Chapter

Boswellia Carries Hope for Patients with Inflammatory Bowel Disease (IBD)

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Abstract

Boswellia serrata is an ancient and valuable herb that was widely used throughout the centuries. *Boswellia* trees grow in India, Northern Africa, and the Middle East from which Frankincense or olibanum resin is taken. The beneficial effects of Boswellia and its active ingredients (Boswellic acids) were thoroughly investigated in many diseases. Where the non-redox and 5-lipoxygenase inhibitory actions were reported. Inflammatory bowel disease (IBD) mainly ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory disorders of the gastrointestinal system. Although the cause is still unclear, the immune system is claimed to have the upper hand in the pathogenesis of IBD. Several studies have demonstrated the ameliorating effect of Boswellic acids on the severity of IBD and the potential role of Boswellia in the induction or maintenance of remission. The aim of this chapter is to explore the the possible effect of *Boswellia* in IBD management as a complementary and alternative strategy.

Keywords: Boswellia, complementary and alternative medicine, inflammatory bowel disease, ulcerative colitis, Crohn's disease

1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory state classified mainly into ulcerative colitis (UC) and Crohn's disease (CD). IBD is associated with abdominal pain, diarrhea and rectal bleeding [1]. The choice of treatment for IBD varies according to the type and severity. A variety of medications such as aminosalicylates, corticosteroids, immunosuppressive and biologic drugs are involved [2]. Despite their crucial therapeutic role, some medications carry the risk of infection and cancer [3]. In addition, these drugs are taken throughout life, which leads to patient incompliance and hence treatment failure [4]. These obstacles in treatment insist on the search for other treatments, safe and effective as alternative and complementary modalities.

2. Pathogenesis of IBD

The exact mechanism of IBD is not completely clear [5]. The interaction between genetic factors, changes in intestinal flora homeostasis, environmental variabilities, and

intestinal hyperimmune response results in chronic intestinal inflammation [6]. Multiple inflammatory mediators are involved in IBD pathogenesis including leukotrienes, cytokines, chemokines, and prostaglandins. Alteration in reactive oxygen and nitrogen species production adds to the pathogenesis [7]. Based on this, attenuation of hyper-stimulated immune response is the target of IBD therapy. Where the treatment passes in 2 ways, the first is to induce remission and the second is to maintain the remission and to ameliorate intestinal chronic inflammation [8]. In normal conditions, there is a balance among many cells in intestinal lamina propria such as macrophages mast cells, neutrophils, dendritic cells (DCs), eosinophils, natural killer (NK), NKT cells, T and B cells. This provides intestinal protection and tolerance. As a response to bacterial infection, the innate immunity cells (macrophages and dendritic cells) upregulate chemokines and cytokines and act as Antigen-presenting cells (APCs) where they feature the microorganism's molecular patterns via toll-like receptors (TLR) [9, 10]. Dendritic cells generate native T cell differentiation in mesenteric lymph nodes [11]. With subsequent generation of T helper (Th) subtypes according to the cytokines produced by APCs [12–15]. Besides proinflammatory cytokines induction, neutrophils stimulate oxidative reactions in the intestinal mucosa [16]. In IBD activity, there is over-expression of many chemokines including macrophage inflammatory proteins (MIP), and Interleukin-8 (IL-8). Under the control of these chemokines, leukocytes are recruited to the inflamed intestine with subsequent oxidative stress [17]. Recruitment of granulocytes and lymphocytes is mediated by adhesion molecules in IBD, such as the intercellular adhesion molecule-1 (ICAM-1), the vascular cell adhesion molecule- (VCAM-) 1, P and E-selectins [18]. In addition, T-cell differentiation and regulation are mediated by cytokines. Th1 differentiation is controlled by IL-12, IL-18, and IL-23 while TNF-α, IL-1β, and IL-6, magnify the immune response by releasing more chemokines and attracting more inflammatory cells [19]. On the other hand, the under-production of IL-10 and Transforming growth factor beta (TGF-β), which are inflammatory attenuating cytokines, contributes to IBD pathogenesis [20, 21].

