

### TURKISH REPUBLIC OF NORTH CYPRUS

## NEAR EAST UNIVERSITY

HEALTH SCIENCES INSTITUTE

# FRANKINCENSE: BIOLOGICAL ACTIVITIES AND THERAPEUTIC PROPERTIES

EMMANUEL CHUKWUDI NWACHUKWU

**MASTERS THESIS** 

A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF HEALTH SCIENCES NEAR EAST UNIVERSITY

BIOCHEMISTRY

**SUPERVISOR** 

Assoc. Prof. Dr. Eda Becer

NICOSIA, 2020



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## THESIS APPROVAL

Thesis submitted to the institute of Health Sciences of Near East University in partial fulfillment of the requirements of the degree of **Master of Science in Biochemistry**.

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#### DECLARATION

Hereby I declare that this thesis study is my own study, I had no unethical behaviour in all stages from planning of the thesis until writing thereof, I obtained all the information in this thesis in academic and ethical rules, I provided reference to all of the information and comments which could not be obtained by this thesis study and took these references into the reference list.

Emmanuel Chukwudi Nwachukwu

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#### ABSTRACT

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From antiquity, frankincense has been used for therapeutic purposes in various. In the search of therapeutic remedies, extracts from frankincense species have been applied. The gum resin of *Boswellia sacra* or *Boswellia carteri, Boswellia frereana*, and *Boswellia serrata* are some. Studies show that the clinical data for treatment remain in their primary state. This is especially for the inflammatory diseases. This research work was carried out to examine the successes and challenges in the application of frankincense in therapeutic procedures. The considerable potential for cancer therapy, anti-inflammatory treatment, diabetes, and other diseases are shown in this study. The traditional application open important prospects that must be explored through medical means to validate them scientifically.

Key words: Frankincense, Boswellia, cancer, therapy

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## Abbreviations

5-LOX	5-lipoxygenase
AKBA	Acetyl-11-Keto-Boswellic Acid
BAs	Boswellic acids
CA3	Cornu ammonis 3
CE	Common Era
COX-2	Cyclooxygenase-2
DNA	Deoxyribonucleic acid
GPx	Glutathione peroxidase
HL-60	Human leukemia 60
IA	Incensole acetate
IBD	Inflammatory bowel diseases
IL-1β	Interleukin-1 beta antagonists
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MDA	Malondialdehyde
NO	Nitric oxide
NOS	Nitric oxide synthase
NSAIDs	Nonsteroidal anti-inflammatory drugs
PGE2	Prostaglandin $E_2$
RNA	Ribonucleic acid
ROS	Reactive Oxygen Species
SOD	Superoxide dismutase

TIM	Traditional Iranian medicine
TNF-α-	Tumor necrosis factor alpha
TRP	Transient receptor potential (TRP)
TRPV	Transient receptor potential vanilloid
ZO	Zinc Oxide

#### **1. INTRODUCTION**

Frankincense, an aromatic resin, is a product of dry fluids (also referred to as Olibannum) is gotten from Boswellia trees especially the *Boswellia sacra*. Originating from various regions of the world, these trees can be found in Yemen and Oman in the Middle East, Somalia and Ethiopia in the Horn of Africa, and India in South Asia. Frankincense was coined from the French word *franc encens*, which has been translated to mean a pure incense of high quality and nobility, showing its level of worth and importance in ancient times. Also, Olibanum another name for frankincense, was coined from the Latin term, oleum libani.

Due to their high pharmacological importance, Boswellic acids (BAs) from Boswellia trees have been essential in both in vivo and in vitro studies and in bioactive ingredients. BAs provide a high degree of anti-inflammatory property of frankincense as a result of its biomechanical and molecular targets. Because of their ability to combine or dissolve liquids or fats, i.e. their being lipophilic nature, this therefore reduces their solubility in aqueous environment as well as their bioavailability. Frankincense or Olibanum also contain a group of pentacyclic triterpenic acids known as the Lupeolic acids (Rashan et al. 2019).

