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REVIEW ON PROPERTIES OF *BOSWELLIA SERRATA* IN INFLAMMATORY AND RHEUMATOID ARTHRITIS (RA) MANAGEMENT

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease which leads to destruction of joints. Since time immemorial, Boswellia species has been used as incense in religious and cultural ceremonies, as well as in medicines. *Boswellia serrata* (Salai/Salai guggul) is a medium to large-sized branching tree of the family Burseraceae (Genus Boswellia) that grows in dry mountainous areas of India, Northern Africa, and the Middle East. *Boswellia serrata* is primarily found in the Indian states of Andhra Pradesh, Gujarat, Madhya Pradesh, Jharkhand, and Chhattisgarh. The resinous part of *Boswellia serrata* contains monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids, and four major pentacyclic triterpenic acids, namely - boswellic acid, acetyl—boswellic acid, 11-keto—boswellic acid, and acetyl-11-keto—boswellic acid. Acetyl-11-keto-boswellic acid is the most potent inhibitor of 5-lipoxygenase, an enzyme involved in inflammation, of the four boswellic acids studied. A special extract of *Boswellia serrata* (BS) is effective in the treatment of rheumatoid arthritis (RA). The primary goal of this review is to scrutinize the anti-inflammatory and anti-arthritic activity of *Boswellia serrata*.

KEYWORDS: *Boswellia serrata*, Boswellic acid, Rheumatoid arthritis and inflammatory disorder.

INTRODUCTION

The Boswellia species (Burseraceae), which are trees native to Ethiopia, Somalia, India, and the Arabian Peninsula, produce olibanum gum resin (frankincense). Traditional medicine in many countries has used the resin of Boswellia carteri and *Boswellia serrata* to treat rheumatoid arthritis and other inflammatory diseases.[1] The dried bark exudate of the *B. serrata* tree is an oleo-gum resin known as Indian Frankincense, Indian olibanum, Incense, or Salai guggal. The dried gum appears in the form of white-yellow lumps or tears. The term frankincense, which means "pure incense," is derived from the ancient French name frankincense.[2] In Arabic, frankincense is also known as "al-luban," which means "white" or "cream," and is the source of its other name, olibanum.[3][4] In Chinese, it is referred to as Ru Xiang. The gum is used to treat a variety of inflammatory diseases affecting the skin, eyes, gums, gastrointestinal tract (GIT), and respiratory inflammatory disorders such as asthma, bronchitis, laryngitis, and others in Ayurveda, an Indian traditional system of medicine[5],[6] For centuries, gum resin extracts of *Boswellia serrata* (BSE) have been discovered as an anti-inflammatory herbal remedy and used for the treatment of inflammatory conditions in traditional Ayurvedic medicine in India.[7] Recent animal and human studies support BSE's potential for treating a variety of inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis, and osteoarthritis.[8] Inflammation is the body's first immune response when it is infected or irritated by an external attack. However, if it is not properly regulated, it can lead to inflammatory diseases. Chronic inflammation has been linked to certain cancers, neurodegenerative disorders, and rheumatoid arthritis in clinical studies.[9], [10], [11] the main constituents responsible for the anti-inflammatory property of *B. serrata* gum resin are the pentacyclic triterpenic acids known as boswellic acids.[12] The main mechanism underlying their anti-inflammatory effect is thought to be inhibition of leukotriene synthesis via 5-lipoxygenase (5-LOX). Boswellic acids (BAs) are non-redox inhibitors of 5-lipoxygenase that have no effect on 12-lipoxygenase or cyclooxygenase (COX) activity.[13], [14] Among the known BAs, 3-O-acetyl11-keto-b-boswellic acid (AKBA) inhibits 5-LOX the most effectively.[15] Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes cartilage and bone destruction within joints by inflammatory cells that migrate to synovial and periarticular tissue.[16], [17] Current RA treatments either provide symptomatic relief (nonsteroidal anti-inflammatory drugs; NSAIDs) or alter the disease process (disease-

modifying anti-rheumatic drugs; DMARDs).[18] In the US, 100,000 hospitalizations and 16,500 deaths per year are linked to NSAIDinduced ulcers and gastrointestinal bleeding in arthritic patients.[19] A study on the effect of BAs in BSA-induced arthritis found that when given orally, BAs (25, 50, and 100 mg/kg/day) significantly reduced the leukocyte population and suppressed its infiltration into the knee joint and also the pleural cavity in a BSA-injected knee. In addition, the electrophoretic pattern of the proteins in synovial fluid was altered.[20] We summarise the effect of *Boswellia serrata* on inflammatory disorders and Rheumatoid arthritis in this study.

