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AN UPDATE ON POTENTIAL THERAPEUTIC ACTIONS OF *BOSWELLIC* ACIDS

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ABSTRACT: In recent years, natural products such as *Boswellic* acids (BAs) have attracted researchers around the globe because of their significant potential against various diseases without any toxic effects. *Boswellic* acids, which belong to the pentacyclic triterpenes type of class, are extracted from the gum-resin portion of *Boswellia serrata* and many other different species such as *Boswellia sacra*, *Boswellia papyrifera*, and *Boswellia carterii*. The *Boswellic* acids obtained from these species are broadly classified into two categories as α-*Boswellic* acids and β-*Boswellic* acids. The six major recognized acids which are obtained from the gum resinous extract of *Boswellia serrata* and *Boswellia carterii includes* α-*Boswellic* and β-*Boswellic* acids, acetylated α-*Boswellic* acids and β-*Boswellic* acids and 3-O-acetyl-11-keto-β-*Boswellic* acid and 11-keto-β-*Boswellic* acid. In recent years, several biological potentials of *Boswellic* acids have been investigated, including inhibition of inflammation, anti-arthritic, anti-microbial, anti-diabetic, anti-asthmatic, anti-cancer, *etc.* In addition to leukotriene inhibiting property, the *Boswellic* acid and their analogues also possess the potential to be used against inflammatory bowel disease and neurodegenerative diseases. The most common are Alzheimer's disease, Parkinson's disease, Huntington's disease, *etc*. Their broad spectrum of pharmacological activities also include shypolipedimic, hepatoprotective, immune-modulatory, antithrombotic, analgesic, antioxidant, dermal safety and diuretic activities. In the present review, an attempt has been made to update the therapeutic potential of various *Boswellic* acids.

INTRODUCTION: A gum resin herbal extract obtained from the Indian frankincense, also known as *Boswellia,* plant species has been used as a natural medicine for a long time. It is considered to be a promising natural source to treat.

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The inflammation and associated conditions, including rheumatoid arthritis, osteoarthritis, inflammatory bowel disease and asthma *Boswellia serrata*, also known as Salai guggul, belong to the family Burseraceae [1].

With around 25 species, the genus *Boswellia* is mainly found in the parts of the north-eastern coast of Africa, Arabia and India. The oleo-gum resins of *boswellia* species contain 35-60% resin, 7-10% of essential oils, which are easily soluble in organic solvents and the rest is formed polysaccharides which are soluble in water. *Boswellia serrata* and

Boswellia sacra are the two most important medicinal species of *boswellia* plant, which consist of *Boswellic* acid [2, 4]. *Boswellic* acids compounds are a series of pentacyclic triterpenoid-type molecules. This has been found as a gum resin isolated from the plant origin of species of *Boswellia*. The six major acids recognized from the gum resin of *Boswellia serrata* and *Boswellia*carteri includes α and β-*Boswellic* acids, acetylated α and β-*Boswellic* acids and 3-O-acetyl-11-keto-β-*Boswellic* acid and 11-keto-β-*Boswellic* acid, The gum resin of this plant have been used as a fragrance not only in cultural and religious practices but also as medicine since the ancient times. *Boswellic* acid appears in the resins of the plant exudates [5, 6]. The genus *Boswellia* consists of many species, out of which more than 20 species of trees grow in Arabia, Africa and India. *Boswellia* extracts have been used for centuries in different parts of African and Asian cities in their traditional method of curing and the traditional folk medicines [1, 3]. The standard dosage of medication contains around 30-40% of *Boswellic* acid. *Boswellic* acids are commonly steroidal in nature; hence they are not soluble in the intestinal fluid; as a result, their systemic bioavailability is limited and observed to be less [7]. The average essential oil content in these plant species was found to be approximately 11%, and the remaining amount is the presence of resins and terpenoids. According to the different species of *boswellia* plant and different plant grades, the amount of chemical constituents varies in different amounts [8]. In addition to this, it has also been investigated that various dietary supplements claim that they are enriched with the content of AKBA and KBA.

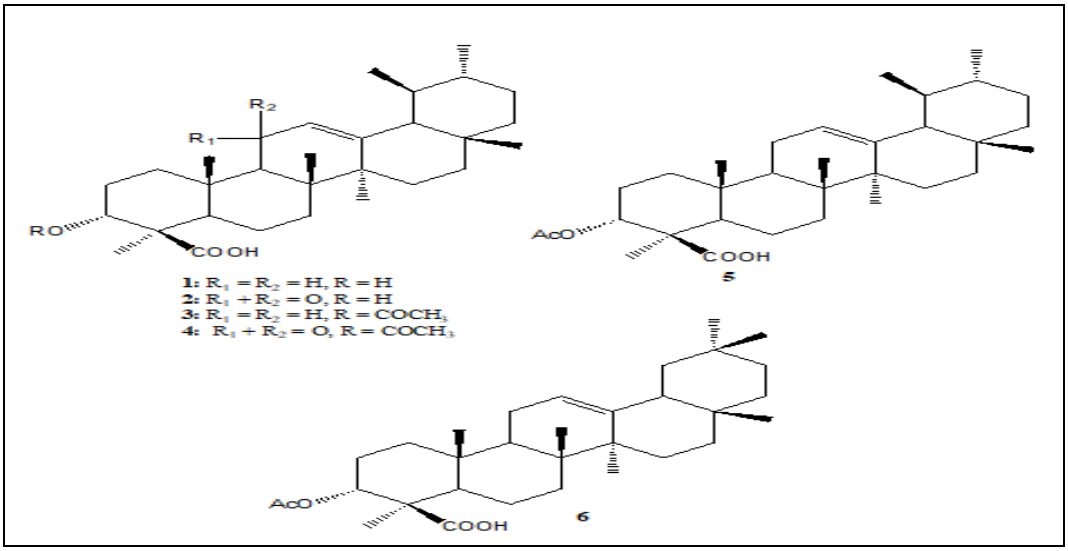

FIG. 1: STRUCTURES OF SOME COMMON *BOSWELLIC* ACIDS

TABLE 1: SOURCES OF *Boswellic* ACIDS AND THEIR GEOGRAPHIC LOCATION 11

Source of *Boswellia* acid	Geographical Location
Boswellia serrata	India
Boswellia avalifoliolata	India
Boswellia sacra	Oman Yemen
Boswelliacarteri	Somalia
Boswelliaalobusa	Simaila
Boswellia frereana	Ethiopia Somalia
Boswellia papyrafira	Ethiopia Sudan
Boswellia bullata	Socotra
Boswellia elongate	Socotra
Boswellia riyae	Socotra

Boswellic acids are obtained from the incision in the bark of *Boswellia* plant species. It is the white milky exudate from the incision of bark which is when exposed to the atmosphere, becomes hard and changes its color to a dull yellowish texture. These are the oleo-gum resins of frankisence [9, 10].

