (CRC), Takahashi et al. (2012) studied the mechanism of chemopreventive actions of Boswellic acids and found that AKBA possesses anti-tumor effects because of upregulating specific miRNA pathways [39]. Recently, in one study, oral management of *Boswellia sacra* gum resin hydrodistillation (BSGRH) showed a chemopreventive impact on urothelial cell carcinoma [40]. As per the previous results of research work, Boswellic acids at low molecular concentration are cytotoxic in brain tumor, and their use resulted in harmonious action. In testing of excessive growth of blockage and anti-proliferative properties, the highest activity was found by the AKBAin list of LTCs and GICs [41].

G. Use of Boswellia gum resin on skin disorders

In China, Frankincense has been used to treat skin injury marks and infected lesion. Also, various studies showed the action of *Boswellia serrata* in reducing redness and inflammation in the skin and AKBA was found to be an effectual agent to reimpose smooth skin and facial lines [42]. Phytosome® form of triterpenoid acid fraction from *Boswellia serrata,* Bosexil® was compared with myrillus and placebo treatment, in which Bosexil® without any augmentation improved proportions (70%), itching (60%) and eczema (50%) in a double-blind experiment.

In 2012, Wang H et al. formulated a percutaneous patch for treating a chronic skin disease, mainly consisting of AKBA [43]. On the other side, they recognized distinct configurations of α-Boswellic acid and β-Boswellic acid that could betray vigorous activities about tegument synthesis enzyme, for which a copyright was filed due to their useful actions on skin disorders. Nevertheless, Indian and Chinese *Boswellia* species extracts are available in the international market for the treatment of skin disorders but the pure form of AKBA Boswellic acid is still to enter into the market.

V. ANTI-HEPATOTOXICITY POSSESSING TRITERPENES OF *BOSWELLIA CARTERII RESIN*

From *Boswellia carterii,* ten tirucallane-type triterpenes and a nor-tetracyclic triterpene, altogether with known compounds were confined, and their configuration was enlightened by pervasive spectroscopic analysis. In vitro check, few compounds (10 μm) acquired balanced hepatoprotective activities opposite to D-galactosamine-induced HL-7702 cell damage. Previous studies found some bioactive compounds in *Boswellia carterii* [44].

A chemical investigation of *Boswellia carterii* species was implemented to identify its pharmacological importance. A chromatographic technique was used to inquire the 95% ethanolic extract of *Boswellia carterii* gum resin which yielded eleven new triterpenes and their structures were defined using 1-D & 2-D Nuclear Magnetic Resonance (NMR). The integrating constants and NOESY spectra detected relative stereochemistry while circular dichroism (CD) spectroscopy detected absolute configurations, and twenty-one triterpenes were separated after clarification of the configurations.

VI. COMPARISON OF CHEMICAL COMPOUNDS IN VARIOUS SAMPLES OF FRANKINCENSE OIL

Frankincense, often known as olibanum is the gum resin of the genus *Boswellia,* which comprises of various species that can be subdivided into dry-tropical and humid-tropical species depending on the regions [45]. Frankincense can be obtained by tapping the bark of the tree but few reports found that gum resins obtained in the first attempt of tapping were of inferior quality and best quality can be achieved in several attempts [46]. Usually, it is also considered as oleo-gum-resin due to its high content in volatiles or as a balsam [47]. The chemical composition of Frankincense oil depends on a variety of species, weather conditions and extracting techniques. As proposed by various authors, several differences were observed in the chemical composition of *Boswellia* resins [48]. Some research found volatiles with octyl acetate and incensole acetate in high amount [49] whereas, other research found α-pinene, limonene and sesquiterpenes in high amount [50]. In this study, the researchers compared the composition of different varieties of *Boswellia* in two separate parts.

A. Comparison of chemical composition of essential oils of relevant Boswellia spp.

In the first part, Niebler J et al. (2016) examined a set of 46 samples which comprised of 13 samples of essential oil and 33 samples of oleo-gum-resin of four significant varieties, i.e. *B. sacra* or *B. carterii*, *B. serrata*, *B. papyrifera* and *B. frereana,* using solid-phase Micro-extraction GC-MS analysis [51]. The 33 samples of gum resin were purchased from different suppliers of Germany and Oman, and the 13 essential oil samples were bought from various suppliers of Germany and Austria. By retention index and mass spectrum, a total of 216 different compounds were identified, out of which 73 compounds were analyzed entirely [52]. The identification rate for each sample varied within the range 70.8% and 98.9%, with an overall average rate of 91.9%. They proposed that as all the *Boswellia* species showed considerable differences in their chemical composition, therefore, these can be determined without any exact quantification of compounds and are based on qualitative and semi-quantitative features. Also, this study suggested the utilization of GC-MS analysis for the simple differentiation of both the oleo-gum-resins and essential oils.