In the past, Frankincense has been used for numerous purposes both traditionally and religiously. It has recently gained a modern use in medicine. It is also applied by the Roman Catholic churches and the orthodox churches as incense in religious worship and is believed to have a symbol of holiness and purity. Known as Luban in North Africa and Arabia, it was a necessary for trade in these regions. In ancient Rome, frankincense also known as Olibanum was something of great worth after gold. It has been used for embalmment as well as in the preservation of the body of Pharaoh Tutankhamun after his death in 1323 in Egypt. Baby Jesus was gifted with frankincense alongside two other gifts by the wise men that came from the East to visit him (Rashan et al. 2019). In India, Olibanum is known in Ayurveda medicine where it is used in the treatment of skin infections, diuretic and blood purifier. It has also been relevant in treating chronic skin diseases and other diseases such as fever, ulcer and leprosy. Frankincense is used for agricultural purposes such as food production, wine production, flavor, and in hygiene. It also serves as insecticides around the world due to the ability its aroma has to expel them. Like many other products, frankincense has its side effects which is experienced when it is taken excessively or abused.

This research work was carried out to examine the successes and challenges in the application of frankincense in therapeutic procedures such as in cancer, inflammatory diseases, asthma, skin treatment, brain tumor, diabetes and many more. Species of frankincense from different locations are considered in this.

#### 2. GENERAL INFORMATION

#### 2.1 Species of Frankincense

The classifications of the species of frankincense are carried out according to their nativity. These species include:

- Boswellia sacra (also known as Boswellia carterii or Boswellia bhawdajiana) Oman, Yemen, Ethiopia, and Somalia
- Boswellia frereana –Somaliland
- Boswellia papyrifera Ethiopia, Sudan
- Boswellia serrata India
- Boswellia neglecta Kenya, Ethiopia
- Boswellia rivae Ethiopia, Somalia

Frankincense (genus Boswellia; family *Burseraceae*) substance is manufactured from trees. The main species listed above Boswellic acid and several compounds (Figure 1) which contribute to the bioactivity of oleogum resin (Assefa et al. 2012).

These species produce a pleasant smell and this is as a result of the resin present in these trees. A cutting such as an incision is made on the tree trunk to collect the light yellowed solidified exudates having a classified aroma. The species are used mainly for commercial purposes. One of the best studied species of frankincense is the *Boswellia serrata*, its gum resin is also studied (*salai guggal*, Indian olibanum). In Ayurvedic medicine, olibanum is useful in the treatment of arthritis or asthma (Aman et al. 2009).

The Frankincense obtained from *Boswellia sacra* found in Somalia and Dhofar region of Oman is considered to have more worth than frankincense obtained from other trees. The gift to Infant Jesus, as mentioned in the Holy Bible is believed as obtained from *Boswellia sacra* from the Dhofar region of Oman. In Sanskrit, frankincense gotten from *Boswellia serrata in* India is known as 'Sallaki'. It is alternatively known as 'Indian olibanum', 'Salaiguggulu' or 'Kunthurukkam'. *Boswellia serrata* tree is distributed from the Sivalic ranges of the Himalaya, dry regions of Rajasthan and up to the southern region

of Kerala. The oleogum resin is exudated from the mature trees of more than 0.9m girth, black dammer (*Canarium strictum*), and frankincense (*Boswellia sacra*).



Figure 1. Constituents of Boswellia oleogum resin (Assefa et al. 2012)

Another species of *Boswellia*, known as *Boswellia ovatifolia*, is found in the Eastern Ghats of south India. Frankincense differ in its grades and is based on their color, texture, shape, clump size, smell and lucidity. The prices or cost of resin depends on the grade of each resin thus making the product with more fragrant much more expensive than the product with a lesser fragrance. Unlike resin harvested during the summer and winter season, resin harvested during the monsoon season have more quality than they do.