Therapeutic Potential of *Boswellic* Acid and Its Analogues: Various pharmacological actions of *Boswellia serrata* as a bioactive herb with their mechanism of action has been documented. Anti-inflammatory or anti-arthritic activity is because of the inhibition of 5-lypoxygenase, TNF-α, IL-β, and pro-inflammatory mediators. Antimicrobial activity is seen against both gram (+) and gram (-) bacteria. Antiviral activity was reported by acetyl-11keto-β-*Boswellic* avid and β-*Boswellic* acid. Anti-cancer activity was reported by inhibition of IL-1β, IL-6,

IL-8, IL-10 and TNF-α in different cell lines. Neuroprotective activity in Alzheimer's disease was a result of the elevation of acetylcholine and reduction of Ach enzyme activity in brain homogenate [12]. In a recent study, it has been established that frankincense shows different pharmacological activities based on inflammatory responses. The gum resin from frankincense has been proved to be beneficial in several diseases such as diabetes, asthma, arthritis, epilepsy and cancer.

It also plays a major role in treating and preventing various neurodegenerative diseases such as Alzheimer's, Parkinson's, and some infection and allergies described on the basis of anti-inflammatory effects [13]. *Boswellic* acids (BAs) have been found to show anti-arthritic, analgesic, antimicrobial, anti-inflammatory, anti-cancer or antitumor, hypolipidemic, immune-modulatory, hepatoprotective, hypoglycemic, anti-asthmatic, antidiarrheal, diuretic and neuroprotective potential. It has been found to be useful on skin and psoriasis to [14, 15, 17]. *Boswellia* significantly prevents the tumor necrosis factor-α which induces expression of matrix metalloproteinases and adhesion of the molecules and induce the expression of the mediators of apoptosis [16, 19].

Anti-Microbial Activity: The hydroalcoholic extract of *Boswellia serrata* at different concentrations of 50 mg/ml, 100 mg/ml, and 200 mg/ml resulted in the inhibition of some oral micro-organisms such as *Candida albicans*, *Streptococcus mutans*, *Candida krusie*, and *Candida glabrata* [20]. According to the findings, the essential oils obtained from *Boswellia serrata* by supercritical fluid carbon dioxide method show high antimicrobial activity. The essential oils responsible for this activity are α-thujene, camphene, myrcene, and limonene via well diffusion and microdilution broth assay [21]. In arecent study, it was depicted that the essential oils of *Boswellia* species are responsible for antibacterial activity against *Sterptococcus pneumoniae* and *Klebsiella pneumoniae* with the inhibition zone of 2-30 mm diameter [22]. The hydroalcoholic extract of *Boswellia serrata* has shown antibacterial activity and proved to be effective in treating periodontal diseases [23]. According to various findings, the resinous extract of *Boswellia serrata* powder is said to possess anti-microbial activity. *Boswellia serrata* was investigated to have a relatively wide inhibition zone against the tested strains. The anti-microbial activity was checked with respect to minimum inhibitory concentration (MIC), which is the concentration required for inhibiting the growth of microorganisms from portraiting the anti-microbial activity. The acidic fractions of *Boswellia carterii* and *Boswellia serrata* are characterized by increased antibacterial activity. *Boswellia carterii*, exhibited an antibacterial activity by acetyl-keto-*Boswellic* acid, 3-oxo-tirucallic acid, and alpha and beta-*Boswellic* acid. The potential of these compounds has been recorded to be stronger in *Boswellia serrate*. After further evaluation in post-antibiotic effect (PAE) studies and biofilm susceptibility assays, the most potent antibacterial activity exhibited by acetyl-keto-β-*Boswellic* acid (AKBA).

The antibacterial action of acetyl-keto-β-*Boswellic* acid (AKBA) was investigated to be due to fissure of the microbial membrane structure [14, 17]. According to an experimental activity, a culture of bacterial preparation was prepared with Mueller Hinton agar, and then different concentrations of resin powdered extract were added on Whatman filter paper 1, and it was inoculated with a loop of the test organism. This experiment is done in triplicate, and the plates were kept in the incubator at 37 °C for about 24 h.

The zone of inhibition was measured, and minimum effective concentration was determined, and this was compared with the standard antibiotic drug ciprofloxacin. The inhibitory activity of the extract against different organisms was found in the order: *Escherichia coli* > *Staphylococcus aureus* > *Bacillus subtilis* > *Salmonella typhi* > *Klebsiella pneumonia* > *Streptococcus pneumonia* > *Enterobacter aerogenes* > *Proteus vulgaris*. Hence, it was proved that *Boswellia serrata* extract possesses the bacteriostatic property [24]. Acetyl-11-keto-β-*Boswellic* depicts the characteristics of antimicrobial activity. They majorly target the oral cavity pathogens, especially the *Streptococcus mutants*. The most active agent against bacterial pathogens was found to be AKBA. This compound is explored to have a wider range of activities against different strains of bacteria such as

Streptococcus mutans, *Enterococcus faecium*, *Enterococcus faecalis*, *Streptococcus sanguis*, *Porphyromonas intermedia*, *Porphyromonas gingivalis*, and *Actinomyces viscosus*. It is highly effective against aerobic and anaerobic bacteria as compare to 11-keto-β-*Boswellic* acid. It shows a bacteriostatic antibacterial potential [25].