Based on the data obtained by solid-phase micro-extraction GC-MS analysis, researchers proposed that *Boswellia sacra* consisted of a variety of sesquiterpenes whereas; *Boswellia papyrifera* had a high amount of aliphatic esters. Also, *Boswellia serrata* was easily identifiable due to the phenylpropanoids, and *Boswellia frereana* exhibited several peaks of dimers of α-phellandrene. Several studies suggested octyl acetate and incensole acetate as primary components in *Boswellia carterii* species [53],[54] but, this study proposed incensole acetate and octyl acetate as the main components of *Boswellia papyrifera* and they both were not present in *Boswellia sacra* or *Boswellia carterii* species. However, to facilitate the difference between commercial gum resins or essential oils based on their volatile profiles, they suggested chemotaxonomic marker substances.

B. Analysis of chemical components in essential oils of rare Boswellia spp. and their hybrids

In this second part of the study, the volatiles of the remaining five gum resins and four essential oils of rarely known *Boswellia* species and hybrids were investigated using SPME-GC/MS [55]. The four samples of essential oil consisted of *Boswellia neglecta* and *Boswellia rivae* species, and the five samples of gum resin consisted of *Boswellia ameero*, *Boswellia elongata*, and *Boswellia popoviana*. Also, the two species of hybrids were donated by. The gum resin samples were analyzed by solid-phase micro-extraction (SPME) method, which is a procedure commonly used in case of solid samples such as Frankincense. Similarly, the samples of essential oil were analyzed by GC/MS and used CH_2Cl_2 as a dilutor. In this part of the study, total 157 chemical components were identified, out of which 84 components were tentatively identified. Also, a total peak area of 92.1% was defined for each sample that varied between 81.2% and 99.4%.

This study proposed that the composition of *Boswellia* species differs from the four important species. Also, they found that to identify the properties of the respective *Boswellia* species, large sets of the sample are necessarily required. For the first time, this study reported the chemical composition of *Boswellia popoviana*, similarly as the chemical composition of two hybrids, i.e., *Boswellia supersacra* and *Boswellia sacrana* were identified in detail. Both hybrids exhibited a strong dynamism regarding germination rate, seedling property and ability to tolerate lowest temp., and the primary components (incensole acetate and incensole) were absent. However, when *Boswellia supersacra* cross-pollinate, then germination rate and seedling property increased rapidly in comparison to *Boswellia sacrana*.

VII. OPTIMIZATION OF ETHANOLIC SFE OF BOSWELLIC ACID OF *BOSWELLIA SERRATA* USING BOX-BEHNKEN MODEL

Steam distillation, soxhlet extraction, and solvent extraction are the techniques mainly used for extraction of bioactive components and volatiles from olibanum. *Boswellia serrata* extract consists of Boswellic acids, mainly Acetyl α boswellic acids and AKBA that possess anti-inflammatory activity [56]. As AKBA is the most potent of all other Boswellic acids, it applies pharmacological action by hindering 5-lipoxygenase enzyme and has some therapeutic effects that cure cancer, ulcers and bacterial diseases [57]. Supercritical fluid extraction (SFE) is an eco-friendly technique and has various benefits over solvent extraction techniques such as short duration, good quality, and high extraction rate. This technique used carbon dioxide as a solvent since it has low viscosity, density, high diffusivity and surface tension. SFE optimization is a long duration procedure that works on the principle of one factor at a time and does not support interactions of process variables.

To optimize SFE extraction, many researchers prefer Box-Behnken model which is a mathematical tool and analyze and optimize the relation between process variables [58]. As per their knowledge, literature assessment found no reports on optimization and extraction of AKBA from olibanum using ethanolic SFE so, to obtain the maximum yield of AKBA several parameters were analyzed and final yield obtained was compared with batch extraction (BE), and ultrasound-assisted extraction (UAE). After comparison, it was observed that ethanolic SFE had a maximum yield of AKBA but with higher duration in comparison to ultra-sound assisted extraction and batch extraction [59].

The SFE process can be carried out by solvation, and its features are dependent on changing temperature and pressure, viscosity and density. Batch extraction extracts oil with a solvent with low extraction efficiency while UAE is the process of cavitation releasing the components from damaged cell to the surroundings. Therefore, extraction of AKBA bioactive compounds from plants is increased by CO_2 without harming the environment as a result of which, SFE was proved to be an easy process in case of AKBA from *Boswellia serrata* [60]. Also, the purity level of AKBA obtained in batch extraction, ultrasound-assisted extraction and SFE was 23%, 24% and 24% which showed no difference in purity level of AKBA in all above extraction methods.

VIII. BENEFITS OF *BOSWELLIA CARTERII* COMPONENTS TO ANTI-INFLAMMATORY ACTIVITY OF OLIBANUM BY HINDERING CYCLOOXYGENASE-2

After analyzing Boswellia carterii, α-pinene, 1-octanol, linalool, limonene, octyl acetate, α-thujene, and (E)-β-ocimene et al. were the major components that possess analgesic and anti-inflammatory activities. The resin part of this species is responsible for the anti-inflammatory activity, the gum portion for antioxidants and the essential oil for anti-cancerous and anti-bacterial activities. Traditionally, it was depicted by Chinese medicinal system that olibanum from *Boswellia carterii* could be helpful to cure inflammation and pain by increasing qi-circulation and initiating blood stagnation.