Olibanum was grouped into five different categories by the traditional medical texts in India. These groups included colours such as grey, white, red, dark, and also golden a highly valued ingredient for medical preparations. "Dammar" is the exudates gotten from the family of different Burserceae and Dipterocarpaceae. Obtained from Canarium strictum, black dammar gotten was considered to be a low quality of variant on olibanum and belongs to the family of Burseraceae. In India black dammar is widely used for aromatic fumigation as an alternative of olibanum. It is used traditionally to cure skin diseases and also serves for skin lightening. The usefulness of Black dammar serves for plastic industries as it is an ingredient for rubber, varnish and wax. Oil is usually extracted from the seeds of *Canarium strictum* is used for cooking and lighting lamps. The six *Canarium* species found across India produces exudates that are locally used as incense. Vateria indica produces the exudates called white dammar, called Indian copal. It is a member of the Dipterocarpaceae family. White dammar is an ingredient of different traditional medicinal oils, and is used in treating leprosy and was also used in the production of incense sticks and candles. The Vateria indica contains about 25% fat which is known as Malabar tallow. The fat is also useful in the production of soap and candles. 'Sal dammar' is another useful dammar, obtained from the tree Shorea robusta. Oleogumresin is a category which frankincense belongs to and it contains oil, gum and resin. Frankincense contains essential oil (5-9%), alcohol soluble resin (65-89%), and water soluble gum. Steam distillation is a method to apply in order to separate the essential oil portion, and when alcohol is added to the portion that is left, the resin is obtained and the portion that is insoluble is separated as gum. While the gum is used in the production of textiles and incense sticks, the resin serves as an ingredient in the resin serves as an ingredient in the production of soap, varnish and paint industries. An alternative of the turpentine oil which is extracted from pine trees is this essential oil. The oil is essential for patients with respiratory issues as it helps ease difficulty in breathing; it is also a treatment for asthma and is useful in aroma therapy practice. Plant sources are primary in determining the composition of frankincense. The major ones of Boswellia sacra origin are monoter penoids alpha - pinene, limonene and myrcene along with sesquiter penoids, while boswellic acid, a triterpenoid is major constituent of the resin and is attributed to a variety of bioactivities. Several diterpenoids are present in the resin as well. Galactose, arabinose, xylose and uronic acid are the most significant carbohydrate constituent of the gum. Olibanum is an aromatic plant product obtained from a non-timber forest plant found in India. Many tribal communities in India are dependent on these forest produce for their daily income hence produce such as the Indian olibanum obtained from *Boswellia serrata*, white dammar obtained from *Vateria indica* and black dammar obtained from *Canarium strictum* are of great value to them. For small scale industries that process these raw materials, resin is a crucial raw material/ ingredient. In the production of torches resin and oils from obtained from seeds were of great worth and useful in lighting lamps. Taking into account the high oil yield and traditional use of these produce as a form fuels and looking at the scarcity of fossil fuel around the globe, these plants may be considered a means for biofuels (Herrmann et al. 2012).

#### 2.1.1 Boswellia serrata

Historically, plant products have been used as sources of shelter, medicine, food, flavor, and clothing. They have now been extensively used as fragrances especially natural resins. In antiquity, Indians of Hindu roots, Romans, Babylonians, Greeks, and other empires used these resins for cultural purposes. Burning of these resins in fire produced smells for ceremonial rituals (Qurishi et al. 2010).

*Boswellia serrata* is a specie of frankincense. The tree, which is moderately large (figure 2), grows in dry regions like India. The Burseraceae family (figure 3) comprises 17 genera and 600 species. The first specie grown in Arabia is *Boswellia sacra* Flueck. *Boswellia carterii* Birdw is the Somalia specie.

The sources in India include Gujarat, Chhattisgarh, Jharkhand, Madhya Pradesh, and Andhra Pradesh. *Boswellia serrata* is obtained from the tree trunk with a semi-solid gym resin. It is stored in a bamboo basket for about 30 days. This period sees a fluid, known locally as 'ras', continuously flowing out. The resin slowly hardens, producing an aromatic smell, and its impurities are removed. The final product is graded into four

categories according to flavor, colour, shape, and size. The categories are Superfine, Grade I, Grade II, and Grade III.

A gummy oleo-resin is found under the bark of the Boswellia serrata tree. Representing almost 45% of the oil,  $\alpha$ -pinene is the major component of the hydro distilled colourless essential oil of *Boswellia serrata*. Based on finding from past investigations, the oil is said to be made up of a major constituents which include:  $\alpha$ -thujene (12%),  $\alpha$ pinene (8%), sabinene (2.2%),  $\beta$ -pinene (0.7%), myrcene (3.8%),  $\alpha$ -phellandrene (1%), pcymene (1%), limonene (1.9%), linalool (0.9%), perillene (0.5%), methylchavicol (11.6%), methyleugenol (2.1%), germacrene D (2.0%), kessane (0.9%), cembrene (0.5%) and cembrenol (1.9%). A monoterpene 5.5-dimethyl-1-vinyl-bicyclo- hexane (2%) and two diterpenoid components, m-camphorene (0.7%) and p-camphorene (0.3%), were isolated and identified from the essential oil of Boswellia serrata. Its resinous product contains monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids, as well as four major pentacyclic triterpenic acids responsible for the suppression of pro-inflammatory enzymes. These acids include the  $\beta$ -boswellic acid, acetyl- $\beta$ -boswellic acid, 11-keto- $\beta$ boswellic acid, and acetyl-11-keto-β-boswellic acid. Out of these four boswellic acids, acetyl-11-keto-β-boswellic acid is the most potent inhibitor of 5-lipoxygenase, an enzyme responsible for inflammation. In *Boswellia carterii* and *Boswellia sacra* α-pinene, limonene and  $\beta$ -caryophyllene are the major constituents. *Boswellia serrata* is dominated by  $\alpha$ -Thujene (Siddiqui, 2011).