Anti-Inflammatory Activity: It has been established that oral administration of *Boswellic* acid with *Piper longum* enhances the bioavailability and better efficacy against inflammatory diseases [26]. The 3-O-actyl-11-keto-β-*Boswellic* acid has been observed to be an effective anti-inflammatory candidate by performing the *in-silico* studies and checking the docking score by the mechanism of inhibition of 5-lipoxygenase, C2 convertase, and topoisomerase [27]. According to one research, the *Boswellic* acid inhibits the bisphenol-A induced lung toxicity by its anti-inflammatory activity. It decreases the oxidative damage of the bio-molecules (NADPH and MDA) and inflammatory variables (IL-6, TNF-α, and MPO). It also inhibits lung inflammation by preventing JNK/ERK/cFos pathway [28].

Boswellic acids obtained from different *Boswellia* plant species have been investigated to depict effective anti-inflammatory activity by the 5-lipoxygenase pathway. 5-lipoxygenaseenzyme (5-LOX) is more efficiently inhibited by acetyl-11-keto-β-bo-swellic acid molecule. The inhibition of the formation of pro-inflammatory mediators and decreased production of leukotrienes has also been demonstrated for*boswellic* acid from *Boswellia carterii*. The inhibition of the production of pro-inflammatory enzymes, 5-hydroxyeicosatetraenoic acid, lipoxygenase enzyme, and leukotriene B4 inhibition during the *in-vitro* studies in animal models has been demonstrated for the *Boswellic* acid [29]. According to recent studies it has been investigated that the series of *Boswellic* acids obtained such as 11-keto-beta-*Boswellic* acid (KBA) and acetyl-11-keto-beta-*Boswellic* acid (AKBA) have been researched to show a well-known anti-inflammatory property. The gum-resinous part of *Boswellia serrata* includes monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and major pentacyclic triterpenic acids *i.e. beta-Boswellic* acids are responsible for inhibition of pro-inflammatory enzymes [30, 31]. *Boswellia serrata* plant extract also elicits anti-inflammatory properties in human peripheral blood mononuclear cells (PBMCs) and mouse macrophages by inhibiting the tumor necrosis factor-alpha (TNF-α) and preventing interleukin-1-β (IL-1-β), NO and mitogen-activated protein (MAP) kinases production. This compound has been tested on animal models for its anti-inflammatory property, and it has been found to inhibit the 5-lipoxygenase enzymes [32]. 9-α-hydroxy-11-keto-β-*Boswellic* acid analogues constituted with variable functionality at ring A have been synthesized from 3-O-acetyl-11-keto-β-*Boswellic* acid. This compound has been investigated to have an anti-inflammatory activity as opposed to the pro-inflammatory cytokine and tumor necrosis factor-α, which results in proving the anti-inflammatory potential of this derivative of *Boswellic* acid [33, 34].

Analgesic Activity: Experiments were conducted with the extracts of *Boswellic serrata* in various analgesic animal models such as acetic acid-induced writhing in rats and tail flicking models in mice which proved to be very effective and successful. *Boswellia sacra* extract was used in the analgesic model of acetic acid-induced and formalin-induced pain in rat models. Acetyl-11-keto-β-*Boswellic* acid is one of the major pentacyclic triterpenic acids present in the acidic extract of *Boswellia serrata*, which has been found to be a very effective 5-lypoxygenase inhibitor, thereby inhibiting the leukotriene synthesis via interaction with the 5-lypoxygenase activated protein. This compound has been proved to have antinociceptive activity for at least 60 min when tested in an acetic acid-induced writhing model. Antinociceptive activity was achieved by inhibition of LTB4 and HETE factors and also prevents capsaicin activation [35].

In one of the studies, a randomized clinical trial was conducted with healthy volunteers to check the efficiency and efficacy of Boswellia serrata compared with the placebo effect for analgesic effect. In this clinical trial, the pain threshold force and their time is taken, and the pain tolerance force and its time were evaluated. This study was done by Randall selitto or paw pressure test using the apparatus Ugo Basile Analgesymeter which was used for producing mechanical pressure on the

nailbed of non-dominant hand index finger, for producing pain-like sensation. It has been proved that pentacyclic triterpenes of *boswellia* extract causes inhibition of 5-lypoxygenase and cyclooxygenase enzyme. As a result of this study, it was concluded that the pain tolerance force and time were increased from the baseline after administration of *boswellia* extract after every 1hour as compared to placebo; hence it was proved that *Boswellic* acids present in *boswellia* plant show pharmacological activity as analgesic agent [36].

Immunomodulatory Activity: It has been found that *Boswellia papyrifera* and *Boswellia serrata* show therapeutic benefits in patients of multiple sclerosis by anti-inflammatory, antioxidant, and immune-modulatory activity [37]. The compound 3-O-acetyl-α-*Boswellic* acid obtained from *Boswellia carteri* has been evaluated to suppress T-lymphocytes and suppress the immune system. It is based on the nuclear factor of activated T cell (NFAT) mechanism and inhibits the proliferation of (CD-3 and CD-28) activated human T lymphocytes, hence proved as immune-suppressing agent [38].