In ancient times, Frankincense was soaked in water or sesame oil before applying on the external skin as it brings relief in pain and has no side effects of oral care. However, to their knowledge, there were no reports on the benefits of olibanum oil to the recent anti-inflammatory and analgesic activities. In this study, the absorption efficiency of Frankincense oil extract (FOE) and Frankincense water extract (FWE) were compared on in vivo animal models elucidating the effective components to identify the recent analgesic and anti-inflammatory activities. Frankincense oil extract and Frankincense water extract have been treating external swelling and pain for so long and compositions of both extracts were analyzed by gas chromatography-mass spectrometry (GC-MS).

The anti-inflammatory and analgesic activities possessed by FOE and FWE extracts and their major components were analyzed and compared by histological maculation in a formalin-inflamed hind paw model and a xylem-induced ear edema model. A xylene-induced ear edema model was caused by 20 μL xylene as a solvent whereas a formalin-inflamed mouse hind paw model was accomplished by 20 μL formalin as a solvent between the layers of skin, after which the mice were treated externally with these samples [61]. The results obtained indicated that FOE possesses higher anti-inflammatory and analgesic activities by hindering COX-2 in the inflammatory tissues, also had higher contents of α-pinene, linalool, and 1-octanol (active components) than those in FWE. FOE can be assisted as a promising therapeutic agent in the treatment of long-lasting pain [62].

IX. EFFECT OF ESSENTIAL OIL OF *BOSWELLIA SACRA* EXTRACTED BY HYDRODISTILLATION ON HUMAN PANCREATIC CANCER CELL

Several studies demonstrated that essential oil of *Boswellia spp*. possess anti-neoplastic and anti-cancer activities. In the United States, the pancreatic cancer cell has been positioned as one of the most occurring causes of cancer-related death and across the world. In 2002-2008, the data obtained by Surveillance, Epidemiology, and End Results (SEER) evaluated altogether 5-year survival was 5.8%, with 23.3% for patients with confined disease and 1.8% for distant development while, these factors resulted in deficient reactions and drug defiance [63]. Winking et al. (2000) found that in a rat glioma model, olibanum oil causes cell death and extends survival rate [64].

A clinical study showed that extracts of Indian Frankincense that possess anti-cancer activity resulted in the reduction of brain edema in patients. The goal of this study to use hydro-distilled essential oil of *Boswellia sacra* was to evaluate the preparation and environmental conditions that cause toxicity in human pancreatic cells and, establish a connection between olibanum oil composition and anti-cancer activity in living organisms. Olibanum oil was found to be effective in rescuing and crushing tumor cell growth and leading to tumor cell death in a heterotopic xenograft human pancreatic cancer mouse model. As per results, anti-cancer activity of olibanum oil depends on factors such as duration, temperature, and molecular weight.

Boswellia sacra gum resins were divided into four different fractions depending on temperature and extraction time and then hydro-distilled. The chemical composition and boswellic acids of essential oil obtained from all fractions were analyzed by gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography (HPLC).

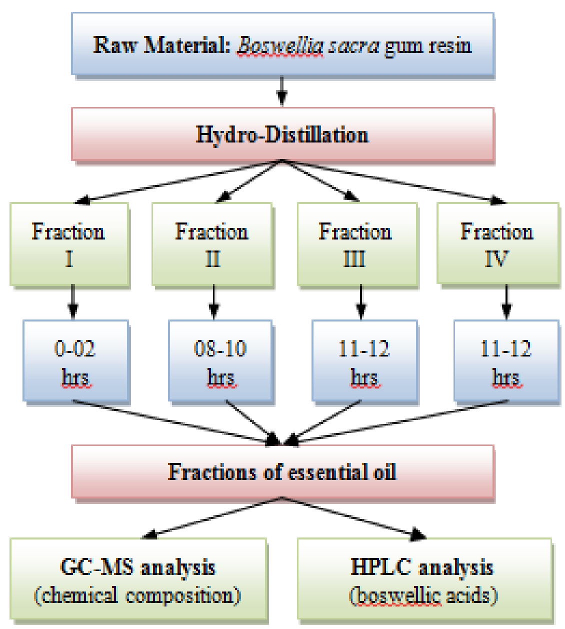

Fig. 3 Flowchart of the experimental work

After GC-MS analysis, comparison of all fractions of essential oil showed that the long duration one resulted in good quality and with a high amount of sesquiterpenes. The major components identified in the first three fractions were α-Thujene, α-Pinene, β-Pinene, and myrcene but due to the longer duration and increasing temperature, copiousness of α-Pinene decreased. Components identified in essential oil obtained in Fraction III & Fraction IV were same, but Fraction IV consisted of higher quantities of components with retention time starting from sabinene due to high temperature. Similarly, HPLC analysis also showed that boswellic acids are dependent on long extraction time and high temperature. Boswellic acids were found in high amount in Fraction III and Fraction IV and were found more potent to possess their anti-cancer activity.

Therefore, results proposed that Fraction IV essential oil enriched with high molecular weight compounds was more powerful in causing pancreatic cancer cell death than Fraction I, II, and III [65]. However, due to complexion, the active component responsible for anti-cancer activity has not been identified in this study.