Inflammatory Disorders

Inflammation is the body's first reaction to tissue damage caused by mechanical, chemical, or microbial stimuli. Tumor necrosis factor-alpha (TNF), interleukins (IL-1 and IL-6), interferons, and colony stimulating factors are some of the main molecules involved in the inflammatory response (CSFs). Monocytes/macrophages, polymorphonuclear leucocytes (PMNs), and endothelial cells are the primary cells involved in the inflammatory response. When such cells get to be activated, they aggregate and infiltrate tissue, where they undergo a respiratory burst, increasing oxygen consumption and the production of cytokines, reactive oxygen species (ROS), and other inflammatory mediators.[21], [22]

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the synovial joint lining and is associated with progressive disability, premature death, and socioeconomic burdens.[23] While there is currently no cure for RA, the treatment strategy aims to accelerate diagnosis and achieve a low disease activity state as quickly as possible (LDAS). There are numerous composite scales that measure disease activity, including the Disease Activity Score using 28 joints (DAS-28), the Simplified Disease Activity Assessment Index (SDAI), and the Clinical Disease Assessment Index (CDAI).[24] Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have been shown to be effective in relieving stiffness and pain, but they do not halting disease progression. The efficacy of DMARDs has received a lot of attention in the last 20 years because they can effectively reduce disease activity and significantly reduce and/or delay joint deformity.[25] TNF-inhibitors (Amjevita, Renflexis, Erelzi, Cyltezo, and Imradl), anti-CD20 antibodies (Truxima, Rixathon), IL-6 receptor antibodies (Kevzara), RANKL antibodies (Pralia), and JAK inhibitors are among the new biological DMARDs (Olumiant). Despite the increasing number of new drugs and treatment

regimens, many patients do not achieve complete long-term disease remission, necessitating the development of new drugs and treatment regimens.[26]

Furthermore, abnormalities in CD4 T cell repertoire (**Figure 1**) and phenotype in RA patients strongly suggest that these patients have an accelerated immune system ageing, which leads to oligoclonality and senescence of T cells, making these lymphocytes auto reactive. Understanding the mechanisms underlying these systemic alterations will be essential for the development of more effective therapies for RA treatment. Understanding the mechanisms underlying these systemic changes will be critical for the development of more effective RA therapies.