The isolation and identification of some compounds including triterpenoids, has been shown by immune modulatory bioassay-guided fractionation of the oleo-gum resin extract of *Boswellia carterii*. The 11-keto-β-*Boswellic* acid (KBA) and acetyl-11-keto-β-*Boswellic* acid have been investigated to be the most active compound among the various *Boswellic* acids. It is also recorded that *Boswellic* acid derivatives increase phagocytosis of macrophages. By interaction with the release of cytokines they affect the cellular defense system. *Boswellic* acids and their derivatives down-regulates and inhibits the tumor necrosis factor-α (TNF-α) and also decrease the production of interleukins (IL-1, IL-2, IL-4, IL-6) and interferon-γ (IFN-γ). It has been found that extracts from the gum-resin of *Boswellia serrata* and *Boswellia papyrifera* have an action on the defense system. 11-keto-β-*Boswellic* acid (KBA) and acetyl-11-keto-β-*Boswellic* acid have been found to show immune-modulatory activity. In the humoral defense system, a mixture of *Boswellic* acid derivatives at elevated doses decreases primary antibody titres and, on the other hand, reduces doses enhanced secondary antibody titres, this was observed with sheep erythrocytes treatment [39, 40]. The triterpenoids obtained from the *Boswellia carterii* which have been resulted and proved to have immune-modulatory activity includes β-*Boswellic* acids such as 11-keto-β-*Boswellic* acid, acetyl β-*Boswellic* acid, acetyl 11-keto-β-*Boswellic* acid and α-*Boswellic* acid *i.e.*, acetyl-α-*Boswellic* acid and 3-oxo-tirucallic acid and 3-hydroxy-tirucallic acid. These derivatives of *Boswellic* acid activate the mitogen-activated protein kinase (MAPK) pathway (p42 and p38) isolated from human polymorph nuclear leukocytes. Their oleo-gum resin has been proved to have immune-modulatory activity [40]. 11-keto-β-*Boswellic* acid & acetyl-11-keto-β-*Boswellic* acid extracted from the gum resin of *Boswellia serrata* also displays immune defense property. The action of NFkB and subsequent NFkB-dependent cytokine production by macrophages in the form of signals was remarkably reduced when acetyl-11-keto-β-*Boswellic* acid was administered systemically or locally in a mouse with psoriasis [41].

Anti-Cancer Activity: The 11-keto-α-*Boswellic* acid was evaluated for the anti-tumour activity in the breast cancer cell line. It resulted in cytotoxicity against triple-negative breast cancer cells and also induced apoptosis in the cell line [42]. The *Boswellic* acids have been proven to have cytotoxic activity. According to recent studies, it has been established that acetyl-keto-β-*Boswellic* acid, keto-β-*Boswellic* acid, and their analogues show a toxic activity in cells affected with cancer; hence, it has been considered to be an effective therapy for anti-cancer drug discovery [43]. A modification in the hydroxyl or carboxyl group of 11-keto-β-*Boswellic* acid depicts anti-cancer activity by nuclear fragmentation in the cells and it has been found to be potent against tumour cancer cells MCF-7 (breast cancer cells) and LNCaP (prostate cancer cells) [44].

The pentacyclic triterpendiol obtained from *Boswellia* serrata was observed to have apoptic and cytotoxic effects in the human cancer cell lines. It causes DNA damage and expression of the pro-apoptotic protein such as TNF-R1, cytochrome C and PARP cleavage in HL-60 cells [45]. Among all the species of *boswellia* plant, the most effective species found to be is *Boswellia serrata*.

The pentacyclic triterpenes obtained from the *Boswellia serrata* has been profound to be effective as cancer drug sensitizing agent. They show antitumor effects in various cells such as liver, brain, prostate, colon, breast and leukocytes. The AKBA has been reported to be useful in the case of brain cancer, prostate cancer and pancreatic cancer, while 11-carbonyl-β-*Boswellic* acid was investigated to have an inhibitory effect on lung cancer cells. Keto-β-*Boswellic* acid and acetyl-11-keto-β-*Boswellic* acid has been found to inhibit proliferation, enhancing the caspase-3 activity, IL-6 levels and TNF-α and inducing apoptosis through caspases-8 pathway in the liver cancer cells to prevent liver cancer. 3-O-acetyl-β-*Boswellic* acid was found to be used in the treatment of breast cancer. Analogues of *Boswellic* acids show anti-cancer effects on colon cells to prevent continuous growth by various mechanisms.

The α-keto-*Boswellic* acid acts on the NFκB and the STAT-3 related pathways and demonstrated an inhibitory effect, which also enhances the processes of apoptosis and inhibiting the angiogenesis in neoplastic cells. Moderation of breast cancer and brain tumour metastases has been shown by *Boswellia serrata* extract. The main derivatives which have been found to show an anti-carcinogenic activity are 11-dien-24-oic acid, 3-hydroxy-urs-9, 24-dien-21-oic acid, 3-alpha-hydroxy-tirucall-8, 3-O-11-hydroxy-beta-*Boswellic* acid, 3-beta-hydroxytirucall-8, 24-dien-21-oic acid, and α-amyrin [46, 47]. Acetyl-keto-β-*Boswellic* acid has depicted cytotoxic action on meningioma cells by inhibiting the extracellular signal-regulated kinases signal transduction pathway.

Acetyl-11-keto-β-*Boswellic* acid has been observed to inhibit the cell growth by the inhibition of Ki-67, CD31, Cycloxygenase-2, MMP-9, CXCR4, and VEGF in cancerous cells of pancreas [48]. The major analogues of β-*Boswellic* acid, such as 3-O-acetyl-β-*Boswellic* acid and 11-keto-β-*Boswellic* acid have been found to have an anti-tumour activity in leukaemia in which there is inhibition of DNA, RNA and protein synthesis in the human leukemia-60 cells. *Boswellic* acids have repressed tumours and inflammation in mice. *Boswellia serrata* extract has also been scrutinized for anti-carcinogenicity in mice with Ehrlic ascites carcinoma and S-180 tumour and reduces tumor cell proliferation and induces apoptosis [49, 50]. Acetyl-keto-β-*Boswellic* acid has depicted cytotoxic action on meningioma cells by inhibiting the extracellular signal-regulated kinases, signal transduction pathway. Acetyl-11keto-β-*Boswellic* acid has been observed to inhibit cell growth by the inhibition of Ki-67, CD31, Cycloxygenase-2, MMP-9, CXCR4, and VEGF in cancerous cells of pancreas [51].