The anti-cancer activity of boswellic acids in living organisms was studied using heterotopic and orthotopic xenograft human pancreatic cancer mouse models. After further confirmation of efficiency of extracts of *Boswellia sacra* resins obtained from hydro-distillation, it might constitute a new therapeutic action on the treatment of pancreatic cancer in humans. Additionally, to optimize the administration frankincense essential oil for cancer treating therapy, pharmacokinetics and pharmacodynamic studies are required.

X. FRANKINCENSE ODORANTS IDENTIFICATION IN BOSWELLIA SACRA SPECIES BY VARIOUS ANALYSES

The most cherished species of 19 different *Boswellia* species, *Boswellia sacra* are produced from the Yemen and Oman coasts on the Arabian Peninsula, whose taxonomy and phylogenetics is still in the scientific and research discussion. It is stored in the bark canals of the tree and is discharged when hurt or injured as it acts as a defense mechanism against in vivo for wound healing. Odorants analysis from a pack of foods and other products shown that the contents with low concentration, being of high potential on altogether odor reaction are misplaced in chemo-analytic approach [66].

In this study, the main odorants of six different samples of *Boswellia sacra* were identified by odor quality, retention time and mass spectra by aroma extract dilution analysis (AEDA) using a sensory-guided screening approach, also stereochemistry of the analyzed components was not determined [67]. Odor properties were finalized by harmony to define one specific fragrance of this Frankincense, but samples showed incomprehensible variations with main components. The aroma extracts of Boswellia sacra gum resins were extracted by solvent assisted flavor evaporation (SAFE) and were analyzed by one-dimensional and two-dimensional gas chromatography-olfactometry/mass spectrometry.

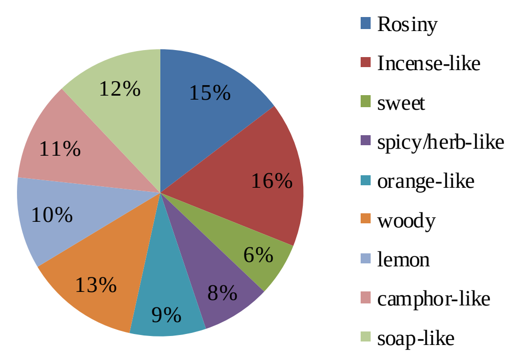

Fig. 4 Odor distribution of each sample from *Boswellia sacra*

As per fig. 4, incense-like and rosiny were rated the highest, camphor-like, lemon, woody and soap-like were found with an average rating and sweet, spicy/herb-like and orange-like were ranked as the lowest one. The first and fifth sample showed the most substantial deviation in rosiny and incense-like, while all six samples from Somalia and Oman were almost the same in odor profile. Although, among several distinctions rosiny was found to be the altogether odor reaction thus matching α-Pinene as the most potent odorant in the aroma extract. These prospects for few monoterpenoids have been discussed in previous studies where authors claimed that some people were able to differentiate between the two species just by the smell of samples.

The Olfactory analysis on the basis of enantiomeric ratios suggested limonene as minor component compared to α-pinene for aroma composition in both species, and carvone as the best chiral compound to differentiate the smell. The GC-olfactometry analysis defined the presence of the mixture of both (R)-carvone and (S)-carvone in different enantiomeric ratios and assigned serratol as S (_)-cembra-3E, 7E, 11E-triene-1-ol [68]. Also, serratol was renamed as cembrenol, which is known for its woody, rosiny and incense-like smell and after a very far duration, it was found only in *Boswellia spp*. Hence, the main odorants in the chemo-analytical sample of *Boswellia sacra* gum resin were identified using a sensory-guided screening approach. GC-O analysis detected total 23 odorants, out of which 17 were identified entirely and their ratings were framed in aroma extraction dilution analysis.

This research observed that monoterpenes and sesquiterpenes dominated the odorants quality of *Boswellia sacra* gum resin. The motive of this research was to clear the aroma composition of *Boswellia sacra* for a better understanding of its pharmacological, therapeutic and ritual applications.

XI. CONSEQUENCES OF AQUANOVA MICELLATION TECHNOLOGY ON THE POOR BIOAVAILABILITY OF *BOSWELLIA SERRATA* EXTRACT

Boswellic acids being the most crucial characteristic of *Boswellia* species are the active ingredients of *Boswellia Serrata* gum resin, known for their anti-inflammatory activities. Also, it was shown that the Boswellic acids inhibit the polar enzymes of *Boswellia Serrata*. However, several types of research revealed the potent of *Boswellia Serrata* to treat the chronic inflammatory diseases, but due to their hydrophobicity and low water solubility, very few amounts of Boswellic acids are absorbed after oral intake [69]. The Boswellic acids suffer from poor bioavailability due to hydrophobicity and their poor water solubility and thus, constitute the major limitation to the efficiency of this species [70].

The application of AQUANOVA micellation technology on various herbal substances resulted into enormous increase in oral bioavailability of curcumin, known for its poor absorption. Based on this fact, this study investigated the consequences of micellation technology on the poor bioavailability of *Boswellia Serrata* extract in rats in comparison to its original form.