Figure 2. Boswellia serrata from the trunk of a tree (Siddiqui, 2011).



Figure 3. Burseraceae tree ("Boswellia Serrata," 2015)

*Boswellia Serrata* is known as *Boswellia carterii* (figure 4) in some places. It exudes the resin of the Boswelia tree from the tree bark which is cut to allow a white, milky resin to flow. Researchers such as Wang et al. (2011) found out that the most studied oils of olibanum is the *Boswellia carterii* essential oil. Octyl acetate is the main component of the oil resin, with 60% predominance in the oil. The pale yellow oil is the hydrodistillate of *Boswellia craterii* with its major constituents made up of α-thujene (1.7%), α-pinene (10.9%), camphene (1.0%), sabinene (0.7%), β-pinene (0.7%), myrcene (0.5%), hexylacetate (0.3%), p-cymene (1.4%), Z-β-ocimene (0.4%), E-β-ocimene (1.7%), limonene (1.5%), 8-cineole (1.2%), 1-octanol (11.9%), linalool (2.1%), α-pinene epox-ide (0.5%), trans-verbenol (0.4%), terpinene-4-ol (0.4%), octyl acetate (39.3%), bornylacetate (2.2%), geranylacetate (0.4%), *E*-nerolidol (0.2%), cembrene A (2.1%), cembrene C (0.1%), verticilla-4(20),7,11-triene (6.0%), incensole (1.0%) and incensole acetate (2.3%). Diterpenoid constituents and octyl acetate were found to be present in the extract called with a little amount monoterpenoid constituents.



Figure 4 Boswellia carterii (Frankincense, 2019)

#### 2.2 Boswellia resin

The frankincense product has four different types of proteoglycans and glyco. Major components of the water-soluble poly-meric substances from the resins of *Boswellia carterii* and *Boswellia serrata* are classical arabinogalactan proteins. These proteoglycans are basically made up of D-galactose units in the core chains, which are highly branched at positions 3 and 6. Uronic acids, glucuron-ic acid, terminal 4-O-methyl-glucuronic acid and the arabinose are in the side chains. In the polymer group, there are high contents of fructose, mannose and glucosamine are in the polymer group showing that glycoproteins occurs. This contains L-arabinose and D-galactose. The protein parts are made of two hydroxyproline and serine which are amino acids. *Boswellia serrata* has a higher protein content than *Boswellia carterii* (Camarda et al. 2007).

#### **2.3 Essential Oils**

Frankincense essential oils are used in aromatherapy (also called essential oil theraphy). Aromatherapy uses plant extracts for therapeutic purposes. The oils are sourced from the frankincense species. Their natural ingredients include pinen, sclarene, thunbergol, octanol, octy formate, decyl acetate, O-methylanisole, verticiol, and 9-cisretinal (figure 5).



Figure 5. Chemical structures of Boswellia essential oil ingredients (Ben-Yehoshua et al. 2012)

#### 2.4 Frankincense Extracts and Gums

Extracts and gums from the stem bark of frankincense species from India are applied in the treatment of various diseases. The gums exude from the stem bark of *Boswellia serrata*. The other constituent called Boswellic acid has anticancerous, anti-inflammatory, and, anti-ulcerous activities. The inflammation pathway contains kinases, toposiomerase I and II, 5-lipoxygenase, leukotriene (inflammatory chemical messengers), and human leukocyte elastase, (Poeckel and Werz 2006). Studies focusing on finding out if a cardio protective effect can be offered by gum resin extract interrupting complex interactions. Based on information gathered, antithrombotic properties have never been in *Boswellia serrata's* gum resin. The initiation of thrombocytes function means there is a

chance for stopping thrombosis. Anticoagulant and antithrombotic drugs such as heparin have been used. With the long-term effects that come with the use of heparin, drugs used as its alternative drugs are on high demand. In India, Ayurvedic medicinal plant is a system used with *Boswellia serrata*. Pentacyclic triterpenic acids are in the Ayurvedic plant and possess the several pharmacological activities. In spite of the medicinal compound of the BAs their activities are restricted because of the low aqueous solubility following its nature which results in a poor bioavailability (Shen and Lou 2008).