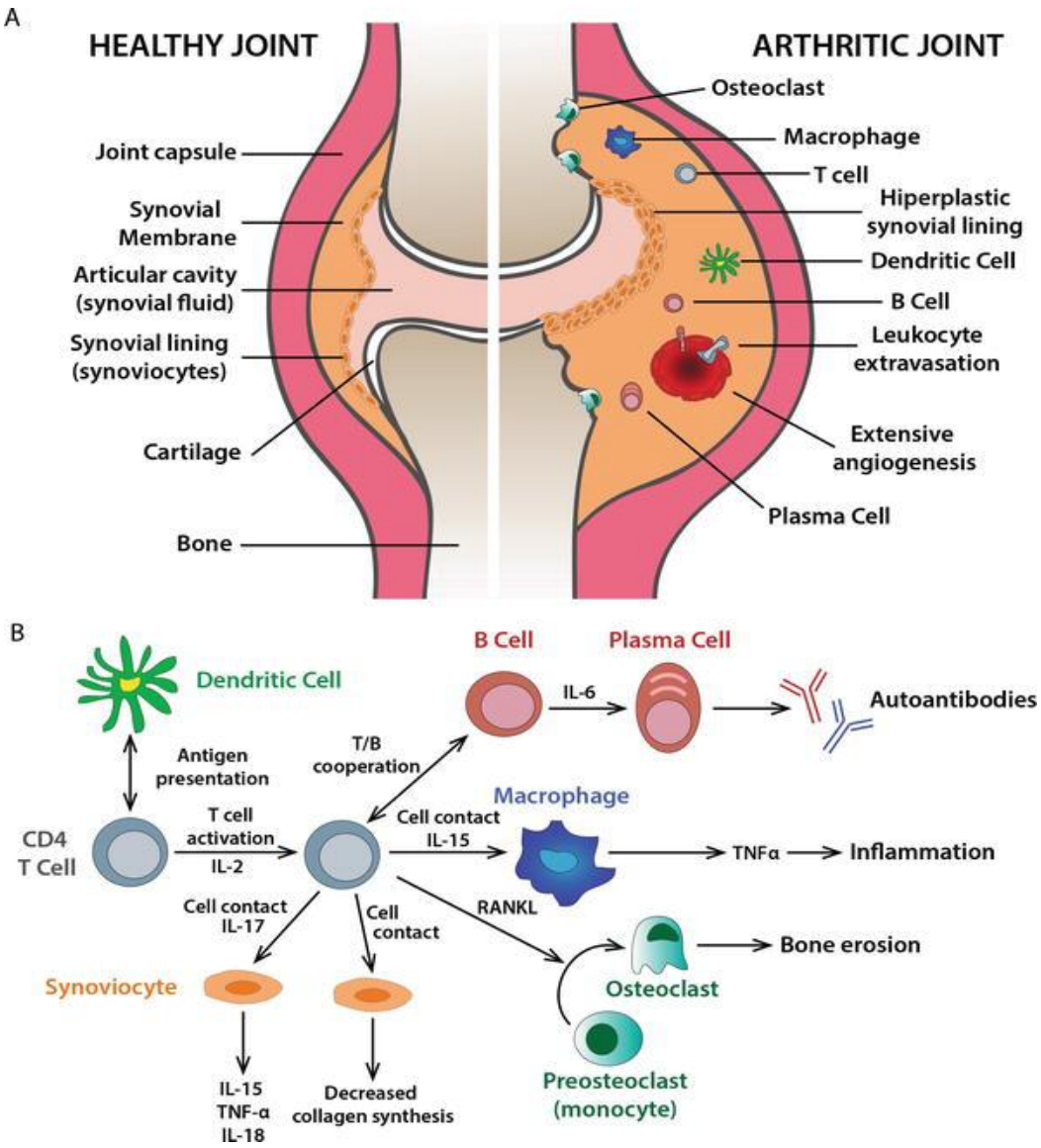

Figure 1: Role of cd4 t cells in rheumatoid synovitis. (a) in a healthy synovial joint (left), a thin layer of synoviocytes delimits the joint capsule. by contrast, in ra (right),

synoviocytes form an invasive synovial lining and leukocytes infiltrate the synovial membrane. (b) Activated cd4 t cells play a central role in inflammatory responses in the synovial membrane, including autoantibody production by plasma cells, secretion of inflammatory cytokines by macrophages and synoviocytes, bone erosion by osteoclasts and inhibition of collagen secretion by synoviocytes.[27]

PHARMACOLOGY OF *BOSWELLIA SERRATA* AGAINST ANTI-INFLAMMATORY AND ANTI-ARTHRITIC ACTIVITIES

Anti-inflammatory and anti-arthritic activities are tested against carrageen in-induced paw edema adjuvant arthritis in rats. DAESG treatment caused inhibition of the carrageen in induced rat hind paw oedema by 39.75% and 65-73%, administered orally (p.o) in dose ranges of 50-200 mg per kg-1 and interaperitoneal (i.p.) in dose range of 50-100 mg per kg respectively compared to 47% inhibition seen with phenylbutazone (50 mg/kg-1 p.o.). The anti-inflammatory effect was equally well marked in adrenalectomized rats. Within the anti-arthritic study on the mycobacterial adjuvant-induced poly-arthritis in rats, salai guggal showed 34% and 49% inhibition of paw swelling with 50 and 100 mg per kg (p.o.) doses respectively as compared to controls. Phenyl butazone in doses of 50 and 100 mg per kg (p.o.) showed 26% and 60% inhibition respectively.[28][29]

Curcumine from Curcuma longa and *Boswellia serrata* gum resin, both of which have been shown to be anti-inflammatory in in-vivo animal models, were studied in a series of in vitro experiments to elucidate the mechanism of their beneficial effects. Curcumine inhibited 5-lipoxygenase activity in rat peritoneal neutrophils, as well as 12-lipoxygenase and cyclooxygenase activity in human platelets. Curcumine demonstrated significant antioxidative activity in a cell-free peroxidation system. Thus, its effects on dioxygenases are most likely due to its reducing capacity. Boswellic acids were isolated and identified as the active principles from the gum resin of *Boswellia serrata*. Boswellic acids inhibited leukotriene synthesis via 5-lipoxygenase but had no effect on the activities of 12-lipoxygenase or cyclooxygenase. Furthermore, boswellic acids had no effect on the peroxidation of arachidonic acid by iron and ascorbate. The findings indicate that boswellic acids are non-redox inhibitors of leukotriene synthesis, either by interacting directly with 5-lipoxygenase or by blocking its translocation.[30]

