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REVIEW

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

Adel A. Gomaa[1] · Hamdy S. Mohamed[3] · Rasha Bakheet Abd-ellatief[1] · Mohamed A. Gomaa[2]

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Abstract

The most severe cases of COVID-19, and the highest rates of death, are among the elderly. There is an urgent need to search for an agent to treat the disease and control its progression. *Boswellia serrata* is traditionally used to treat chronic inflammatory diseases of the lung. This review aims to highlight currently published research that has shown evidence of potential therapeutic effects of boswellic acids (BA) and *B. serrata* extract against COVID-19 and associated conditions. We reviewed the published information up to March 2021. Studies were collected through a search of online electronic databases (academic libraries such as PubMed, Scopus, Web of Science, and Egyptian Knowledge Bank). Several recent studies reported that BAs and *B. serrata* extract are safe agents and have multiple beneficial activities in treating similar symptoms experienced by patients with COVID-19. Because of the low oral bioavailability and improvement of buccal/oral cavity hygiene, traditional use by chewing *B. serrata* gum may be more beneficial than oral use. It is the cheapest option for a lot of poorer people. The promising effect of *B. serrata* and BA can be attributed to its antioxidant, anti-inflammatory, immunomodulatory, cardioprotective, anti-platelet aggregation, antibacterial, antifungal, and broad antiviral activity. *B. serrata* and BA act by multiple mechanisms. The most common mechanism may be through direct interaction with IκB kinases and inhibiting nuclear factor-κB-regulated gene expression. However, the most recent mechanism proposed that BA not only inhibited the formation of classical 5-lipoxygenase products but also produced anti-inflammatory LOX-isoform-selective modulators. In conclusion a small to moderate dose *B. serrata* extract may be useful in the enhancing adaptive immune response in mild to moderate symptoms of COVID-19. However, large doses of BA may be beneficial in suppressing uncontrolled activation of the innate immune response. More clinical results are required to determine with certainty whether there is sufficient evidence of the benefits against COVID-19.

Keywords Boswellic acids/*Boswellia serrata* · Antioxidant · anti-inflammatory · Antiviral immunomodulator · COVID-19

Abbreviations

ARDS	Acute respiratory distress syndrome
B. serrata	*Boswellia serrata*
BA	Boswellic acids
KBA	11-Keto-β-boswellic acid
AKBA	3-*O*-Acetyl-11-keto-β-boswellic acid
ACE2	Angiotensin-converting enzyme 2
Bax	Bcl-2-associated X protein
COX-2	Cyclooxygenase-2
GATA3	GATA binding protein 3
GSK-3β	Glucogen synthase kinase-3 beta
GSH	Glutathione
HLE	Human leukocyte elastase
iNOS	Inducible nitric oxide synthase
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
JAK	Janus kinase
JNK	C-Jun N-terminal kinase
KBA	11-Keto-β-boswellic acid
5-LOX	5-Lipoxygenase
LTB4	Leukotriene B4
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
MERS-CoV	Middle East respiratory syndrome coronavirus

✉ Adel A. Gomaa
a.gomma@aun.edu.eg

[1] Department of Medical Pharmacology, Faculty of Medicine, Assiut University, Assiut, Egypt

[2] Department of Plastic Surgery, Faculty of Medicine, Assiut University, Assiut, Egypt

[3] Department of Internal Medicine, Faculty of Medicine, Sohage University, Sohâg, Egypt

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NF-κB	Nuclear factor kappa B
SASP	Senescence-associated secretory phenotype
SARS-CoV	Severe acute respiratory syndrome coronavirus
STAT	Signal transducer and activator of transcription
SOD	Superoxide dismutase
TNFα	Tumor necrosis factor alpha

Introduction

Coronavirus disease 2019 (COVID-19) is a kind of viral pneumonia caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The emerging COVID-19 pandemic has caused a major global health threat. Also, it has caused a lot of economic damage to most countries of the world (Rothan and Byrareddy 2020). Acute respiratory distress syndrome (ARDS) in severe cases is the main cause of death associated with COVID-19. The deadly uncontrolled systemic inflammatory response results from the release of large amounts of pro-inflammatory cytokines and chemokines. The cytokine storm triggers a violent attack by the immune system on the body, causing ARDS and multiple organ failure, and finally leading to death in severe cases of SARS-CoV-2 infection (Xu et al. 2020; Huang et al. 2020).