Anti-arthritic Activity: According to the meta-analysis report of a clinical trial involving 545 patients, Boswellia, and its extract effectively relieve pain in the joints and may be an effective treatment option for osteoarthritis patients with administration for the duration of four weeks [52]. A unique composition containing the acidic and nonacidic fractions of *Boswellia serrata* gum resin named LI13019F1 (also known as Serratrin) is depicted to have activity against osteoarthritis. This composition strongly inhibited 5-LOX activity with the half-maximal inhibitory concentration (IC50) of 43.35 ± 4.90 μg/ml. Also, LI13019F1 strongly inhibited the leukotriene B4 (IC50, 7.80 ± 2.40 μg/ml) and prostaglandin E2 (IC50, 6.19 ± 0.52 μg/ml) productions in human blood-derived cells. Besides, LI13019F1 also reduces TNF-α production with the IC50 of 12.38 ± 0.423 μg/ml [53]. A novel extract of *Boswellia serrat*a named *Boswellin* comprising of 3-acetyl-11-keto-β-Boswellic acid with β-*Boswellic* acid was tested on approximately 48 patients suffering from osteoarthritis to this double-blind, randomized controlled trial, it was observed that it reduces osteocytes and exerts anti-inflammatory and anti-arthritic activity [54].

Kumar *et al.* in their research study, observed that *Boswellia serrata* extract was effective in the treatment of rheumatoid arthritis. This activity was confirmed by complete Freund's adjuvant-induced arthritis in wistar rats. This activity was assessed by his pathological examination and various other parameters such as ankle diameter, paw volume, and arthritis index [55]. A novel synergistic composition derived from *Boswellia serrata* gum resin is Aflapin. Improvement in pain with osteoarthritic knee function has been demonstrated by *Boswellia serrata* in clinical trials [56]. *Boswellic* acids have been explored and observed to inhibit toll-like receptor (TLR)-mediated activation of

monocytes, inhibiting LPS-induced production of nitric oxide, IL-1β and TNFα. The derivatives comprising of *Boswellic* acids have been demonstrated to significantly suppress interleukin-β induced apoptosis of chondrocytes and also TNFα induced production of matrix metallo proteinases-3 (MMP3) by synovial fibroblasts thus exhibiting the therapeutic potential of the crude drug in the treatment of osteoarthritis. Patients suffering from osteoarthritis of the knee have been recommended for *Boswellia* extract. Various experiment have been demonstrated to show that *Boswellic* acid is a potential anti-arthritis drug with significant tolerance and free from toxic effects [57]. Reduced arthritic scores, decreases paw edema with marked suppression of local tissue TNF-α- and IL-1β in rats that have been observed with acetone extract of *Boswellia carterii* gum-resin. The patients receiving *Boswellia* treatment resulted in a decreased knee pain, increased knee flexion, and enhanced walking distance. The swelling of the knee joint was also decreased. 3-acetyl-11-keto-β-Boswellic acid is used in topical gel in the form of polymeric nano micelles gel, which portrays much higher anti-arthritic activity for a longer duration of [58].

Anti-diabetic Activity: The recent *in-silico* research performed on *Boswellic* acid derivatives involving molecular docking has proven that *Boswellia serrata* gum resin contains a large number of compounds that are beneficial in antidiabetic activity. Auto dock Vina tool was used in this study [59]. According to recent research, the *Boswellia* species have beneficial effect on various metabolic disorders such as diabetes mellitus, hyperglycemia, hypertension, and dyslipidemia. The antidiabetic effect resulted from a reduction in insulin resistance and it also helps restore the pancreatic beta-cell to prevent depletion in the blood glucose level [60].

Anti-diabetic property of *Boswellia serrata* extract was tested on non-insulin-dependent diabetes mellitus in a streptozocin-induced diabetic rat model, which was found to decrease blood glucose level compared to phenformin significantly. The formulations in question worked by affecting hepatic gluconeogenesis, influencing pyruvate carboxylase and phosphoenolpyruvate carboxykinase systems. The effect of Acetyl-11-keto-β-Boswellic acid was studied in an experiment for a period up to 12 weeks, and the reduction of blood glucose level was recorded [61, 62].11-keto-β-Boswellic acid has been investigated to be the significant potential compound as an anti-diabetic agent. 11-keto-β-Boswellic acids were researched to suppress the induction of diabetes, overcome the cytokine burst, lead to the initiation of insulitis, and down-regulate the blood glucose level in the mouse model of multiple low-dose streptozotocin-induced diabetes thereby weakening the stimulation of pro-inflammatory responses [62].

Antioxidant Activity: Beghelli *et al.* in their research showed that the different extracts of *Boswellia serrata* have different concentrations of acetyl-keto-β-*Boswellic* acis, and they have been proved to be effective in the antioxidant activity via the DPPH assay [63]. Studies have revealed that the *Boswellia serrata* methanolic leaves extract contains high amounts of total phenolic and flavonoids used as strong reducing agents and show antioxidant activity. An analogue of Boswellic acid secluded from the oleo-gum resin of *Boswellia carteri*i, a pentacyclic terpenoid, has also been investigated for its antioxidant property. These studies have been conducted using different in vitro animal models such as 1,1-diphenyl-1,2-picryl hydrazyl (DPPH) radical scavenging activity and nitric oxide (NO) radical scavenging activity, the most common models [64, 65]. Methanolic or aqueous extract of *Boswellia serrata* quenched with nitric oxide NO donor shows a good antioxidant activity. The presence of antioxidant principles in the extract competes with oxygen to react with nitric oxide (NO), which concludes in the formation of reactive nitrogen species [66].

Antithrombotic Activity: The β-*Boswellic* acid a triterpenoid compound obtained from *Boswellia serrata* ameliorates the plasma coagulation factors and enhances nitric oxide and cyclic level guanosine 3, 5-monophosphate in the carotid artery of blood stasis in rats. The β-*Boswellic* acid attenuates the knockdown of the eNOS signaling pathway, showing a protective effect on blood stasis induced endothelial dysfunctioning, thereby depicting anti-thrombotic potential [67]. The water and hydroalcoholic extract have been investigated to have anti-platelet activity by inhibiting the thrombin protein. This extract also decreases the

thrombin anti-thrombin complex and increases the content of prostacyclin (PGI2) in blood when administered in rats. They also inhibit clotting factors Xa and XIa, which prove that *boswellia* also have anti-coagulating potential [68]. In a research study it has been observed that when rats are fed with high fat-diet, they have a tendency of developing platelet aggregation, but when they are administered with *boswellia* extract, this prevents the story effect. Platelet hyper-aggregation in hip late let aggregation thereby showing anti-aggreggh fat diet rats is due to the inflammation and increased production of reactive oxygen species (ROS) hence when they are gives *Boswellic* acid extracts it causes oxidative stress and show an inhibitory effect on interleukin-1β, cyclooxygenase-1 and tumor necrosis factor-α thereby depicting an anti-platelet activity [69].

