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Chemistry, Pharmacology and Medicinal Property of Frankincense (Boswellia Species): From the Selection of Traditional Applications to the Novel Phytotherapy for the Prevention and Treatment of Serious Diseases

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Abstract- Frankincense, the resinous extract from the trees of the genus *Boswellia*, has been used for centuries in ceremonial, cosmetic, cultural and as a traditional medicine to treat a variety of ailments especially inflammatory diseases including asthma, arthritis, cerebral edema, chronic pain syndrome, chronic bowel diseases, cancer and some other illnesses. Boswellic acids are the active compounds of frankincense and AKBA (3-O-acetyl-11- keto-β-boswellic acid) is the most important and effective acid among them. Some studies have shown that the use of frankincense can also improve the learning and enhance the memory in animals and human. It seems that frankincense might have a potential ability to be used as an alternative natural medicine not only for chronic and inflammatory diseases but also for the patients with brain and memory disorders.

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I. INTRODUCTION

Frankincense is a French word, meaning “pure incense”. It is popularly known as Indian olibanum, Salai guggal, Loban, or Kundur. It has been used as an incense and fumigating preparation for religious rituals, in cultural ceremonies and as a traditional remedy for treating various diseases.^[1] The oleogum resins are secreted by trees of the *Boswellia* species which are tropical, deciduous trees and usually grow as small trees or shrubs with the limited natural growing range.^[2] The growing of the trees has been extended by cultivation to meet the worldwide demand.^[3] The resin is obtained by making scrapes in the trunk of the various *Boswellia* species (Burseraceae), and later collecting the dried resin gums from the trees.^[2,4] The good quality of resin is produced only for three years and after this period, the quality of collected resin decreases

significantly, then the tree should be left to rest for some years after the harvesting period.^[5]

Olibanum is produced mainly by four species from different regions such as *Boswellia serrata* from India, *Boswellia carterii* from East Africa and China, *Boswellia frereana* from Northeast Africa (Somalia) and *Boswellia sacra* from Middle East.^[6,7] Today the most traded frankincense is produced in Oman, Yemen and Somalia.^[3]

Since ancient times, Frankincense has been used in many countries such as Africa, China, India and Middle East countries for the prevention and treatment of various illnesses especially chronic inflammatory diseases.^[2,8] In Indian system of medicine, Frankincense (salai guggal) has been used as an anti-inflammatory, anti-arthritic, anti-proliferative and analgesic agent for the treatment of related diseases.^[9] In Traditional Chinese Medicine (TCM), frankincense of *Boswellia carterii* is commonly used as a remedy for improving blood circulation and as relieving pain in leprosy, gonorrhoea and cancer patients.^[10]

In the last decade, the use of olibanum has become more popular in European countries for the treatment of variety of chronic inflammatory problems such as arthritis, chronic bowel diseases, asthma, peritumoral brain edema and other diseases.^[11]

The mechanism of anti-inflammatory activity of the *Boswellia* extract is due to the boswellic acids which are the active principals of frankincense. The chemical structure of boswellic acids closely resembles steroids,^[9] which their actions are different than painkillers or NSAID (non-steroid anti-inflammatory drug) and is related to the component of the immune system and the inhibition of 5-lipoxygenase.^[11]

II. COMPOSITION

There are many different compounds found in a variety of *Boswellia* species.^[11] The composition of the essential oil and other contents changes from species to species, and differs depending on the climate, harvest conditions and geographical locations.^[11,12]