3. Complementary and alternative (CAM) treatment of IBD

There is a growing worldwide interest in complementary and alternative remedies in IBD treatment [22, 23]. The use of CAM is common for IBD children and adult patients [24, 25]. CAM is found to be commonly used among young, females, at a high educational level or with medication adverse effects [26, 27]. Patients who received massive corticosteroid therapy [28] or suffering from extraintestinal manifestations [24] are more inclined to CAM remedies, as well. Many alternative modalities have been tried in IBD patients including herbs, probiotics, acupuncture and hypnotherapy [8]. Phytochemicals are popularly utilized because of their safety and effectiveness on IBD patients [4, 29]. The variable active herbal ingredients which act on multiple inflammatory pathways and mediators support this preference [25]. *Aloe vera*, *Artemisia absinthium*, *Boswellia serrata* and *Curcuma longa* were widely studied for their effect on IBD [30].

4. *Boswellia serrata*

4.1 Structure of *Boswellia serrata*

Boswellia serrata oleo-gum resin, Indian frankincense was widely used for centuries in traditional medicine. Antioxidant and anti-inflammatory actions have been

extensively investigated in several studies on different diseases like colitis, bronchial asthma, arthritis and malignancies [31–35]. *Boswellia serrata* resin is composed of monoterpenes, diterpenes, triterpenes, pentacyclic triterpenic acids (boswellic acids) and tetracyclic triterpenic acids [36–39]. Boswellic acids (BA) compose up 30% of the resin of *Boswellia serrata*. They are organic acids, formed of a pentacyclic triterpene, a carboxyl group and at least one other functional group [40]. Among boswellic acids, 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid (AKBA) are the most active [41].

4.2 Pharmacological activities *of Boswellia serrata*

4.2.1 Anti-inflammatory action

Boswellia has variable pharmacological activities, anti-inflammatory properties were widely investigated in many studies. Acetyl-boswellic acids block leukotriene production through the downregulation of enzyme 5-lipoxygenase (5-LOX) mediated by a non-redox reaction [42, 43]. In a double-blind placebo control clinical study alcohol extract was given in a 300 mg thrice daily dose for 6 weeks. 70% of asthmatic patients gained clinical improvement [44]. Similarly, gradual control of asthma, regarding the frequency of attacks, pulmonary function tests improvement, and lowering levels of leukotrienes were obtained by another study [45]. In addition, Boswellia ameliorated the inflammation in arthritis [46–48]. Anti-anaphylactic and mast cell stabilizing effects were also reported where Boswellia suppressed mast cell degranulation [49]. Moreover, boswellic acids were found to possess anti-complement activity [50]. Roy et al. studied the genetic basis of anti-inflammatory effect of BA. Tumor necrosis factor alpha (TNFa) is one of the most crucial mediators of inflammation. TNF alpha induces inflammation by multiple mechanisms, one of them is by upregulation of the expression of adhesion molecules such as microvascular cellular adhesive molecul-1, VCAM-1 in a system of TNF alpha-induced gene expression in human microvascular endothelial cells (HMEC). Of 522 genes that were induced by TNFa 113 genes were highly sensitive to BE treatment both in vivo and in vitro. The function of these genes is linked to inflammation, and cell adhesion [51].

4.2.2 Anti-microbial action

Boswellia oils showed anti-microbial activity against five organisms. Minimum inhibition concentration ranged from 4 to 16 mg/ml against *Staphylococcus aureus*, 1.5–8.3 mg/ml against *Bacillus cereus*, 4.0–12.0 mg/ml against *Escherichia coli*, 2.0–12.8 mg/ml against *Proteus vulgaris* and 5.3–12.0 mg/ml against *Candida albicans* [52]. This effect may help in controlling intestinal infection in IBD management.