In this study, around 250 g of female albino Wistar rats were administered with different Boswellic acids. The samples were characterized into two parts - Native and Solubilized *Boswellia* extract. Both the samples were analyzed by liquid chromatography-mass spectrometry (LC-MS) method to define the individual content of boswellic acids. Among all the boswellic acids identified, 11-keto-β-boswellic acid (KBA), acetyl-11-keto-β-boswellic acid (AKBA), α-boswellic acid (α-BA), β-boswellic acid (β-BA), acetyl-α-boswellic acid (A-α-BA) and acetyl-β-boswellic acid (A-β-BA), were found to be effective for most of the pharmacological activities.

Solubilized *Boswellia* extract resulted in a high amount of Boswellic acid in plasma than Native *Boswellia* extract, in which the highest increment was observed in case of AKBA. Also, solubilized -BE did not affect the time expected to fulfill the maximum concentration in plasma. Nevertheless, it was demonstrated that AQUANOVA micellation solubilization of Boswellic acids could amend absorption of Boswellic acids and this technology proved to be a promising approach for increasing the bioavailability of the substances with low water solubility. Therefore, it can be expected that a lower dose of *Boswellia serrata* extract may possess higher therapeutic effects.

XII. CONCLUSION

Boswellia species of Frankincense which has been used in religious ceremonies from ancient times and valued like gold in trading has relished popularity in both modern medicine and traditional system due to its multiple beneficial anti-bacterial, anti-inflammatory, anti-microbial, hepatoprotective and therapeutic properties. Boswellic acid AKBA showed promising results in experimental and clinical studies. Volatiles that were identified in different studies, none of them determined a specific fragrance of olibanum.

Therefore, the enantiomeric distribution and resulting consequences of the chiral compounds identified in *Boswellia sacra* for the odor impression of Frankincense should be investigated in future studies. In this review, the studies summarized have focused on compounds with high abundances. Therefore, further research is required to elucidate the specific contribution to the aroma-profile of frankincense. The composition of Frankincense depends on factors such as climate, origin, harvesting time and other environmental conditions. When comparing various results of the samples of same species, some variance might be obtained.

Also, to upgrade the bioavailability of boswellic acids, several strategies are urgently required to ease more from the therapeutical potent of *Boswellia*. For optimization of Frankincense essential oil, pharmacodynamic and pharmacokinetics studies are required. Further research is required to understand the molecular mechanisms at the cellular level, drug-drug interactions; develop methods to improve the pharmacokinetic properties, especially oral bioavailability and formulation of a stable preparation.

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REFERENCES

[1] S. Dharmananda, - Myrrh and frankincense, spiritual significance, Internet J. vol. 2, pp. 1–6, 2003.

[2] M. Padhi, and S. Mahapatra, - Boswellia serrata: a review of its traditional uses, phytochemistry and pharmacology, Int. Rev. Biophys. Chem. vol. 4, pp. 74-83, 2013.

[3] C.L. Woolley, M.M. Suhail, B.L. Smith, K.E. Boren, L.C. Taylor, M.F. Schreuder, J.K. Chai, H. Casabianca, S. Haq, H.K. Lin, A.A. Al-Shahri, S. Al-Hatmi, and D.G. Young, - Chemical differentiation of Boswellia sacra and Boswellia carterii essential oils by gas chromatography and chiral gas chromatography-mass spectrometry, J. Chromatogr. A. vol. 1261, pp. 158-163, 2012.

[4] S. De Rapper, S.F. Van Vuuren, G.P. Kamatou, A.M. Viljoen, and E. Dagne, - The additive and synergistic antimicrobial effects of select frankincense and myrrh oils-a combination from the pharaonic pharmacopoeia Lett. Appl. Microbiol. vol. 54, pp. 352-358, 2012.

[5] B.K. Chhetri, N.A. Ali, and W.N. Setzer, - A survey of chemical compositions and biological activities of Yemeni aromatic medicinal plants, Medicines vol. 2, pp. 67-92, 2015.

[6] P.R. Vuddanda, S. Singh, and S. Velaga, - Boswellic acid – medicinal use of an ancient herbal remedy, J. Herb. Med. 2016.

[7] M.Z. Siddiqui, - Boswellia serrata, a potential anti-inflammatory agent: an overview, Indian J. Pharm. Sci. vol. 73, pp. 255-261, 2011.

[8] M. Thulin, and A.M. Warfa, - The frankincense trees (Boswellia spp., Burseraceae) of northern Somalia and southern Arabia, Kew Bulletin. vol. 42, pp. 487–500, 1987.

[9] R. Hamidpour, S. Hamidpour, M. Hamidpour, M. Shahlari, - Frankincense (Rǔ Xi_ang; Boswellia species): from the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases, J. Trad. Comp. Med. vol. 3, pp. 221-226, 2013.

[10] O. Boutin, and E. Badens, - Extraction from oleaginous seeds using supercritical CO2: experimental design and products quality, J. Food Eng. vol. 92, pp. 396–402, 2009.

[11] M.K. Senghani, and P.M. Patel, - Pharmacognostic and phytochemical study of Oleo gum resin from Boswellia serrata, Res. J. Pharmacog. Phytochem. vol. 5, pp. 244-250, 2013.

[12] Y.N. Pan, X.X Liang, L.Y. Niu, Y.N. Wang, X. Tong, H.M. Hua, J. Zheng, D.Y. Meng, and X.Q. Liu, - Comparative studies of pharmacokinetics and anti-coagulatory effect in rats after oral administration of Frankincense and its processed products, J. Ethnopharmacol. vol. 172, pp. 118–123, 2015.