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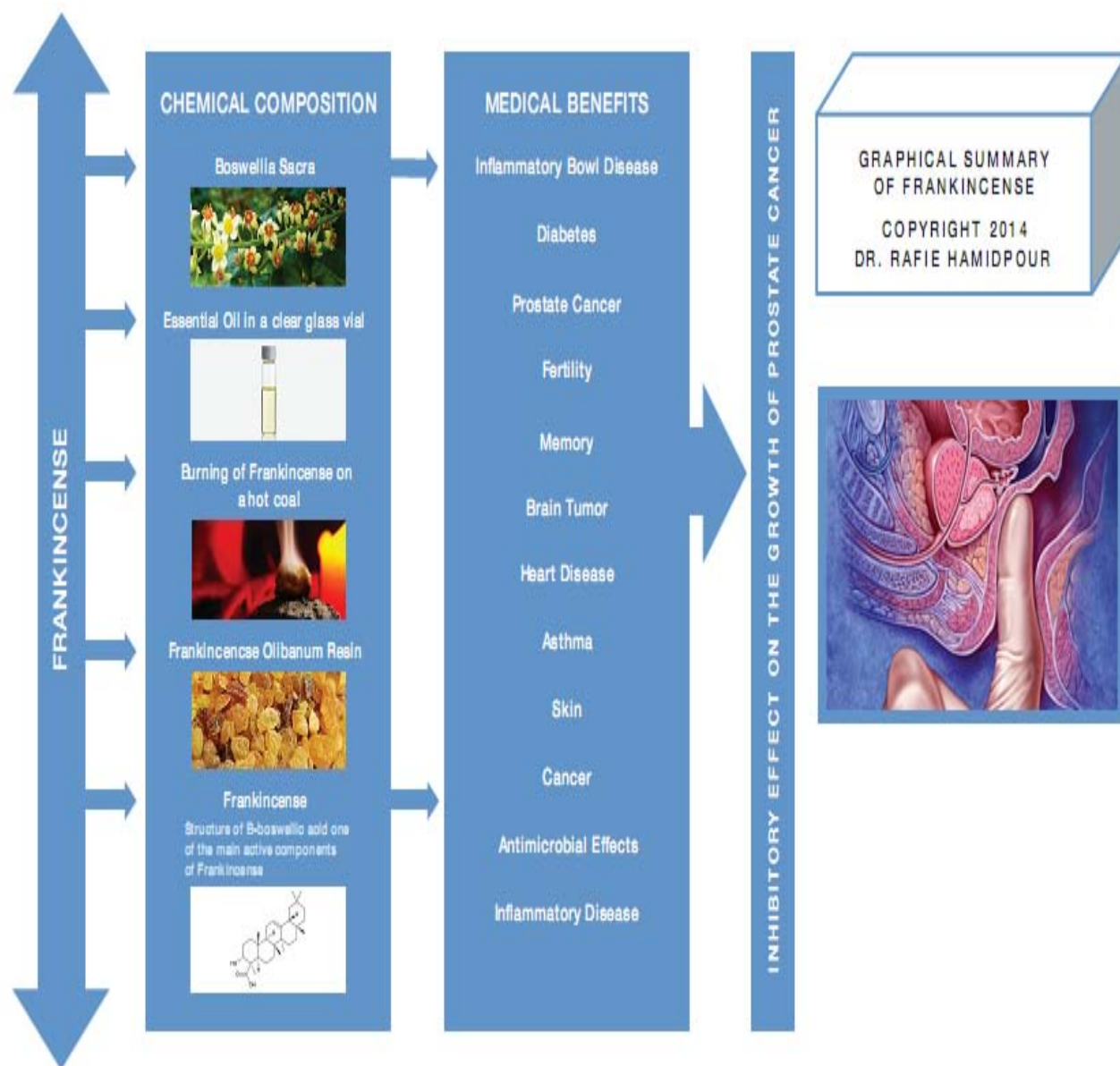
Frankincense is reported to contain 60-85% resins (mixtures of terpenes), 6-30% gums (mixture of polysaccharides) and 5-9% essential oil. [13] Resin portion is composed of pentacyclic triterpenes which boswellic acid is the active functional group. [14] Gum portion is consisting of pentose and hexose sugar with some oxidizing and digestive enzymes. The essential oil is the mixture of monoterpenes, diterpenes and sesquiterpenes. [14]

In a study was reported that the resinous part of *Boswellia serrata* contains terpenes: monoterpenes (α -thujone); diterpenes (macrocyclic diterpenoids such as incensole, incensole oxide, iso-incensole oxide, a diterpene alcohol [serratol]); triterpenes (such as α - and β -amyryns); pentacyclic triterpenic acids (boswellic acids); tetracyclic triterpenic acids (tirucall-8, 24-dien 21-oic acids). [5]