In one of the recent study it was observed that the resin gum extract of *Boswellia serrata* obtained from stem bark used in the form of water extract and hydroalcoholic extract which consist of 3-acetyl-11-keto-β-Boswellic acid shows anti-thrombotic and anti-coagulant activity. According to this study it has been observed that water and hydroalcoholic extracts act on ADP-induced platelet aggregation using the apparatus multimode detection plate reader and blood coagulation activity was detected with the help of automated blood coagulation analyzer. Result obtained from the study was the *boswellia* extracts inhibits the platelet aggregation by preventing the endogenous aggregating agents involved in thrombus formation. It enhances the pro thrombin time and activated partial thromboplastin time which are considered as the diagnosis tests for coagulation of blood, hence increased prothrombin time and activated partial thromboplastin time illustrates that it also have an anti-coagulant property [70].

Anti-Asthmatic Activity: It has been observed that the oil obtained from the tree of *Boswellia* genus consists of various *Boswellic* acids which are responsible for the inhibition of NF-kB, IL-1, IL-2, IL-4, IL-6 and LOX-5 which can indirectly cause hindrance in the pathophysiology of asthma. *Boswellia serrata*, *Curcuma longa* and *Glycyrrhiza glabra* in combination can be used for asthma treatment [71]. *Boswellia serrata* was evaluated for trachea contractility with respect to anti-asthmatic potential. In the experiment, *Boswellia serrata* extract resulted in bronchodilator efficacy by inhibiting the airway smooth muscle contraction. This can prove the validation of the use of *Boswellia* serrata in the treatment of airway diseases [72]. *Boswellia serrata* extract was evaluated for lung disorder treatment by different fractions with diverse mechanisms. It has been observed to inhibit the leukotriene C4 synthase activity, leukotriene A4 hydrolase activity and COX-2 activity by IC50 of 12.5 μg/ml at 50 and 100 mg/kg B.W. in BALB/c mice which proves that it can be used in lung disorder such as allergy and asthma [73]. About 70-75% of the patients with a prolonged history of asthma were observed to show better results in physical signs and symptoms of dyspnea, a number of asthma attacks, and stimulates the mitogen-activated protein kinase pathway MAPK and intracellular Ca2+movement with alcoholic extract of salai guggal. Significant reduction in Th2 cytokines, suppressed airway inflammatory cells infiltration induced by allergens, resulting in reduced eosinophil and total inflammatory cells in BALF has been recorded in various studies of *Boswellic* acid testing. These results supported that *Boswellic* acid appears to be effective for the treatment of allergic asthma and can be developed as an anti-asthmatic agent [74, 75].

Anti-ulcer Activity: Patients consuming NSAIDs have a major issue of developing the ulcer. H. pylori infection is also a major cause of this disease. As an alternative herbal medication, *Boswellic* acids have been found to exhibit ulcer protective activity by various mechanisms such as degradation of matrix metalloproteinase and prevention or inhibition of cyclooxygenase and lipoxygenase enzyme, which indirectly depicts ulcer protective property [76]. *Boswellia serrata* gum resin is an important Indian medicinal plant, and in various studies, it has been found that *Boswellic* acid was useful in many gastrointestinal conditions.

The usefulness in treating 2, 4, 5-trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats has been observed, which supports its use in patients with ulcerative colitis. In the pyloric ligation, ethanol/HCl, acetylsalicylic acid, cold restraint stress, and indomethacin models of study, it is said to possess antiulcer effects [77]. 3-O-acetyl-9, 11-dihydro-β-Boswellic acid has been found to be the

most potent compound in urease inhibitory activity, which helps in anti-ulcer activity. This compound has been found to be the most effective activity against urea se enzyme. Other derivatives such as 3-O-acetyl-11-hydroxy-β-Boswellic acid, 11-keto-β-Boswellic acid, 3-O-acetyl-11-keto-β-Boswellic acid possess the lesser activity [78]. Various studies have proved to have anti-ulcer genic effect different animal models such as pylorus ligation induced, ethanol/HCl induced, aspirin-induced, indomethacin-induced, and thermal stress-induced gastric ulceration. *Boswellic* acids have been proved to inhibit ulcers in these various models of ulceration in animals. The ulcer pathology induced by aspirin and indomethacin is mainly because of the biosynthesis of cytoprotective prostaglandin, resulting in overproduction of leukotriene and other inflammatory mediators of 5-lipoxygenase pathway, hence due to the lipoxygenase inhibitory pathway, the Boswellic acids provides anti-ulcer effects [79].

Hypolipedimic and Cardiovascular Activity: *Boswellic* acids were also evaluated for the cardioprotective activity with the help of the model involving doxorubicin-induced cardiotoxicity. The blood was withdrawn via cardiac puncture, and various biological parameters were measured such as SGOT, LDH, CPK and troponin T level. It was observed and concluded that the *Boswellic* acids decrease the severity of myocardial infarction by lowering the level of cardiac biomarkers [80]. According to one recent research, hypertension considered a metabolic disorder was found to be curative because of the protective effect of boswellia species by modifying the blood lipid profile and elevating the adiponectin level TNF-<UNK> and TNF-α and IL-1β levels [81].