#### 2.5 Health and Benefits of Frankincense

Anti-inflammatory effects are revealed in frankincense and its ingredients act against immunological diseases. Data are provided and are meant give a firm reason to trust the clinical trials conducted. There has been an isolation of numerous phytochemicals which includes the boswellic acid type, triterpenoids, and non-terpenoids. The development of pharmaceutical drugs has been drawn from semisynthetic derivatives. The outcome of anti-inflammatory have not only been carried out in vitro, it has also been in several in vivo studies, showing this can be transferred. Frankincense and its phytochemicals have shown favorable results towards inflammation-related diseases through using animal models (Governa et al. 2018).

One of the physical changes seen was the reduction of oxidative stress. The production of reactive oxygen species and membrane lipid peroxidation were reduced by a reactive nitrogen species (RNS) (Mbiantcha et al. 2018). The immune system decreased in some regard. Some of which involved mast cell, T-effector cells, T-regulatory cells, and granulocytes. Hepatic symptoms, serum lipids, blood glucose, and atherosclerotic plaques were also affected (Henkel et al. 2012).

#### 2.5.1 Anti-bacterial activity

*Boswellia carterii* and *Boswellia serrata* acid fractions are characterized by high antibacterial activity. *Boswellia serrata* showed a higher activity. A large inhabitation zone against *Proteus vulgaris* was shown by the *Boswellia serrata* aqueous extract. Phenolic acid in Boswellic acid is thought to have resulted in its anti-bacterial resin properties. The effectiveness of energy and protein is enhanced by phenolic compounds (Patel et al. (2012).

This occurs through the reduction of competition for microbes with the host for nutrients. Antibacterial activities of Boswellic acids from *Boswellia serrata* tested in vitro on a clinically significant panel of oral bacteria. Of all four Bosewllic acids acting against all bacterial pathogens, the most effective was Acetyl-keto-boswellic acid (AKBA) (Akihisa et al. 2006).

#### 2.5.2 Anti-arthritic activity

Traditional medicine has been used to treat arthritis. Some of the drugs are steroids and no steroidal anti-inflammatory drugs (NSAIDs). Others are interleukin-1 beta antagonists (IL-1 $\beta$ ), and tumor necrosis factor alpha (TNF- $\alpha$ -). Extract of *Boswellia carterii* gum resin mixed with acetone reduced arthritis. It TNF- $\alpha$ - and IL-1 $\beta$  in rats (Fan et al. 2005). Another study involving 30 osteoarthritis patients decreased knee pain and allowed them walk. The swell in the joints also reduced. Prescriptions of Boswellia extract is offered to such patients (Kimmatkara et al. 2003).

#### 2.5.3 Anti-cancer activity

The activities of Boswellic acid and its derivatives include antitumour, anticarcinogenic, and antihyperlipidemic. These constitute the methanol extract of *Boswellic serrata*. The trepertinoid acids are isolated and characterized using antiproliferative effects (Van Vuuren el al. 2010).

Isolated compounds and oleogum resin extracts have been used in such studies. Extracts and phytochemicals from frankincense species showed their cytotoxicity in cancer cell lines both in vivo and in vitro. This gave a possibility of beginning to explore these extracts as potential agents in drugs fighting cancer just like synthetic ones.

The phytochemicals work in opposition in a wide array of strong carcinoma and sarcoma including those of fibers, breast, prostate, liver, cervix, lung, pancreas, and liver. Others are in hematopoietic tumors (myeloma and leukemia), meningioma as well as glioblastoma. The inhibition of tumour growth remains a very unique in vivo quality of frankincense (Xia et al. 2017).

The gum resin of *Boswellia sacra* has a chemotherapeutic quality. This is derived from its hydro-distillate. It functions to prevent attacks on urothelial cell carcinoma. Results from experiments show that this is potent in human leukemia cells. It decreased cell growth, proliferation, and angiogenesis. (Ranjbarnejad et al. 2017).

#### 2.5.4 Anti-microbial activity

Essential oil gotten from resins of *Boswellia carterii* has been effective in microorganisms of fungi, bacteria (gram-positive and gram-negative). An activity test was conducted in vitro with AKBA, although limited to gram-positive, proving to be the most effective inhibiting agent against pathogens. Also, the outside membrane of lipophilic acid with its lipopolysaccharides and hydrophilic barrier serves as a potent guard against hydrophobic compounds. It is suggested that gram-negative bacteria's resistance against AKBA is important (Rahimi et al. 2010).