Boswellic acids with the molecular formulas of $C_{32}H_{52}O_4$ are the main active component of

frankincense. [12] The four major boswellic acids (pentacyclic triterpenic acids) found in frankincense are: β -boswellic acid (BA), acetyl- β -boswellic acid (ABA), 11-keto- β -boswellic (KBA) acid and 3-O-acetyl-11-keto- β -boswellic acid (AKBA) which they have shown to be responsible for the inhibition of Pro-inflammatory enzymes. [5] Among these four boswellic acids, acetyl-11-keto- β -boswellic acid (AKBA) is the most important inhibitor of an enzyme called 5-lipoxygenase which is responsible for inflammation. [5]

AKBA has shown to be effective against a large number of inflammatory diseases such as arthritis, bronchial asthma, chronic colitis, ulcerative colitis, Crohn's disease and cancer. [15] The mechanism of the action is due to the binding of AKBA to 5-lipoxygenase in a calcium-dependent and reversible and act as a non-redox type, none-competitive inhibitor. [16]



III. INFLAMMATORY DISEASES

Inflammation, generally is the response of the body tissues to irritation, injuries, infections, or disorders of the immune system (auto-immune diseases), which is characterized by pain, redness, swelling and sometimes loss of function.^[11]

Leukotrienes are small mediator chemicals produced by cells in the body which can cause inflammation by promoting free radical damages, autoimmune responses, cell adhesion, and migration of the inflammatory producing cells to the inflamed area.^[17]

Many inflammatory diseases can be caused by leukotrienes including asthma, colitis, rheumatism, arthritis and psoriasis.^[17] Boswellia has shown to be the specific inhibitor of leukotrienes. Boswellia acts by blocking the synthesis of leukotrienes and therefore inhibiting the inflammation and shrinking the inflamed tissue which is the primary cause of pain and discomfort in many cases.^[17]

Frankincense has shown to be effective in treating various inflammatory diseases and based on data obtained from the experiments done in vitro and vivo, boswellic acids are assumed to be the pharmacological active principals of frankincense which are responsible for the anti-inflammatory and anti-tumorigenic actions.^[18] In a study the anti-inflammatory effects of the extracts and powder of frankincense on the plaqueinduced gingivitis showed the improvement of inflammation of periodontium after using the extract and powder of the frankincense.^[19]

a) Heart Disease

Frankincense, the oleogum resins of Boswellia species have been used in traditional medicine for the treatment of various inflammatory diseases and today they are used as a complementary and alternative medicine for the treatment of some chronic inflammatory diseases.^[20]

Atherosclerosis is the build up of plaque on the inside of blood vessels, causing the hardening of the arteries. Atherosclerosis is the major cause of coronary heart disease and it has been found to be linked with inflammation.^[20] All the data clearly indicates that AKBA reduces chronic inflammation through the inhibition of NF- κ B (nuclear transcription factor) system which is a very important factor in developing and progress of chronic inflammatory diseases.^[20] Therefore therapeutic approaches targeting this transcription factor to treat chronic inflammation in atherosclerosis could be developed.^[20]

b) Asthma

Frankincense traditionally has been valued for its effect on the respiratory system and has been used in steam inhalations, baths and massages to treat cough, catarrh, bronchitis, and asthma.^[9] Boswellic

acids found in frankincense have shown to be responsible for the inhibition of leukotrienes biosynthesis and therefore can reduce and prevent the inflammation in many chronic inflammatory diseases like asthma.^[21] In a study several patients with chronic bronchial asthma were treated with the Boswellia serrata preparation of 300 mg thrice daily for a six-week period. The improvement of the disease was obvious for 70% of the patients by disappearance of physical symptoms and signs such as dyspnoea (Difficulty in breathing), rhonchi (hissing lung sound) and number of attacks. The data show a definite role of gum resin of Boswellia serrata in the treatment of bronchial asthma.^[21]

c) Skin

Studies have shown that the presence of Boswellia serrata extract reduces the redness and irritation in the skin and produces an even skin tone.^[22] In China frankincense has been used as skin remedies for bruises and infected sores.^[4] The extracts of Boswellia family have shown to have a soothing effect for irritated skin and that is caused by the pentacyclic triterpene (steroid-like) structure shared in different Boswellic acid compounds.^[22]

