AARDS
COVID-19 LONG HAULER CLINIC

Preventing and Treating Long-Haul COVID-19 and Other Types of Inflammation

All active ingredients being included are considered GRAS in the US. **Generally recognized as safe (GRAS)** is a United States Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts.

Boswellia Serrata (AKBA)

Boswellic acids/Boswellia serrata extract as a potential COVID-19 therapeutic agent in the elderly:

B. serrata has been traditionally used in folk medicine for centuries to treat coughs, asthma, and various chronic inflammatory diseases of the lung. It contains many active ingredients responsible for the inhibition of pro-inflammatory cytokines, 5-lipoxygenase, and leukotriene production which is responsible for inflammation (Bosworth et al. 1983; Rashan et al. 2019). Boswellic acids and *B. serrata* extract have been demonstrated to suppress human leukocyte elastase (HLE), which may be involved in the pathogenesis of cystic fibrosis, chronic bronchitis, ARDS, and emphysema. HLE (a serine protease) is responsible for initiation of injury to the tissues and triggers the process of inflammation. HLE reduces the elasticity of the lungs and removal of mucus. It also constricts the lung passages and damages the secretion of mucus in the lungs. Boswellic acids and *B. serrata* extract have unique character owing to the dual inhibition of 5-lipoxygenase and HLE (Safayhi et al. 1997; Siddiqui 2011; Zhang et al. 2019; Roy et al. 2019). In a recent study, Gilbert et al. (2020) investigated the precise effect of *B. serrata* extract on the production of leukotienes, inflammatory mediators associated with asthma, by studying the structural changes and molecular mechanism of 5-lipoxygenase inhibition by AKBA. They observed that AKBA not only inhibited the formation of classical 5-lipoxygenase products but also caused a switch from the production of pro-inflammatory leukotrienes to the formation of anti inflammatory LOX-isoform-selective modulators.

There are a large number of findings in the literature showing the antioxidant and anti-inflammatory effects of *B. serrata* and its phytochemicals. They have multiple modes of action, e.g., by inhibiting interleukin-1β (IL-1β), IL-6, inducible nitric oxide synthase (iNOS) mRNA expression, NF-B phosphorylation, synthesis of leukotriene and 5-lipoxygenase activity, and ameliorating oxidative stress (Miao et al. 2019; Efferth and Oesch 2020). Several investigations have suggested that boswellic acids and *B. serrata* extract can counteract free radicals that cause inflammation and thereby prevent tissue damage. It has been shown that *B. serrata* treatment alleviated oxidative stress and improved total antioxidant capacity in the liver, and reduced the expression of TNFα, NF-κB, TGFβ, IL-6, and

cyclooxygenase-2 (COX-2) (Eltahir et al. 2020). On a histopathological level, *B. serrata* treatment also exhibited antifibrotic activity (Eltahir et al. 2020). The anti-inflammatory activity of *B. serrata* extracts on endothelial cells leads to a therapeutic application for cardiovascular and respiratory health (Bertocchi et al. 2018).

The anti-inflammatory and antioxidative effects displayed by *B. serrata* extract suggest a new supportive treatment option in acute systemic inflammation and wound healing (Loeser et al. 2018; Pengzong et al. 2019). Also, *B. serrata* extract and boswellic acids both counteract free radicals (ROS) and significantly protect the intestinal epithelial barrier from inflammatory damage and inhibit NF-B phosphorylation induced by inflammatory stimuli (Catanzaro et al. 2015). Additionally, acetyl-11-keto-beta-boswellic, in a dose-dependent manner, prevents testicular torsion/detorsion injury in rats with induced upregulation of 5-LOX/LTB4 and p38-MAPK/JNK/Bax pathways and their concomitant inflammatory and apoptotic pathways. It works by inhibiting the 5-LOX/LTB4 and p38-MAPK/JNK/Bax/Caspase-3 pathways (Ahmed et al. 2020). This protective effect is mediated by suppressing levels of intracellular oxygen free radicals, lipid peroxidation, oxidative DNA damage, and inflammation (Sadeghnia et al. 2017; Ahmad et al. 2019). The neuroprotective activities of *Boswellia* extract and boswellic acids mediated through the inhibition of the oxidative stress were observed also against glutamate toxicity-induced cell injury (Bai et al. 2019; Rajabian et al. 2016, 2020).