Biofilms are multilayered cells made up of *Staphylococci* making them difficult to be altered. Biofilms are resistant against antibiotics which makes them infectious. Conversely, AKBA inhibits staphylococcal biofilm by reducing its performance. Thus, AKBA can cause a reduction in the production *Staphylococcus aureus* and *Staphylococcus epidermidis*. This makes AKBA the most effective compound against pathogens gram-positive bacteria (Raja et al. 2011).

Boswellic acid was also found to have antimicrobial activity in oral cavities. In this, AKBA was also the most effective antibacterial and thus has been adapted as a component of mouthwash products to prevent and treat oral infections (Raja et al. 2011).

#### **2.6 Inflammatory Diseases**

The body tissues respond to pain, swelling, redness and loss of function in several ways (figure 6). These result from infections, immune disorders, injuries, and irritations. These changes may be in form of oxidative stress or inflammation (Ammon 2006).

Inflammation is as a result of small chemicals called mediators produced by body cells. They cause migration of cells to Leukotriene. They also promote free radicals, cell adhesion, and autoimmune reactions (Birkner 2006).

Leukotrienes cause inflammations leading to psoriasis, arthritis, asthma, rheumatism, and colitis. Boswellia inhibits leukotriene by blocking its synthesis and shrinking inflamed tissues resulting in pain and discomfort (Siemoneit et al. 2011).

Frankincense has shown therapeutic characteristics against diseases. Studies conducted both in vitro and in vivo, showed pharmacological activity against inflammation and tumors. It was also observed that gingivitis was effective against inflammation of periodontium. Extracts and powders of frankincense resulted in reduction of these effects (Khosravi Samani et al. 2011).

#### 2.7 Controlled Release of Drugs

Drugs are channeled to required tissues by a system known as controlled drug delivery. In experiments involving frankincense a drug embedded matrix was applied to direct tablets. There was a need for safety and efficiency. This was in spite of various matrix and polymers used. The goal was to control and improve bioavailability of the drugs (Chowdary and Reddy 2012).

The controlled release of natural resins, nifedipine, and colophony were used and resulted in gradual and spread of drugs in 24 hours. Olibanum, used for microencapsulation, was the most suitable resin (Chowdary et al. 2009).



Figure 6. Anti-inflammatory changes elicited by Frankincense (Efferth and Oesch 2020)

Olibanum was also used as an agent in natural lipophilic polymer. Its resins were also used for other drugs such as carbamazepine and diclofenac. Drug release decreased as the concentration of the resin increased (Rao et al. 2009).

#### 2.7.1 Preparation and dosages

There are various methods for drug administration including rectal, oral, and parenteral. For frankincense studies, the oral method was preferred. Drugs in form of capsules or tablets were prepared using diluents such as lubricants, binding, disintegration, and wetting agents.

Injections are administered intramuscularly, intravenously, intra-arterially or subcutaneously. Preparations in single or multiple doses can be in form of suspensions, emulsions or solutions. The dosage of Boswellia is difficult to ascertain but a 300-400mg to be taken thrice a day is generally recommended. (Siddiqul 2011).

#### 2.7.2 Safety

Frankincense continues to be used as a remedy for diseases. The anti-inflammatory effects of Boswellia appears to have the least negative effects when compared to other anti-inflammatory chemical drugs. It does not adversely affect respiration, heart rate, or blood pressure. Its resin is also of low toxicity. It has been endorsed as a food additive by the United States Food and Drug Administration (USFDA).

It is sold in the market where oral preparations of *Boswellia serrata* extract containing AKBA can be bought over the counter. Clinical examinations show that it has high tolerance and minimum side effects of rheumatoid arthritis and CD. When taken in the right dosages, it is very safe (Siddiqul 2011).

#### 2.8 Psychoactivity of Frankincense

Many plants have been used in mythological, religious, and cultural customs. Some of them have essential roles. A few are *Salvia divinorum*, *Nicotiana tabacum*, *Aryan soma*, *Cannabis sativa*, *Ipomoea violacea*. The psychoactivity of frankincense has not been a recent study. It was recognized in the first century C.E. by Dioscorides who said it causes insanity. Also, it was given to prisoners in Jewish Talmud to make their senses numb and in Ethiopia for its calming effect. (Moore 2006).