The elderly are more likely to get ARDS, so the most severe cases of COVID-19, and the highest rates of death, are among the elderly. However, the elderly are more likely to die from other causes, and the virus is more likely to affect the heart in the elderly, so it has been shown that people with COVID-19 die from heart attacks or stress on the body in general (Yanez et al. 2020; Lloyd-Sherlock et al. 2020). The impaired immune response in older individuals, i.e., immunosenescence and inflammaging play a major role in contributing to the significantly higher mortality rates seen in the elderly (Chen et al. 2021). Immunosenescence and inflammaging are key features of the aging immune system as the accumulation of senescent immune cells contributes to its degradation and, at the same time, an increase in inflammatory phenotypes leads to immune dysfunction (Bajaj et al. 2021). It has been suggested that senotherapeutic agents can reduce RNA virus replication in senescent cells and may have potential therapeutic activity against COVID-19 (Malavolta et al. 2020).

Older adults are less able to respond to new antigens because of the decreased frequency of naive T cells. They cannot frequently clear the virus through an efficient adaptive immune response as in young people. Indeed, antibody-secreting cells and follicular helper T cells are thought to be less effective than in young patients (Kadambari et al. 2020). As a result of failure to elicit an effective adaptive immune response, the elderly are more likely to have the uncontrolled activation of the innate immune response that leads to cytokine release syndrome and tissue damage (Cunha et al. 2020).

Currently, there is no registered treatment for COVID-19; therefore, scientists are concerned with searching for a drug to treat this disease. The availability of the SARS-CoV-2 vaccines to a large proportion of the population is, unfortunately, something that currently differs greatly between different countries. Furthermore, virus mutations may be a major problem in the effectiveness of the vaccines based on viral-encoded peptides. Many treatment regimens have been tried in the treatment of COVID-19; some show initial promise. On the basis of their antiviral effect against COVID-19 in vitro studies, the anti-rheumatoid chloroquine and hydroxychloroquine with or without azithromycin have received the most attention among antiviral treatments (Gao et al. 2020; Dong et al. 2020). However, the incidence of drug toxicity as QTc prolongation and retinal toxicity should be considered before the use of the drug (Fedson 2016; Singh et al. 2020).

More recently, many investigators have suggested that JAK inhibitors, typically used as anti-inflammatory and anti-rheumatoid arthritis agents, are a novel treatment strategy for COVID-19. Several clinical trials confirmed that baricitinib has a dual action, demonstrating its ability to block the entry of the virus into target cells and reduce markers of inflammation (Stebbing et al. 2021). It inhibits the pro-inflammatory cytokine interleukin-6 (IL-6) signaling causing cytokine storm mediated by the JAK-STAT pathway in severe COVID-19 (Zhang et al. 2020; Wu and Yang 2020). Plasma levels of IL-6 have been reported to be a predictive indicator of mortality (Stebbing et al. 2020). Anti-inflammatory combination therapy of baricitinib and dexamethasone in severe COVID-19 was associated with greater improvement in lung function when compared to corticosteroids alone (Seif et al. 2020; Rodriguez-Garcia et al. 2021; Kim et al. 2021; Pum et al. 2021).

Several herbs have been identified as anti-inflammatory and immunomodulating agents that have been suggested to treat coronavirus (Editorial, Nature Plants 2020). It is reported that traditional Chinese medicine has been used in the control of infectious disease and many patients with SARS-CoV infection have benefited from these herbal treatments (Yang et al. 2020; Luo et al. 2020).

Gum resin extract of *Boswellia serrata* (*B. serrata*) has been used for centuries to treat a wide range of inflammatory diseases such as arthritis, diabetes, asthma, cancer, or inflammatory bowel (Roy et al. 2019). Zang et al. (2019) confirmed that the anti-inflammatory effect of *B. serrata* could be a potential therapy for the treatment of several inflammatory diseases. Phytochemical examination by thin-layer chromatography showed the main components present in the gum resin of *B. serrata* included terpenoids, phenolic

compounds, flavonoids, and phenylpropanoids (Ayub et al. 2018). More than 12 different boswellic acids have been identified as components of the *B. serrata* extract, but only KBA (11-keto-β-boswellic acid) and AKBA (3-*O*-acetyl-11-keto-β-boswellic acid) have received marked pharmacological interest (Katragunta et al. 2019) (Fig. 1). The limited aqueous solubility and lipophilicity of these pentacyclic triterpenic acids decrease their bioavailability and pharmacological activity. The pharmaceutical development of KBA and AKBA has been extremely limited because of their low oral bioavailability (Sharma and Jana 2020). Other components such as phenolic compounds and flavonoids (quercetin, kaempferol) also play important roles in the anti-inflammatory actions of *B. serrata* (Gohel et al. 2018).