Studies on alcoholic extract of salai guggal (AESG) revealed anti-inflammatory activity in carrageenan-induced paw edoema in rats and mice, as well as in Dextran-induced edoema in rats and adrenalectomized rats.[31] [32] [33]

In another study, AESG was found to have anti-arthritic properties against formaldehyde-induced arthritis. The alcoholic extract also inhibited inflammation-induced increases in serum transaminase and leukocyte count, but no antipyretic or analgesic effect was observed. Shrivastava et al. (2003) concluded that BAs work by inhibiting the synthesis of 5-LOX products. They also inhibit the enzymes topoisomerase, elasase, and C-3 convertase.[34] [35]

In an anti-arthritic study, it was identified that oral administration of BAs at doses of 25, 50, and 100 mg/kg/day to BSA-induced arthritic rabbits reduces the population of leucocytes in the BSA-injected knee and changes the electrophoretic pattern of synovial fluid protein. Local injection of BAs (5, 10, and 20 mg) into the knee 15 minutes before BSA reduces leukocyte infiltration into the knee joint and pleural cavity and inhibits polymorph nuclear leukocyte (PMNL) migration *in vitro.*[36]

According to Afsar et al. (2012) reveals, the methanol fraction prepared from *B. serrata* leaves contains a high concentration of total phenolics and total flavonoids, as well as strong reducing power, antioxidant activity and anti-inflammatory activity.[37] *B. serrata* also asserted fair to excellent anti-inflammatory results in 88 percent of patients in one of the clinical trials, with no adverse side effects.[38] BAs have anti-inflammatory properties due to the inhibition of leukotriene synthesis via 5-LO; however, it has no effect on the activities of 12-lipoxygenase (12-LO) and cyclooxygenase (COX) enzymes. Furthermore, BAs had no effect on the peroxidation of arachidonic acid by iron and ascorbate. The authors propose that BAs inhibit leukotriene synthesis by blocking translocation or directly interacting with 5-LO, acting as a potent anti-inflammatory agent. BAs administration alters the electrophoretic pattern of synovial fluid protein and decreases the number of leucocytes. The extract of *B. serrata* is also used to treat chronic polyarthritis.[39]

Khosravi et al. conducted a double blind randomized clinical trial in 2011 to evaluate the efficacy of Boswellia in moderate plaque induced gingivitis. They reported that Boswellia extract and powder have the ability to reduce periodontal inflammation associated with plaque-induced gingivitis due to anti-inflammatory effects produced by multiple mechanisms.[40]

BAs' anti-inflammatory action in various biological models was thought to be due to interference with the human glucocorticoid receptor (GR), resulting in suppression of the release of pro-inflammatory cytokines, and was thought to be similar to that of glucocorticoids (GCs). Scior et al. used radiometric binding assays and the GR response element dependent luciferase reporter assay method with dexamethasone (DEX) as a functional positive control to determine the molecular targets and binding of natural BAs ligands to the GR protein site. BAs were revealed to bind strongly to GR, despite the fact that they do not activate GR in comparison to DEX.[41]

In a prospective randomized clinical trial, Notarnicola et al. compared the efficacy of BA-Mehtylsulfonylmethane (MSM) to Glucosamine (GS) as an effective supplement in the management of knee arthritis. The obtained results were found to be consistent with the previously established anti-inflammatory and chondroprotective effects. The BA-MSM combination produced promising results and was found to be acceptable in terms of GS.[42],[43]

CONCLUSION

Frankincense, which was once used in religious ceremonies and traded for as much as gold, has gained popularity in both traditional and modern medicine due to its numerous health benefits. Therapeutic qualities BAs, or pent acyclic triterpenoids, are the most common type of pent acyclic triterpenoids. Acetyl-11-keto-beta-boswellic acid (AKBA) has bioactive phytoconstituents of boswellia. Experimental and clinical studies have yielded promising results. They can target a number of key players in the pathogenesis of these diseases. BA treatment has been shown to affect a variety of important molecular targets, including LO, MAPK, NF-B, TNF-, Erk-1/2, and others, all of which play important roles in the development of various chronic diseases. However, concerns about the pharmacokinetic properties have had a significant impact on the development of this compound as an effective drug. As a result, Boswellia serrata extract has significant phytomedicine potential and may represent an alternative to traditional medicine treatments for chronic inflammatory as well as rheumatoid arthritis.

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