Assays were used in experimental studies to examine the physiological, behavioral, and pharmacological examination of Incensole acetate (IA). Mice models were used to examine the anti-depressive and anxiolytic quality of frankincense (Moussaieff et al. 2008).

Transient receptor potential (TRP) channels which has a sub-family called TRP vanilloid (TRPV) is made up of six groups: TRPV1-TRPV4. It produces varying temperatures that measure the psyoactivity of frankincense (Petit-Demouliere et al. 2005).

A range of 31–39°C was used for TRPV3 causing warmth feeling resulting in the activation of chemical agents that are found to be agonists (Moqrich et al. 2005).

#### **3. MATERIALS AND METHOD**

#### **3.1 Systematic Search**

The first step was to conduct a literature search. This was done over the course of one week using the following databases: Science, PLOS One, TOPNET, Google Scholar, and Elsevier. The search process was organized and performed in a structured and preplanned way by considering search terms, selection of resources (including databases), choice of search methods, and reflecting on the search results obtained during the process. Advanced researched works spanning the 21st century from 2001 to 2020 were considered. The search language was English. This was applied across board.

The layers of keywords focused on were: (1) frankincense species and essential oils (2) keywords for frankincense in disease therapy such as cancer, diabetes, anti-inflammatory disease (3) side effects of frankincense.

In applying this systematic way, there was a greater chance of avoiding disparities and selection bias. It also allowed the identification of gaps in existing research and minimizing the reproduction of already existing research.

The search for the primary indicator (frankincense essential oils) was performed on the search bar. The second indicator was searched in title, abstract, keywords, and introduction. The "press" checklist was used as it is the most prominent and it aims to develop evidence-based guidelines to peer review of electronic search strategies.

Key texts were identified based on the research objective and their accessibility and prominence within the Near East University systematic reviewing practice. Several guidance documents were identified. These documents provide guidance for different types of reviews including interventions, technologies, qualitative research studies, and therapeutic topics.

#### 3.2 Inclusion Criteria

Publications that met the criteria of search strategy were downloaded in pdf format, studied, and reviewed by the student. The primary sources were are identified based on the question, related keywords and appropriate range of publication years. The summary of studies was presented in a logical flow using themes. This was succinct and adequately represents the reviewed literature/knowledge based on the topic.

Summaries/paraphrasing of material (direct quotes of content used only for specific purposes and referenced appropriately) was done. After that critical review of study methods, outcomes and applicability was done.

To form a coherent study, there was an assessment of study quality, using accepted review 'criteria' to analyze strengths, weaknesses or limitations and conflicts or gaps in information. This helped to link studies together and form a new and logical whole.

#### **4. DISCUSSION**

The application of frankincense in inflammatory diseases has gained recent traction especially in chronic cases. In Atherosclerosis, which occurs when plaques build up in blood vessels and hardens the arteries, inhibition of nuclear transcription factor-kappa B (NF- $\kappa$ B) by AKBA has been of therapeutic use. This method could be further developed. (Cuaz-Perolin 2008).

In non-modern medicine, frankincense has its importance as an agent for respiratory improvement. It has been applied in stem inhalations and baths. In this regard, it has been used to treat and manage catarrh, cough, asthma, and bronchitis. In asthma, leukotriene biosynthesis is inhibited by Boswellic acids. This reduces and prevents inflammation. In some cases, 70% improvement was recorded in patients. Physical symptoms like breathing difficulty and rhonchi was seen to have either reduced or completely disappeared. This research used the gum resin of *Boswellia serrata* to treat bronchial asthma (Nusier et al. 2007).

Extract of *Boswellia serrata* has also been used to reduce skin diseases such as redness, irritation, and skin tone. In China, it has been used to treat bruises and sores. The pentacyclic triterpene structure provides a delicate effect on irritated skins. *Boswellia serrata* extract is dissolved needs to be dissolved or dispersed in either fatty acids or alcohols. It is then added with other derivatives. These include those that enhance skin or hair protection and ensure the product is stabilized. This is needed to prevent side effects (Qurishi et al. 2010).

Inflammatory bowel diseases result from chronic diseases of the intestine such as UC and CD. In many cases, the actual cause of IBD remains elusive. However, two factors seem to contribute. First is a genetic or environmental factor. The second is an abnormal gastrointestinal (GI) tract luminal factor. Some are microorganisms, oxidative stress elements, and defects in the intestine. The role of leukotriene cannot be ignored in chronic inflammatory diseases. This is enhanced by Boswellic acids. They are gum resins have a

characteristically specific, and non-competitive inhibitors of the important enzyme of leukotriene called 5-lipoxygenase (Rahimi et al. 2010).