Atherosclerosis results from plaque formation in the lining of blood vessels/arteries and the blood capillaries lead to the thickening and hardening of the blood capillaries. An investigation done on the effect of acetyl-keto-β-*Boswellic* acid (AKBA) in Apolipoprotein E-deficient mice was visualized that it inhibited NFkB. Hence this is a remedy for conventional treatment strategies against chronic inflammatory diseases like atherosclerosis might be the plant resins from the *Boswellia* family [82]. The reduction in total cholesterol (38-48%) and elevated high-density cholesterol level (22-30%) in rats fed on atherogenic food diet by water-soluble fraction of Boswellia serrata extract proved its effectiveness hypolipidemic potential. The same fraction in *in-vitro* inhibits the nitric oxide production that has been induced by lipopolysaccharide in rat macrophages. Feeding of rats with salai guggal reduced cholesterol levels in Wistar rats which were due to significant decrease in cholesterol biosynthesis. Acetyl-α-*Boswellic* acid derivative has resulted in inhibiting the NFkB, and p38 MAP kinase pathway is activated macrophages. It has also been investigated that it lowers the level of low-density cholesterol, thereby showing a strong cardio-protective property [83].

Hepatoprotective Activity: A recent study on *Boswellic* acids has indicated hepatoprotective and cardioprotective activity against two very common environmental pollutants: bisphenol-A and Gamma-radiations. For hepatoprotective activity, it was observed that *Boswellic* acid plays a major role in upregulating the hepatic PPAR-α/p 38 signaling against bisphenol-A and γ-radiations to prevent liver damage [84].

The anti-oxidant, anti-inflammatory, and anti-fibrotic effects of *Boswellia serrata* gum resin were evaluated against CCl_4 induced liver toxicity. The depressed oxidative stress and improved antioxidant capacity of the liver and the downregulation of expression of TNF-α, COX-2, TGF-β, IL-6, and NF-kB result in hepatoprotective potential [85]. A reduction in the level of titer of SGPT, SGOT, aminotransferase, and serum enzymes has been shown by the alcoholic extract of *Boswellia* species in endotoxin/galactosamine induced hepatic damage in mice model, which suggest its use as hepatoprotective.

The alcoholic extract of *Boswellia ovalifoliolata* has been tested to have a hepatoprotective potential. This alcoholic extract has been proved to be hepatoprotective against paracetamol-induced hepatotoxicity. Administration of extract of *Boswelllia ovalifoliolata* is able to mitigate hepatic damage induced by paracetamol. It also prevents the elevation of levels of SGPT, SGOT and LDL levels in blood serum which helps in hepatic productivity [86]. Acetyl-keto-β-*Boswellic* acid has been proved to have GIT protective activity. This compound was used in the experimental model of

ileitis and experimental murine colitis induced model. Oral dose of *boswellia* extract was given, and as a result, this compound was found to show adherence to the leukocyte-endothelial cells. This administration was found to inhibit and reduce the microscopic, macroscopic and microcirculatory inflammatory indication within the gastrointestinal tract, a treatment measure of chronic inflammatory bowel disease. The oleo-gum resin of *Boswellia serrata* was active in treating various gastrointestinal diseases and symptoms such as constipation, diarrhea, vomiting and flatulence [87].

Diuretic Activity: According to the statistical data in a study, it is proved that the aqueous *Boswellia serrata* oleo gum resin extract shows diuretic activity without any signs of toxicity. This property has been evaluated on the basis of the increased level of excretion of urine volume and some electrolyte such as sodium, potassium, bicarbonate, and chloride. The creatinine was found to be at a normal level which shows that there is no toxic effect on the kidney [88]. In another study performed on albino mice with the extract from the leaves of *Boswellia serrata* it was observed that it shows a positive effect in a diuretic property. In this study, the leaf extract was taken and evaluated for acute toxicity study and diuretic activity on albino mice, considering the following parameters: production of urine volume, excretion of electrolytes and the blood urea nitrogen level, and the creatinine levels. According to this study, it was observed that the total urine volume produced was significantly at a high level, excretion of electrolytes is high, which proves the diuretic activity of the extract. The *boswellia* leaf extract showed a controlled level of blood urea nitrogen and creatinine level, which results in a negative toxic effect on the kidney [89, 90].

Dermal Safety Activity: The diterpenoid and triterpenoid obtained from frankincense have been evaluated as a good anti-psoriatic agent by some diverged mechanisms. These compounds act on some possible targets such as TNF-α, IL17, IL13, IL23, IL36-γ, and some inflammatory pathways such as MAPK-2, JAK-1/2/3 and INF-γ, which proves its anti-psoriatic potential [91]. Frankincense has been found to decrease the irritation and redness in the skin to restore the skin tone, and it has also been investigated to treat skin bruises and sores in the dermal layer of skin. *Boswellia* has been researched to reduce wrinkles and fine lines. It helps the skin appear smoother and softer. It also tones the skin and decreases the redness in the skin. According to a research, it has been found that a cosmeceutical formulation of *boswellia* acid known as Bosexil has been investigated to have a beneficial effect on skin disorder *i.e.,* psoriasis and erythematous eczema [92]. According to a randomized clinical trial, it has been investigated that the application of a topical cream containing 0.5% low concentration of *Boswellic* acids when used for 30 days leads to some clinical changes in the skin. The changes in the skin were a reduction in the face line and wrinkles, and skin thickness was enhanced. Facial redness, also called facial erythema, telangiectasia, and enlargement of the sebaceous gland, were enhanced in this study but not at notable level [93].

Neuroprotective Activity: A recent research discussed the effectiveness of *Boswellic* acids against Alzheimer's disease (a neurodegenerative disorder). It was observed that β-*Boswellic* acids lead to the enhancement of MAP polymerization and increase MT length, α-*Boswellic* acids decrease the hyper phosphorylated Tau-protein and can be utilized as a neuroprotective agent [94]. The resin obtained from *Boswellia sacra* consists of *Boswellic* acid which has been evaluated for anti-seziure activity via zebrafish and mouse epilepsy model. The triperpene β-*Boswellic* acid obtained from hexane extract of *Boswellia sacra* was found to show the strongest activity in pentylenetetrazole-induced seizure and hence proved the anti-epileptic activity [95].