[13] P.A. Batista, M.F. Werner, E.C. Oliveira, L. Burgos, P. Pereira, L.F. Brum, G.M. Story, and A.R. Santos, - The antinociceptive effect of (_)-linalool in models of chronic inflammatory and neuropathichyper sensitivity in mice, J. Pain. vol. 11, pp. 1222–1229, 2010.

[14] K. Gerbeth, J. Meins, S. Kirste, F. Momm, M. Schubert-Zsilavecz, and M. Abdel-Tawab, - Determination of major boswellic acid in plasma by high-pressure liquid chromatography/mass spectrometry, J. Pharm. Biomed. Anal. vol. 56, pp. 998-1005, 2011.

[15] B.A. Shah, G.N. Qazi, and S.C. Taneja, - Boswellic acids: a group of medicinally important compounds, Nat. Product Rep. vol. 26, pp. 72-89, 2009.

[16] K.H.C. Başer, B. Demirci, A. Dekebo, and E. Dagne, - Essential oils of some Boswellia spp., myrrh and opopanax, Flav. Fragr. J. vol.18, pp. 153–156, 2003.

[17] K. Sengupta, J.N. Kolla, A.V. Krishnaraju, N. Yalamanchili, C.V. Rao, and T. Golakoti, - Cellular and molecular mechanisms of anti-inflammatory effect of Aflapin: a novel Boswellia serrata extract, Mol. Cell. Biochem. vol. 354, pp. 189-197, 2011.

[18] D. Poeckel, and O. Werz, - Boswellic acids: biological actions and molecular targets, Curr. Med. Chem. vol. 13, pp. 3359-3369, 2006.

[19] H.P.T. Ammon, - Modulation of the immune system by Boswellia serrata extracts and boswellic acids, Phytomedicine. vol. 17, pp. 862-867, 2010.

[20] R.Y. Kuo, K. Qian, S.L. Morris-Natschke, and K.H. Lee, - Plant derived triterpenoids and analogues as antitumor and anti-HIV agents, Nat. Prod. Rep. vol. 26, pp. 1321-1344, 2009.

[21] S. Umar, K. Umar, A.H. Saarwar, A. Khan, and N. Ahmad, - Boswellia serrata extract attenuates inflammatory mediators and oxidative stress in collagen induced arthritis, Phytomedicine. vol. 21, pp. 847-856, 2014.

[22] B. Gayathri, N. Manjula, K.S. Vinaykumar, B.S. Lakshmi, and A. Balakrishnan, - Pure compound from Boswellia serrata extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition of TNFa, IL-1b, NO and MAP kinases, Int. Immunopharmacol. vol. 7, pp. 473-482, 2007.

[23] S.M. Khosravi, H. Mahmoodian, A. Moghadamnia, B.M.A. Poorsattar, and M. Chitsazan, - The effect of Frankincense in the treatment of moderate plaque-induced gingivitis: a double blinded randomized clinical trial, DARU J. Pharm. Sci. vol. 19, pp. 288-294, 2011.

[24] U. Siemoneit, A. Koeberle, A. Rossi, F. Dehm, M. Verhoff, S. Reckel, et al., - Inhibition of microsomal prostaglandin E2 synthase-1 as a molecular basis for the anti-inflammatory actions of boswellic acids from frankincense, Br. J. Pharmacol. vol. 162, pp. 147-162, 2011.

[25] A. Notarnicola, G. Maccagnano, L. Moretti, V. Pesce, S. Tafuri, A. Fiore, et al., - Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: randomized trial, Int. J. Immunopathol. Pharmacol. vol. 29, pp. 140-146, 2016.

[26] A.F. Raja, F. Ali, I.A. Khan, A.S. Shawl, D.S Arora, B.A. Shah, et al., - Antistaphylococcal and biofilm inhibitory activities of acetyl-11-keto-b-boswellic acid from Boswellia serrata, BMC Microbiol. vol. 11, pp. 54, 2011.

[27] A.L. Miller, - Effects of Boswellia serrata on asthma, Altern. Med. Rev. vol. 6, pp. 20-47, 2001.

[28] E.N. Ali, and S.Z. Mansour, - Boswellic acids extract attenuates pulmonary fibrosis induced by bleomycin and oxidative stress from gamma irradiation in rats, Chin. Med. J. vol. 6, pp. 36, 2011.

[29] Z. Liu, X. Liu, L. Sang, H. Liu, Q. Xu, and Z. Liu, - Boswellic acid attenuates asthma phenotypes by downregulation of GATA3 via pSTAT6 inhibition in a murine model of asthma, Int. J. Clin. Exp. Pathol. vol. 8, pp. 236-243, 2015.

[30] M. Hosseini, M.A. Hadjzadeh, M. Derakhshan, S. Havakhah, F.B. Rassouli, H. Rakhshandeh, et al., - The beneficial effects of olibanum on memory deficit induced by hypothyroidism in adult rats tested in Morris water maze, Arch. Pharm. Res. vol. 33, pp. 463-468, 2010.