In chronic colitis, which affects the inner lining of the colon, the gum resin of *Boswellia serrata* has been of therapeutic value especially in Traditional Iranian medicine (TIM). The oleogum resin of *Boswellia serrata* and *Boswellia carterii* reduces inflammation to a significant level. The effect has shown to possess other qualities against ulcer, wound, and diarrheal. A dosage of 350 mg of *Boswellia serrata*, which was administered for three times a day for 6 weeks, showed an 80% remission in patients with ulcer colitis (Shehata et al. 2011).

Brain tumor is a disease in which cancerous tumors take over the brain. As they grow fast and malignant, they surround the brain's tissues. Surgical procedures are used to remove the tumor. However, different factors such as the type, location, and size of the tumor makes this process difficult and mostly impossible. Even a surgical and radio-therapeutic treatment only gives the patient 9 months to live. Very active leukotriene and other inflammatory mediators are formed in the brain and surrounding tumors in these patients. Thus frankincense can be used to attack the leukotriene. (Simmet et al. 2001).

In some patients, the resin of *Boswellia serrata* has been used to treat brain tumor. Or 7 days, there was a 22-48% reduction in peritumoral brain edema. Patients who were not treated showed an increase in 2 weeks (Estrada et al. 2010).

Diabetes mellitus, which shows high blood sugar level over a prolonged period of time, has also been studied with frankincense. Oral administration of aqueous extracts from leaves and roots reduced the blood glucose level. Furthermore, over 28 days there was a reduction in levels of cholesterol, triglyceride, creatinine, and urea. (Kavitha et al. 2007).

Type I diabetes causes beta cell death and insulin problems. *Boswellia serrata* has been used to target mediators relating to this disease. The anti-diabetic effects of the extract can be a defense against diabetes organ complications (Ahmadpour et al. 2012).

Triterpenoids is gotten from Oleogum resins. Synthesis of DNA, RNA, and protein were inhibited in human leukemia (HL-60) using gum resin of *Boswellia serrata*. The most inhibition was caused AKBA. DNA synthesis was observed to be irreversible. There was no influence on cell viability (Alam et al. 2012).

According to studies, boswellic acids are potent apoptotic agents to cancer cells. In six human myeloid leukemia cell lines the boswellic acid acetate through a mediated pathway seems to induce apoptosis which is through the induction of the death receptors 4 and 5 is activated (Xia et al. 2005). AKBA anticancer activity to the inhibitory effect on the lipoxygenases which leads to the inhibition of cell proliferation and induction of apoptosis in tumor cells (Raja et al. 2011).

*Boswellia serrate* inhibits the proliferation of prostate cancer cells. This is largely due to the presence of pentacyclic triterpenoids. AKBA also prevents the growth of factors such as vascular endothelial. This inhibits cancer growth. Tirucallic acid, extracted from oleogum resin of *Boswellia carterii*, is also an effective inhibitor. It applies its cytotoxic effect on human prostate cancer cell lines in vitro and in vivo. Akt, a serine/threonine protein kinase, plays a vital role in several cell processes. These include proliferation, transcription, apoptosis, and migration. (Siddiqul et al. 2011).

It has been thought overtime that frankincense improves both learning and memory especially in the elderly and pregnant women for their offspring (Hosseini et al. 2010). During gestation period, aqueous extract of *Boswellia serrata* was administered. It showed a significant increase in learning at post-learning stage (Sharifabad et al. 2004)

A part of the brain called Hippocampus is important in learning and memory. In rats whose mothers were treated with *Boswellia serrata* extracts, there was an expansion of their terminal dendritic branches. This is important as it serves as a means for information transfer. The control group did not show this expansion. The increase of hippocampal neurons in cornu ammonis is due to improved learning and memory performance in these offspring. This opens an avenue for studying the neurophysiology and future of frankincense in brain diseases (Sharifabad and Esfandiari 2007).

#### **5. CONCLUSION**

The use of frankincense for therapeutic purposes continues from ancient times and now in modern medicine. The traditional use gives vital information for its bioactivity. However, modern medicine needs scientific evidence to establish this. This would help move its discussion from an experienced-based medicine to a more durable evidencebased one.

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