Genus *Boswellia* and their *Boswellic* acids act through several mechanisms to prevent different neurodegenerative diseases. Methanolic extract of *Boswellia serrata* was found to suppress the level of acetylcholine esterase in the brain and serum, nuclear factor kappa light chain enhancer of B-cells, monocyte chemoattractant protein-1 and leukotriene B4 in the brain, which proves the effective treatment in Alzheimer's disease. *Boswellia* resin extract enhances cell viability and decreases apoptotic feature and prevents toxicity in human dopaminergic cell lines, which helps prevent Parkinson's disease [96]. Acetyl-11-keto-β-Boswellic acid was evaluated for a neuroprotective potential *via* sciatic nerve crush injury model rats

with low, medium and high doses. The results indicated the repair of rat sciatic nerve by stimulating the phosphorylation of extracellular signal regulated kinase signaling pathway and formation of myelin sheet of Schwann cells [97]. Boswellic acid have a tremendous role in treatment and prevention of various central nervous system disorders such as Alzheimers disease and Parkinson disease. It has been evaluated that α-*Boswellic* acids are more effective in preventing the progression of alzheimers disease. Antiapoptotic, anti-amyloidogenic effects because of modification of miRNA-155 has been observed for acetyl-keto-β-*Boswellic* acid in neuro-inflammatory animal model of mice.

Alzheimers disease is a neuro disorder which has been investigated to be cured with alpha-*Boswellic* acids. Experimentally induced alzheimers disease in rats were administered with extract of *Boswellic* acid and checked in rotarod test which show better efficacy and performance after administration [98]. Acetyl-11-keto-β-Boswellic acid has been identified as a very potent neuroprotective agent in various studies. This compound has been administered intra-peritoneal to prevent cerebral ischemic injury. It also attenuates oxidative stress and protects the neurons against injury. The role of neuronal protection of this compound is because of Nrf2/HO1 pathway. According to the studies administration of the compound also prevents neuronal apoptosis. AKBA activates the Nrf2 which enhances the protective defense mechanism via HO-1 neuroprotective pathway in ischemic cortex [99].In another study it has been observed that aqueous extract containing β-*Boswellic* acids increases the neurite branching in the primary cell of hippocampal tissue in rats. Acetyl-11-keto-beta-Boswellic acid because of its anti-inflammatory action down-regulates the various inflammatory mediators such as interleukin-1β (IL-1β) and interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) in blood cells and can also reduce neuronal cell death which proves neuroprotective efficacy of the compound. It also inhibits oxidative stress and prevents ischemia. According to investigations it has been found that oxidative stress plays a major role in neurodegeneration of Parkinson disease. This disease is detected on the basis of motor function test in open field arena. It is observed that in rotenone induced Parkinsonism there is decrease in dopamine level, therefore after administration of high dose of *boswellia* extract there is increase in the dopamine level due to as ynergism in the dopaminergic neurons from Nurr1/GPX-1-expressing ES cells and this proves the degeneration of Parkinson's disease [100]. Acetyl-11-keto-β-Boswellic acid acts on the meningioma cells and inhibits the activation of extracellular signal-regulated kinase-1 and 2 by inhibiting its phosphorylation and results in cytotoxic action on the meningioma cells thereby depicting neuroprotection potential [101].

Gastroprotective Activity: *Boswellia serrata* extract is effective in preventing diarrhoea, without leading to constipation-like symptoms in the subjects related to inflammatory bowel disease. It has proved to prevent and inhibit the contraction of smooth muscles in the intestine of the gastrointestinal tract and thereby controls and treats the inflammation caused by acetylcholine and barium chloride, which induces diarrhoea 3. In accordance with the findings, the acetyl-11-keto-β-Boswellicacid (AKBA) derivative showed anti-inflammatory activity against the dextran sodium sulfate-induced acute and chronic colitis in mice. However, further clinical studies need to be done to bring acetyl-11-keto-β-Boswellic as a potential anti-inflammatory drug candidate for the treatment of inflammatory bowel disease [102].

According to a recent study, it has been scrutinized that extract of *Boswellia serrata* works by a different mechanism to depict the potential activity against inflammatory bowel disease. 11-keto-β-Boswellic acid and acetyl-11-keto-β-Boswellic acid are the derivatives that inhibit the P-selectin protein expression in the endothelial leukocyte and in the intestinal microcirculation. It also inhibits the up-regulation of lipid peroxidation and iNOS expression [103].

Boswellia extract consisting of acetyl-11-keto-β-Boswellic acid was tested for inflammatory bowel disease. The results were compared with standard drug such as prednisolone and sulfasalazine in different animal models was concluded that it has potential activity against corn's disease and experimental ileitis condition [104].

Anti-viral Activity: Goswami *et al.* in a research study showed that the *Boswellic* acids present in methanolic extract of *Boswellia serrata* evaluated by MTT and plaque reduction assay resulted in anti-viral potential against the herpes simplex virus-1.

It inhibits the viral replication and down regulation of NFkB and p-38 MAP-kinase promotion [105]. The chikengunia virus has also been evaluated to be treated with the help of *Boswellia* serrata extract. It was observed that the gum resin extract block the entry of chikengunia virus and inhibited the CHKV infection, and also prevents the CHKV from spread in the skin hence proving to possess antiviral potential [106].

CONCLUSION: Frankincense was used in both traditional as well as a modern systems of medicine because of its numerous beneficial therapeutic potential. Various analogues of α-*Boswellic* acids and β-*Boswellic* acids have been reported to possess good pharmacological and therapeutic potential. It can also be noted that β-*Boswellic* acids such as acetyl-11-keto-β-Boswellic acid, 3-O-acetyl-11-keto-β-Boswellic acid, 11-keto-β-Boswellic acid and 3-acetyl-9, 11-dihydro-β-Boswellic acid, etc. have somewhat better therapeutic activities as compared to α-*Boswellic* acids. The different therapeutic activities found in *Boswellic* acids and their effectiveness toward svarious cellular and molecular targets such as growth factors, transcription factors, kinases, enzymes, and receptors in different therapeutic conditions have attracted researchers around the globe to develop and modify these molecules as an effective drug candidate.

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