4.2.3 Anti-tumor action

Boswellic acids induced apoptosis through the upregulation of caspase-8 in colon cancer HT-29 cells [53]. In another study, Boswellia extract altered DNA methylation in colon cancer cells [54]. 4-Amino analogues prepared from β-boswellic acid and 11-keto-β-boswellic acid showed an apoptotic activity mediated by DNA fragmentation [55]. There are multiple pathways by which Boswellia exerts its anti-tumor action such as suppression of topoisomerases I and II [56]. It was also revealed that acetyl keto beta boswellic acid (AKBA) inhibits phosphorylation of ERK pathways and

consequently, impairs signal transduction and tumorigenesis [57]. Oxidative stress and nitric oxide production were mediated by Boswellia with subsequent apoptosis in human leukemia HL-60 cells [58]. This anti-tumor potential of Boswellia protects against colorectal cancer which is a common sequala of IBD [59].

4.2.4 Hepato-protective action

In the models of liver injury, hexane extract of oleo-gum-resin of Boswellia in lower doses (87.5 mg/kg p.o.) reduced marker enzymes and prevented the increase in liver weight with histological evidence of hepatoprotection while a mild effect was obtained by higher dose (175 mg/kg p.o.) [60].

4.2.5 Anti-lipidemic action

The aqueous extract of *Boswellia carterii* with other herbs improved the lipid profile of alloxan-induced diabetic rats [61]. Boswellia showed therapeutic potential for metabolic syndrome. Where Boswellia succeeded in lowering the lipid profile by decreasing the level of TNF-α, IL-1β and increasing the adiponectin level. This action is based on its antioxidant activity [62].

4.2.6 Hypoglycemic action

Herbal formulation containing *B. serrata* oleo-gum-resin induced a significant anti-diabetic activity on non-insulin-dependent diabetes mellitus [63]. Furthermore, a significant reduction in blood glucose levels and HbA1c was observed when *Boswellia serrata* was introduced for 17 days to diabetic rats in another study [64].

Based on the mentioned pharmacological actions, Boswellia can help in IBD in many ways, 5-lipoxygenase (5-LO) suppression, downregulation of Tumor necrosis factor alpha (TNF-α) and interleukins, P-selectin-mediated recruitment of inflammatory cells, decreasing reactive oxygen species (ROS), and by modulation intestinal motility [65–68].

4.3 Preclinical studies of *Boswellia* in IBD

In vitro study demonstrated the role of Boswellia in the suppression of leukotriene synthesis through interfering with 5-lipoxygenase pathway [69]. The anti-inflammatory effects of boswellic acids extended to inhibit the nuclear transcription factor kappa B (NF-κB) activation, this factor expresses and potentiates the proinflammatory cytokines including TNFα, IL-1β, and IL-6 [70, 71]. This effect was confirmed in an in vitro experimental model of intestinal inflammation where pretreatment of Caco-2 cells monolayers by *Boswellia serrata* oleo-gum extract (BSE) and AKBA abolished nuclear factor kappa B (NF-κB) activation, protected against cellular changes and inhibited reactive oxygen species (ROS) [72]. Furthermore, the anti-inflammatory and antioxidant properties of *Boswellia serrata* were explored in acetic acid (AA) induced UC rat model. Daily administration of 34.2 mg/kg of *Boswellia serrata* extract pre- and post-induction of colitis significantly improved tissue lesions, decreased lipid peroxidation and nitric oxide [73]. A semisynthetic form of acetyl-11-keto-β-boswellic acid ameliorated the disease activity and histology in dextran sodium sulfate (DSS) induced murine colitis. This action was mediated by attenuation of adherent leukocytes and platelets into inflamed tissue by blocking P-selectin