It is important to emphasize the ability of *B. serrata* to mitigate the uncontrolled activation of the innate immune response and suppress the release of cytokines. It has been observed that lipophilic extract of *B. carterii* gum resin inhibited the proliferation, degranulation capacity, and secretion of inflammatory mediators of physiologically relevant anti-CD3 and anti-CD28 activated human T lymphocytes in a non toxic concentration (Zimmermann-Klemd et al. 2020). *B. serrata* or boswellic acids inhibit the production of pro-inflammatory cytokines including TNFα, IL-1, IL-2, IL-6, IL-12, and IFNγ (Gayathri et al. 2007; Gomaa et al. 2019). Also, many investigators confirmed that *B. serrata* extracts and their active ingredients boswellic acids significantly inhibited the release of pro-inflammatory cytokines, such as TNFα, IL-1β, IL-6, IL-8, and IL-10 (Schmiech et al. 2019, 2021).

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Boswellia Serrata, A Potential Anti-inflammatory Agent:

In vitro studies and animal models show that boswellic acids were found to inhibit the synthesis of pro inflammatory enzyme, 5-lipoxygenase (5-LO) including 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB-4), which cause bronchoconstriction, chemotaxis, and increased vascular permeability[33–38]. Other antiinflammatory plant constituents, such as quercetin, also block this enzyme, but they do so in a more general fashion, as an antioxidant, whereas boswellic acids seem to be specific inhibitor of 5-LO[39]. 5-LO generates inflammatory leukotrienes, which cause inflammation by promoting free radical damage, calcium dislocation, cell-adhesion and migration of inflammation

producing cells to the inflamed body area. In contrast to non-steroidal antiinflammatory drugs (NSAIDS), which are well known to disrupt glycosaminoglycan synthesis, thus accelerating articular damage in arthritic conditions, boswellic acids have been shown to significantly reduce glycosaminoglycan degradation[40–43]. *In vivo* study examining the effect of *Boswellia* extract and ketoprofen on glycosaminoglycan metabolism showed that *Boswellia* considerably reduced the degradation of glycosaminoglycans compared to controls, whereas ketoprofen caused a reduction in total tissue glycosaminoglycan content[44].

In vitro studies by Ammon *et al*. in 1993 also elucidated that boswellic acids were found to inhibit leukotriene synthesis via 5-LO, but did not affect the 12-lipoxygenase or cyclooxygenase activities, nor did they prevent peroxidation of arachidonic acid by iron or ascorbate. Boswellic acids were, therefore, shown to be specific, non-redox inhibitors of leukotriene synthesis, either interacting directly with 5-LO or blocking its translocation[45,46]. Boswellic acids have also been observed to inhibit human leukocyte elastase (HLE), which may be involved in the pathogenesis of emphysema. HLE also stimulates mucus secretion and thus may play a role in cystic fibrosis, chronic bronchitis and acute respiratory distress syndrome[47,48]. HLE is a serine protease, which initiates injury to the tissues which, in turn, triggers the inflammatory process. This dual inhibitory action on the inflammatory process is unique to boswellic acids. Of these four boswellic acids, 3-acetyl-11-keto-β-boswellic acid (AKBA) is the most potent inhibitor of 5-LO, an enzyme responsible for inflammation.
Singh *et al*.[49] studied the antiinflammatory activity of mixture of boswellic acids and observed 25-46% inhibition of paw oedema in rats and mice. They have also reported that in chronic test of formaldehyde arthritis it exhibited 45-67% anti-arthritic activity in a similar dose range. The fraction was effective in both adjuvant arthritis (35-59%) as well as established arthritis (54-84%). It also showed antipyretic effect, with no ulcerogenic effect. Kulkarni *et al*. and Chopra *et al*. have reported clinical trials of *Boswellia*'s antiinflammatory properties in combination with *Withania somnifera, Zingiber officinate* and *Curcuma longa* and the isolated effects of *Boswellia* on rheumatoid arthritis could not be revealed[50,51]. However, the clinical trials of gum-resin of *Boswellia* alone have shown to improve symptoms in patients with osteoarthritis, and rheumatoid arthritis[52,53]. The boswellic acid from *Boswellia serrata*, when tested on new model i.e. Papaya Latex Model, showed significant activity of mean 35% inhibition of inflammation. Since the new model is reported to be sensitive to slowly acting remission-inducing drugs, its effectiveness on boswellic acid throws some light on its mechanism of action, which seems to be unlike aspirin and steroidal drugs[54]. Poeckel and Werz in 2006 have summarized the biological actions of boswellic acids on the cellular and molecular level and attempted to put the data into the perspectives of the beneficial effects manifested in animal studies and trials with human subjects related to inflammation and cancer[55]. Sharma *et al*.[56] have reported the effect of boswellic acids on bovine serum albumin (BSA)-induced arthritis in rabbits.