To allow for easy incorporation of the extract of Boswellia, containing the boswellic acids and its derivatives, the extract needs to be dissolved or dispersed in a suitable carrier such as fatty alcohols, or fatty acids which help to incorporate the extract or acid into compositions suitable for use on skin or hair and improves the stability of products containing the extract.^[22] In addition, Acetyl-11-keto- β boswellic acid (AKBA) is reported to be an effective topical agent to soften facial lines and relax the skin.^[16]

IV. INFLAMMATORY BOWEL DISEASE

Inflammatory bowel diseases (IBD) refer to the inflammation of intestines and relate to two chronic diseases, ulcerative colitis (UC) and Crohn's disease (CD). Although the exact cause of IBD is still not clear, but two factors are considered to be effective in occurring the disease. First is the immune dysregulation which is caused by genetic or environmental factors and second is abnormal gastrointestinal tract luminal factors such as microorganisms of GI tracts, oxidative stress, and defects in the GI mucosal barrier which allows the penetration of luminal factors into mucosa.^[23]

The leukotrienes play an important role for keeping inflammation active in chronic inflammatory diseases of the colon such as ulcerative colitis. Boswellic acids, which are the active ingredients of the gum resin of Boswellia species have been shown to be specific, non competitive inhibitors of 5-lipoxygenase, the key enzyme of leukotrienes.^[24,25]

The preparation of the gum resin of Boswellia serrata has shown to be effective in the treatment of chronic colitis with the smallest amount of side

effects.^[24] In traditional Iranian medicine (TIM), oleogum resin of *Boswellia serrata* and *Boswellia carterii* is known for reducing the inflammation and one of the efficacious remedy for the treatment of IBD. In addition to anti-inflammatory effects, *Boswellia* has shown to have wound healing, antiulcer, and anti-diarrheal properties too.^[23]

In a study, was found that the use of the gum resin of *Boswellia serrata* was effective to induce the remission in about 80% of the patients with ulcer colitis grade II and III, when was applied 350 mg three times a day over period of six weeks. The study suggests that the effectiveness of frankincense if is not better, at least is similar to the treatment with sulfasalazine which is a chemical drug used in the treatment of inflammatory bowel diseases.^[25]

a) Cancer

Plants are rich sources of antitumor compounds. Oleogum resins from various *Boswellia* species contain triterpenoids with antitumor properties.^[26] In a report, the anti tumor activities of the four triterpenic acids (BA, ABA, KBA and AKBA) isolated from the gum resin of *Boswellia serrata* were studied and it was found that these acids inhibited the synthesis of DNA, RNA and protein in human leukemia HL-60 cells in a dose dependent system. Among them AKBA induced the most pronounced inhibitory effect on DNA, RNA and protein synthesis in which the effect on DNA synthesis was found to be irreversible. This compound significantly inhibited the cellular growth of HL-60 cells, but did not affect cell viability.^[24]

The studies have shown that boswellic acids are potent apoptotic agents to cancer cells. The boswellic acid acetate seems to induce apoptosis in six human myeloid leukemia cell lines through a Caspase-mediated pathway which is activated by the induction of the death receptors 4 and 5 (DR4, DR5).^[27] The anticancer activity of AKBA is attributed to the inhibitory effect on the lipoxygenases leading to the inhibition of cell proliferation and induction of apoptosis in tumor cells.^[15]

b) Prostate Cancer

It has been shown in several studies that pentacyclic triterpenoids found in *Boswellia serrata* have inhibitory effect on the growth of prostate cancer cells.^[26] Among boswellic acids, Acetyl-11-keto- β -boswellic acid (AKBA) has special inhibitory effect in prostate cancer by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis.^[5] Also tirucallic acids isolated from the oleogum resin of *Boswellia carterii* work as an effective Akt inhibitors which apply cytotoxic effects in human prostate cancer cell lines in vitro and vivo.^[26]