stimulation [66]. In an in vitro model of intestinal inflammation, the anti-inflammatory action of *Boswellia serrata* and *C. longa* were tested. *Boswellia serrata* at 1 μg/mL protected the intestinal epithelium with a 25% reduction of ROS generation [74]. The immunosuppressive potential of *Boswellia carteri* gum resin extract was illuminated in an in vitro study, where the extract attenuated human primary T lymphocyte proliferation in a concentration-dependent manner via nuclear factor of activated T-cells (NFAT) dependent mechanism [75]. Metabolism of sphingomyelin induces lipid signals that impact cell proliferation, and inflammation. 3-acetyl-11-keto-β-boswellic acids (AKBA) attenuated the expression of sphingomyelinase in intestinal cells. This provides other anti-inflammatory mechanism of Boswellia [76]. A new herbal formulation that includes Punica granatum L, Boswellia serrata, and Curcuma longa L extracts, inhibited TNF-alfa-induced release of IL-8, IL-6 and Monocyte chemoattractant protein-1 (MCP-1) in Caco-2 cells [77]. Although many studies support the anti-inflammatory action of Boswellia, on the contrary, Kiela et al. claimed that Boswellia showed no effect on improving colitis in dextran sulfate sodium (DSS)- or trinitrobenzene sulfonic acid- (TNBS-) induced experimental models [78]. Anti-fibrotic effect of Boswellia was declared when oral *Boswellia* in combination with significantly improved the inflammation of trinitrobenzene sulphonic acid (TNBS)-induced chronic colitis. There was an improvement in the histological features of colonic fibrosis. Together with a significant reduction in the expression of alpha-smooth muscle actin (α-SMA), collagen I–III, connective tissue growth factor (CTGF) and transforming growth factor-beta1 (TGF-β1) [79].

4.4 Clinical studies of *Boswellia* in IBD

Boswellia serrata in a dose of 350 mg thrice daily for 6 weeks achieved remission in 82% of treated UC patients compared to 75% of patients who were treated with sulfasalazine (1 g thrice daily). Inflammatory parameters were better in Boswellia treated group as well [80]. Another trial was conducted on 30 patients with chronic colitis for 6 weeks. Of 20 patients who received daily 900 mg *Boswellia serrata,* improvement of inflammatory parameters and remission were noticed in (18 and 14 patients, respectively) while after treatment of 10 patients with 3 gm sulfasalazine daily 6 participants showed improvement in inflammatory parameters and remission was achieved in 4 patients [81]. Boswellia tolerability and ability to maintain remission were demonstrated in a 52-week multicenter double-blind, placebo-controlled, randomized Germain study. 82 CD patients were randomly divided, 42 patients received daily Boswellia in 400 mg capsules and 40 patients received a placebo. There was no difference in both groups in parameters of inflammation or disease activity or maintaining remission and Boswellia was well tolerated [82]. Another 4-week trial was conducted on UC patients who were in remission. *Boswellia serrata* extract (BSE) was introduced orally, in a novel delivery form to 22 patients compared to 21 patients with no treatment. Improvement in clinical parameters, a decrease in medication needs and a lowering in fecal calprotectin levels were observed in Boswellia treated group [83]. The effect of Boswellia was tried in patients with collagenous colitis as well, where 400 mg oral BSE was given thrice daily for six weeks compared to a placebo. The remission rate was higher in BSE-treated patients but without any changes in histology or quality of life [34]. We conducted a 6-week clinical trial on 60 patients with active ulcerative colitis to investigate the effect of Boswellia extract on disease activity. 20 patients received Mesalamine 3, 20 patients received Boswellia extract in the form of oral tablets in a dose of 2 gm/day, and 20 patients were given Boswellia

extract plus Mesalamine in the mentioned doses. Clinical and laboratory improvement was noticed in the three groups without a significant difference. There were no recorded side effects of Boswellia during the 6 weeks of the study [84].

5. Conclusion

Based on preclinical and clinical studies, the anti-inflammatory, immune modulation, and anti-cancer activities of Boswellia as well as its safety and tolerability recommend its therapeutic use in IBD patients.

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Conflict of interest

I confirm that there are no conflicts of interest.

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