[31] A. Mahmoudi, A. Hosseini-Sharifabad, H.R. Monsef-Esfahani, A.R. Yazdinejad, M. Khanavi, A. Roghani, et al., - Evaluation of systemic administration of Boswellia papyrifera extracts on spatial memory retention in male rats, J. Nat. Med. vol. 65, pp. 519-525, 2011.

[32] U. Zutshi, P.G. Rao, S. Kaur, G.B. Singh, and C.K. Atal, - Mechanism of cholesterol lowering effect of Salai guggal ex- Boswellia serrata, Indian J. Pharm. vol. 18, pp. 182-183, 1986.

[33] J.J. Liu, W.C. Toy, S. Liu, A. Cheng, B.K. Lim, T. Subramaniam, et al., - Acetyl-keto-b-boswellic acid induces lipolysis in mature adipocytes, Biochem. Biophys. Res. Commun. vol. 431, pp. 192-196, 2013.

[34] M.T. Huang, V. Bacdmaev, V. Ding, Y. Liu, and J.G. Xie, - Anti-tumor and anti-carcinogenic activities of triterpenoid, beta-boswellic acid, Biofactors, vol. 13, pp. 225-230, 2000.

[35] B. Park, S. Prasad, V. Yadav, B. Sung, and B.B. Aggarwal, - Boswellic acid suppresses growth

and metastasis of human pancreatic tumors in an orthotopic nude mouse model through modulation of multiple targets, PLoS One. vol. 6, e26943.

[36] M.M. Suhail, W. Wu, A. Cao, F.G. Mondalek, K.M. Fung, P.T. Shih, et al., - Boswellia sacra essential oil induces tumor cellspecific apoptosis and suppresses tumor aggressiveness in cultured human breast cancer cells, BMC Complement. Altern. Med. vol. 11, pp. 129, 2011.

[37] A. Casapullo, C. Cassiano, A. Capolupo, F. Del Gaudio, R. Esposito, A. Tosco, et al., - β-Boswellic acid, a bioactive substance used in food supplements, inhibits protein synthesis by targeting the ribosomal machinery, J. Mass Spectrom. vol. 51, pp. 821-827, 2016.

[38] R.F. Hoerlein, T. Orlikowsky, C. Zehrer, D. Niethammer, E.R. Sailer, T. Simmet, et al., - Acetyl-11-keto-beta boswellic acid induces apoptosis in HL-60 and CCRF-CEM cells and inhibits topoisomerase I, J. Pharmacol. Exp. Ther. vol. 288, pp. 613-619, 1999.

[39] M. Takahashi, B. Sung, Y. Shen, K. Hur, A. Link, C.R. Boland, B.B. Aggarwal, et al., - Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR 200 microRNA family, Carcinogen. vol. 33, pp. 2441-2449, 2012.

[40] D. Xia, W. Lou, K.M. Fung, C.L. Wolley, M.M. Suhail, and H.K. Lin, - Cancer chemopreventive effects of Boswellia sacra gum resin hydrodistillates on invasive urothelial cell carcinoma: report of a case, Integr. Cancer Ther. vol. 16, pp. 605-611, 2016.

[41] H. Schneider, and M. Weller, - Boswellic acid activity against glioblastoma stem-like cells, Oncol Lett. vol. 11, pp. 4187-4192, 2016.

[42] Y. Qurishi, A. Hamid, M.A. Zargar, S.K. Singh, and A.K. Saxena, - Potential role of natural molecules in health and disease: importance of boswellic acid, J. Med. Plants Res. vol. 4, pp. 2778-2785, 2010.

[43] H. Wang, T. Ren, and J. Li, - Transdermal patch containing natural medicine for treating psoriasis, 2012.

[44] Y.G. Wang, J. Ren, A.G. Wang, J.B. Yang, T.F. Ji, Q.G. Ma, J. Tian, and Y.L. Su, - Hepatoprotective prenylaromadendrane-type diterpenes from the gum resin of Boswellia carterii, J. Nat. Prod. vol. 76, pp. 2074-2079, 2013.

[45] J. Eslamieh, - Cultivation of Boswellia: Sacred Trees of Frankincense; A Book's Mind, Phoenix, Arizona, 2011.

[46] J. Coppen, - Overview of International Trades and Markets. Ed.; E. Casadei, B. Chikamai, Network for Natural Gums and Resins in Africa NGARA, KEFRI, Nairobi, Kenya, 2005.

[47] A.O. Tucker, - Frankincense and myrrh, Econ. Bot. vol. 40, pp. 425–433, 1986.

[48] M. Mertens, A. Buettner, and E. Kirchhoff, - The volatile constituents of Frankincense: a review, Flav. Fragr. J. vol. 24, pp 279-300, 2009.

[49] B.R. Mikhaeil, G.T. Maatooq, F.A. Badria, and M.M. Amer, - Chemistry and immunomodulatory activity of frankincense oil, Zeitschrift fur Naturforschung. C, J. Biosci. vol. 58, pp. 230-238, 2003.

[50] S. Hamm, E. Lesellier, J. Bleton, and A. Tchapla, - Optimization of headspace solid phase microextraction for gas chromatography/mass spectrometry analysis of widely different volatility and polarity terpenoids in olibanum, J. Chromatogr. A. vol. 1018, pp. 73-83, 2003.