Gayathri *et al*.[57] in 2007 have reported that pure compound from *Boswellia serrata* extract exhibits antiinflammatory property in human peripheral blood mononuclear cells (PBMCs) and mouse macrophages through inhibition of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta),

NO and mitogen activated protein (MAP) kinases. Incensole acetate, a novel antiinflammatory compound isolated from *Boswellia* resin inhibits nuclear factor-kappa B activation[58]. Boswellic acids are direct 5-LO inhibitors that efficiently suppress 5-LO product synthesis in common *in vitro* test models. However, the pharmacological relevance of such interference *in vivo* seems questionable[59]. Acetyl-11-keto-β-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2- mediated angiogenesis[60].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3309643/

Role of nutraceuticals in respiratory and allied diseases:

Boswellia serrata (family *Burseraceae*) is commonly found in many regions of the world, such as South Asia, Northern Africa, and the Middle East. Traditional medicine using extracts made from this plant has long been used to treat asthma. These extracts contain resin, amino acids, phenols, terpenes, polysaccharides, and β-boswellic acid, the major active antiinflammatory component. Extracts of *B. serrata* or β-boswellic acid have been reported to inhibit hypersensitivity reactions by regulating both the humoral and cellular immune systems. They decrease primary antibody synthesis, inhibit polymorphonuclear leukocyte proliferation and infiltration, enhance the phagocytic function of macrophages, suppress the classical and alternative complement pathways, and suppress the inflammatory process, one of the critical pathological features in asthma (Khajuria et al., 2008). They also inhibit histamine release from MCs challenged with G protein stimulator c48/80 in a dose dependent manner (Pungle et al., 2003). β-Boswellic acid can downregulate the synthesis of prostaglandins by inhibiting COX-1 in intact human platelets (Siemoneit et al., 2008). It has been shown that β-boswellic acid inhibits the production of proinflammatory cytokines, including TNF-α, IL-1, IL-2, IL 6, IL-12, and IFN-γ, by suppressing the activation of NF-κB (Gayathri et al., 2007). These results suggest that *B. serrata* might be effective in controlling the inflammation process and contraction of airway smooth muscle in asthmatic conditions by inhibiting enzymes required for the production of proinflammatory mediators and bronchoconstrictors. Preliminary clinical investigation has shown that *B. serrata* has a potential therapeutic effect on asthma (Ammon et al., 1991). Clinical study results suggest that *B. serrata* extract has potential benefit for asthma patients (Gupta et al., 1998). A novel herbal composition LI13109F, containing extracts of *B. serrata* gum resin and *Aegle marmelos* fruit, improved asthma symptoms by reducing IL-4 levels and increasing IFN-γ in a double-blind controlled clinical trial (Kaluza et al., 2018).

https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/boswellia-serrata

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