Akt is a serine/threonine protein kinase which has an important role in multiple cellular processes such as cell proliferation, apoptosis, transcription and cell

migration. Akt1 has been associated as a major factor in many types of cancer since it can block apoptosis and promote the survival of the cell.^[26]

c) Brain Tumor

Brain cancer is a condition in which malignant tumors develop within the brain. These tumors are fast growing and invade surrounding tissues. The surgical removal of brain tumors is a hard and detailed procedure and in many cases the complete removal of the tumor is not possible because of the size, type and location of the tumor. For these reasons, the average survival of brain tumor patients is only about nine months even after the treatment of surgery and radiotherapy are combined.^[28] In addition the use of chemotherapy is able to prolong the survival of only about 10% of the patients.^[28] In patients with malignant brain tumors, highly active forms of leukotrienes and other inflammatory mediators are produced in the brain and around tumors, causing localized fluid build-ups and damages to the healthy nerve cells.^[29]

The impact of *Boswellia serrata*, with its anti inflammatory effect has been studied in patients with brain tumors.^[29] An ethanolic extract from the gum resin of *Boswellia serrata* contains the boswellic acids which the study have shown after the application of this preparation which is called phytopharmacon H15 for the period of seven days a reduction of the peritumoural brain edema of 22 to 48% was observed. In contrast to the cells of untreated patients, the cells of the treated tumor tissue show no tendency to proliferate within two weeks.^[28]

The report on patients with malignant glioma showed that the use of 3600mg/ day of *Boswellia* extract (60% boswellic acids), seven days prior to surgery caused decrease of the fluid around the tumor with average of 30% in 8 of the 12 patients and the signs of brain damage decreased during the treatment.^[29] Recently the detailed study in patients with malignant cerebral tumors who were receiving radiotherapy plus certain amount of *Boswellia* extract, showed that after the end of radiotherapy the 75% reduction of cerebral edema was observed in 60% of the patients receiving *Boswellia* extract. The study also shows the ratio of tumor over volume decreased in these patients, suggesting anti-tumor effect in addition to the anti-edema activity.^[29]

d) Diabetes

The effect of *Boswellia* has been known on wide variety of diseases, including inflammatory diseases and diabetes mellitus.^[30] The study has shown that the oral administration of aqueous extract of the leaves and roots of *Boswellia glabra* decreased the blood glucose level in diabetic patients. The continuation of the use of leaf and root extract for 28 days showed a decrease in serum glucose, cholesterol, triglyceride, urea and

creatinine levels and enzyme activities in addition to significant hypoglycemic effects.^[30]

Type I diabetes is an autoimmune disease in which a chronic inflammatory process finally causes beta-cell death and insulin deficiency. Extracts from gum resin of *Boswellia serrata* have been shown to possess anti-inflammatory properties especially by targeting factors or mediators related to autoimmune diseases.^[31] The study shows that *Boswellia* extract has anti-diabetic effects and could prevent complications of diabetes in the kidneys and liver.^[32]

e) *Antimicrobial*

The essential oil isolated from the oleogum resin of *Boswellia carterii* has shown to have antimicrobial activities against various microorganisms such as fungi, Gram-positive and Gram-negative bacterial strains.^[23] In a study the antibacterial activity of boswellic acids were tested in vitro on a group of clinically significant Gram-positive and Gram-negative bacteria. Among the boswellic acids Acetyl-11-keto-beta-Boswellic acid (AKBA) was the most active inhibitor of bacterial pathogens. However the activity of AKBA was limited to Gram-positive bacteria.^[33] The resistance of Gram-negative bacteria to lipophilic AKBA might be as a result of the presence of lipophilic outer membrane which is composed of primarily of lipopolysaccharide molecules and forms a hydrophilic permeability barrier providing protection against the effects of highly hydrophobic compounds.^[33]

Biofilms are multilayered community of bacterial cells. Staphylococci are known to form biofilms on an implanted medical device or damaged tissues which are difficult to disrupt. The infections caused by biofilms are difficult to treat due to their inherent antibiotic resistance.^[33] In a study, AKBA effectively inhibited the staphylococcal biofilm and also reduced the performed biofilm of these bacterial pathogens. This is the report which shows that AKBA can prevent as well as reduce the *S. aureus* and *S. epidermidis* generated biofilms.^[33] AKBA was found to be the most active compound against the entire gram positive bacterial pathogens tested.^[33]