[51] J. Niebler, and A. Buettner, - Frankincense Revisited, Part I: Comparative analysis of volatiles in commercially relevant Boswellia species, Chem. Biodivers. vol. 13, pp. 613-629, 2016.

[52] R.P. Adams, - Identification of Essential Oil Components by Gas Chromatography/Mass Spectrometry; 4th Edition, Allured Business Media, Carol Stream, IL, 2012.

[53] Y. Chen, C. Zhou, Z. Ge, Y. Liu, W. Feng, S. Li, G. Chen, and T. Wei, - Composition and potential anticancer activities of essential oils obtained from myrrh and frankincense, Oncol. Lett. vol. 6, pp. 1140-1146, 2013.

[54] S. Hayashi, H. Amemori, H. Kameoka, M. Hanafusa, and K. Furukawa, - Comparison of volatile compounds from olibanum from various countries, J. Essent. Oil Res. vol. 10, pp. 25–30, 1998.

[55] J. Niebler, J. Eslamieh, and A. Buettner, - Frankincense Revisited, Part II: Volatiles in rare Boswellia species and hybrids, Chem. Biodivers. vol. 13, pp. 630-643, 2016.

[56] G. Culioli, C. Mathe, P. Archier, and C. Vieillescazes, - A lupane triterpene from frankincense (Boswellia sp., Burseraceae), Phytochemistry. vol. 62, pp. 537–541, 2003.
[57] H. Safayhi, T. Mack, J. Sabieraj, M. Anazodo, L.R. Subramanian, and H.P.T. Ammon, - Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase, J. Pharmacol. Exp. Ther. vol. 261, pp. 1143-1146, 1992.
[58] H. Kamali, N. Aminimoghadamfarouj, and A. Nematollahi, - Optimization of variables for pressurized fluid extraction of essential oil from Lavandula angustifolia using box-Behnken design, Int. J. Chemtech Res. vol. 6, pp. 4844–4852, 2014.
[59] S.S. Niphadkar, and V.K. Rathod, - Extraction of acetyl 11-keto-β-boswellic acids (AKBA) from Boswellia serrata using ultrasound, Sep. Sci. Technol. vol. 52, pp. 997–1005, 2017.
[60] C. Yang, Y.R. Xu, and W.X. Yao, - Extraction of pharmaceutical components from Ginkgo biloba leaves using supercritical carbon dioxide, J. Agric. Food Chem. vol. 50, pp. 846-849, 2002.
[61] H. Hosseinzadeh, and H.M. Younesi, - Antinociceptive and anti-inflammatory effects of Crocus sativus L. stigma and petal extracts in mice, BMC Pharmacol. vol. 2, pp. 7, 2002.
[62] X.J. Li, Y.J. Yang, Y.S. Li, W.K. Zhang, and H.B. Tang, - α-Pinene, linalool, and 1-octanol contribute to the topical anti-inflammatory and analgesic activities of frankincense by inhibiting COX-2, J. Ethnopharmacol. vol. 179, pp. 22–26, 2016.
[63] E.K. Jeon, H.S. Won, Y.H. Ko, I.S. Lee, T.H. Hong, Y.K. You, and M.A. Lee, - Comparison of the efficacy and the toxicity between gemcitabine with capecitabine (GC) and gemcitabine with erlotinib (GE) in unresectable pancreatic cancer, J. Cancer Res. Clin. Oncol. vol. 138, pp. 1625–1630, 2012.
[64] M. Winking, S. Sarikaya, A. Rahmanian, A. Jodicke, D.K. Boker, - Boswellic acids inhibit glioma growth: a new treatment option? J. Neurooncol. vol. 46, pp. 97–103, 2000.
[65] N. Xiao, M.M. Suhail, Q. Yang, A. Cao, K.M. Fung, R.G. Postier, C. Woolley, G. Young, J. Zhang, and H.K. Lin, - Frankincense essential oil prepared from hydrodistillation of Boswellia sacra gum resins induces human pancreatic cancer cell death in cultures and in a xenograft murine model, BMC Complement. Altern. Med. vol. 12, pp. 253, 2012.
[66] R. Clery, - High-impact odorants in essential oils, Flav. Fragr. J. vol. 25, pp. 117–120, 2012.
[67] W. Grosch, - Determination of potent odorants in foods by aroma extract dilution analysis (AEDA) and calculation of odor activity values (OAVs), Flav. Fragr. J. vol. 9, pp. 147–158, 1994.
[68] T.J. Schmidt, M. Kaiser, and R. Brun, - Complete structural assignment of serratol, a cembrane-type diterpene from Boswellia serrata, and evaluation of its antiprotozoal activity, Planta Med. vol. 77, pp. 849–850, 2011.
[69] H.P. Ammon, - Boswellic acids and their role in chronic inflammatory diseases, Adv. Exp. Med. Biol. vol. 928, pp. 291–327, 2016.
[70] M. Abdel-Tawab, O, Werz, and M. Schubert-Zsilavecz, - Boswellia serrata: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Clin Pharmacokinet. vol. 50, pp. 349-369, 2011.