The antimicrobial activity of boswellic acid molecules was studied against oral cavity pathogens. The results showed that AKBA is the most potent antibacterial compound against all the bacteria tested in this experiment.^[15] AKBA can be used in the development of antibacterial agent against oral pathogens and can be used in mouthwash for preventing and treating oral infections.^[15]

f) *Memory*

In traditional medicine, Frankincense or olibanum is believed to improve the learning and memory after the consumption and it has been used in elderly for enhancement of memory and in pregnant women to increase the memory and intelligence of their

offsprings.^[34] The result of a study shows that there is a significant increase in the power of learning at post-learning stage, short-term memory and long-term memory in rats which their mother received aqueous extract of *Boswellia serrata* orally during the gestational period.^[35]

Hippocampus is a sensitive region of the brain involving in certain aspects of learning and memory functions.^[36] The dendritic systems are the functional core of neuronal collections as they signify most of the receptive surface of neurons which their organization is essential for integration and transfer of information at the synaptic level.^[36] The study indicated that the young rats whose mothers were treated with *Boswellia* during gestation showed more dendritic branches in CA3 (Cornu Ammonis) pyramidal neurons.^[36] In the experiment with prenatally *Boswellia* treated young rats, the CA3 cells showed obvious expansion of their terminal dendritic arborizations, when compared to the control group.^[36] Better learning and memory performance in the offsprings of the mothers who were consuming frankincense during their pregnancy is related to an increase in the somal volume of hippocampal neurons in Cornu Ammonis.^[36] These findings suggest that the frankincense and its compounds need to be extensively studied in neurophysiology and possibly for the future treatment of neurodegenerative disorders.^[37]

The pharmacological effects of *Boswellia serrata* was studied by its effect on memory deficits of hypothyroid rats.^[34] Many studies have shown that thyroid hormones play a significant role in cell division, maturation, and function of mammalian central nervous system. The deficiency of thyroid hormones in prenatal period can cause growth retardation as well as severe cognitive impairment such as attention, memory processing and general intelligence deficits.^[34]

In a study, which hypothyroidism was induced by methimazole in adult male Wistar rats, caused them a significant decline in learning and memory. The use of frankincense has shown to be effective in preventing this deficiency. This result supports the traditional believe that olibanum has beneficial effect in enhancing memory and learning functions.^[34]

g) *Fertility*

Fertility regulation with plant preparation has been reported in traditional medicine and a number of plant species have been tested for their effects on fertility and some of them have been supported by national and international agencies.^[9] Frankincense is used by Jordanian population as aphrodisiac and fertility promoting agent. The gum resin of frankincense contains boswellic acids and other pentacyclic triterpenes, which have a chemical structure similar to steroids.^[9] In a study which was conducted to examine the effect of Frankincense on the reproductive system

and fertility of adult male rats, the oral administration of Frankincense (*Boswellia thurifera*) increased fertility in the rats. In addition, the number of implantation and the number of viable fetuses also increased, which may possibly be due to the increase in sperm motility and sperm density.^[9] The drug may act on the pituitary gland and increase main hormones of spermatogenesis. Significant increase in sperm motility of cauda edydidymis was observed in treatment group which can be due to the effect of frankincense (*B. thurifera*) on the enzymes of oxidative phosphorylation.^[9]

In conclusion, Frankincense (*B. thurifera*) resin is a useful compound in fertility mainly by having an effect on pituitary gland cells. More studies are needed to identify the specific method of action of frankincense.^[9]

h) *Controlled Release of Drugs*

Controlled released drug delivery systems are intended to direct the delivery of the drugs to targeted tissues, in desirable and sustaining rates. Among a variety of approaches, preparation of drug-embedded matrix tablets is widely used for this purpose.^[38] Although a wide variety of polymers are used in matrix tablets for controlling the drug delivery or improving the bioavailability of the contained drug, the need for safe, natural and effective matrix tablets has always existed.

The use of olibanum resin is considered suitable for the controlled release of diclofenac over 24 hr. (once a day administration).^[38] Also in a study on the control release of nifedipine, olibanum and colophony, two natural resins were used as a microencapsulation agents which caused the slow and spread release of the drug over 24 hour.^[39]

Olibanum resin is a natural lipophilic polymer which is used as a microencapsulating agent for the good controlled release of the drugs.^[40] The result of studies on the matrix tablets formulated with the use of olibanum resin in several drugs like diclofenac, 18 nifedipine, carbamazepine have shown that as the concentration of olibanum resin in the matrix tablets increased the drug release was decreased,^[38] which this means the longer stay of drug in the body.^[39]

i) *Preparation and Dosages*

Although different methods of preparations can be formulated for oral, rectal and parenteral administration, the preparations of oral administration are preferred. The pharmaceutical preparations for oral administration may be in the form of tablets or capsules prepared with the use of diluents, such as binding agents, fillers, lubricants, disintegration agents or wetting agents.^[28]

The compounds can also be formulated for injection, preferably intravenous, intraarterial, intramuscular, intracranial, intrathecal or subcutaneous and can be in unit dosage form, e.g. in ampoules, or in multiple dose containers with the preservative added.

The preparations may be in the form of suspensions, solutions, or emulsions in oily or aqueous carriers.^[28]

Boswellia is generally taken orally as a capsule, tablet or its bark decoction. The standardization of *Boswellia* products is difficult because of variety of *Boswellia* products.^[5] The suggested dosages for inflammatory or asthmatic conditions are 300 to 400 mg of standardized extract (containing 60% boswellic acids) three times daily.^[5]

j) *Safety*

Frankincense, the gum resin of *Boswellia*, which has been used as a remedy for more than thousands of years has not shown any severe side effects and is considered to be 19 safe.^[25] The anti-inflammatory effects of *Boswellia* unlike of many anti-inflammatory chemical drugs, dose not cause any adverse effects on blood pressure, heart rate, respiration or other autonomic responses with remarkably low toxicity.^[17] Gum resin of *Boswellia* is included in the list of safe substances and its use is permitted by USFDA as a food additive.^[15]

Oral preparations of boswellic serrata extract containing AKBA are sold in the market over the counter as anti-inflammatory formulations.^[15] The results of many clinical studies have shown that *Boswellia* is well tolerated in the treatment of rheumatoid arthritis and Crohn's disease with minimum side effects.^[29]

Taken together, the side effects of Frankincense, is relatively very low and not severe when compared to modern drugs and their side effects. Then they can be considered quiet safe when are taken in the required and therapeutic dosages.

V. CONCLUSION

Frankincense has been used in traditional and modern natural medicine for the treatment of variety of illnesses with very minimal side effects. The anti-inflammatory, anti-arthritic, anti-proliferative, anti microbial and analgesic effect of this gum resin can reduce the inflammation and pain in the body and relieve the related symptoms of many diseases. The effect of frankincense is remarkable in increasing the number of dendritic segments and branching in the neuron cells of hippocampus, causing more synaptic connections in that area and therefore improvement of learning and memory. Extensive studies on frankincense and its effect on neurophysiology could be a right approach in finding a possible new complementary or alternative natural medicine to control, cure or 20 prevent some variety of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases.

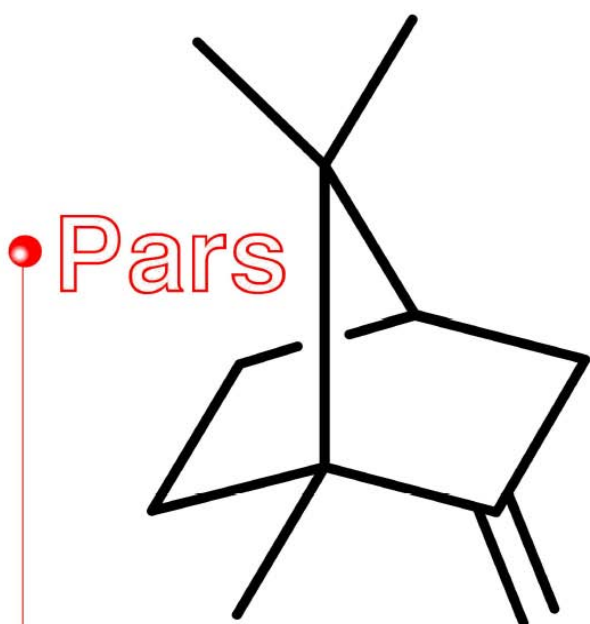
a) *Disclosure Statement*

There is no conflict of interest in connection with this manuscript.

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