This review aims to highlight currently published research that has shown evidence, based on the activity of *B. serrata* against pulmonary lesions, oxidative stress, inflammation, immune disturbance, viruses, and secondary microbial infection, for the potential therapeutic effects of boswellic acids (BA) and *B. serrata* extract against COVID-19 and the conditions associated with it.

Methods

We reviewed the published information up to March 2021. Studies were collected through a search of online electronic databases (academic libraries such as PubMed, Scopus, Web of Science, Google Scholar, and Egyptian Knowledge Bank).

Therapeutic basis of the potential use of BAs and *B. serrata* extract against SARS-CoV-2

Based on scientific evidence, a recent publication suggested that some plant extracts or their components could have a role in the prevention and early treatment of symptoms of viral respiratory infections, and their rational management may also become a complementary treatment for patients with COVID-19 and post-COVID-19 (Firenzuoli et al. 2020). In *B. serrata* and in *Glycyrrhiza glabra*, several bioactive ingredients can reduce the production of ILs and leukotrienes. These medicinal plants are widely used in traditional Chinese medicine with some evidence of the effectiveness in the management of hepatitis B, HIV, SARS-CoV, and COVID-19 (Firenzuoli et al. 2020; Gomaa and Abdel-Wadood 2021). In our perspective review, we will discuss and evaluate the different effects of BAs and *B. serrata* extract that may be useful in combating SARS-CoV-2 and neutralizing any tissue-destructive effects of the virus (Fig. 2).

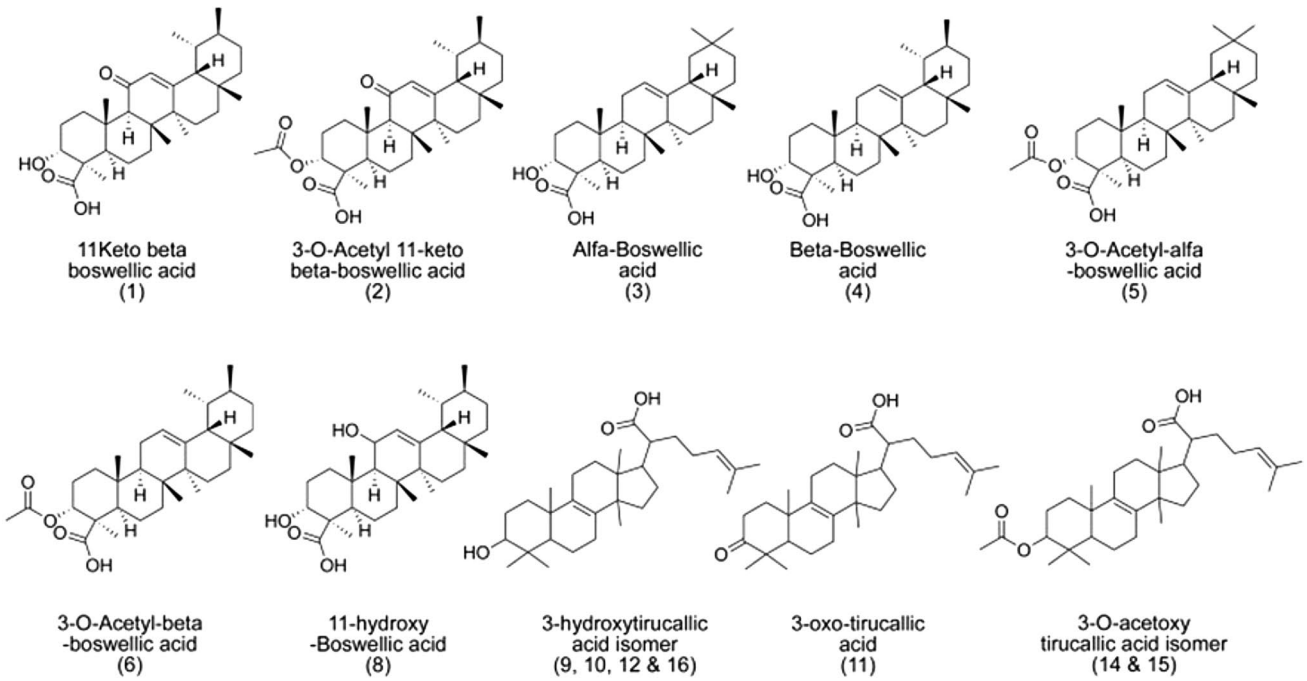

Fig. 1 Chemical structure of boswellic acids (Katragunta et al. 2019)

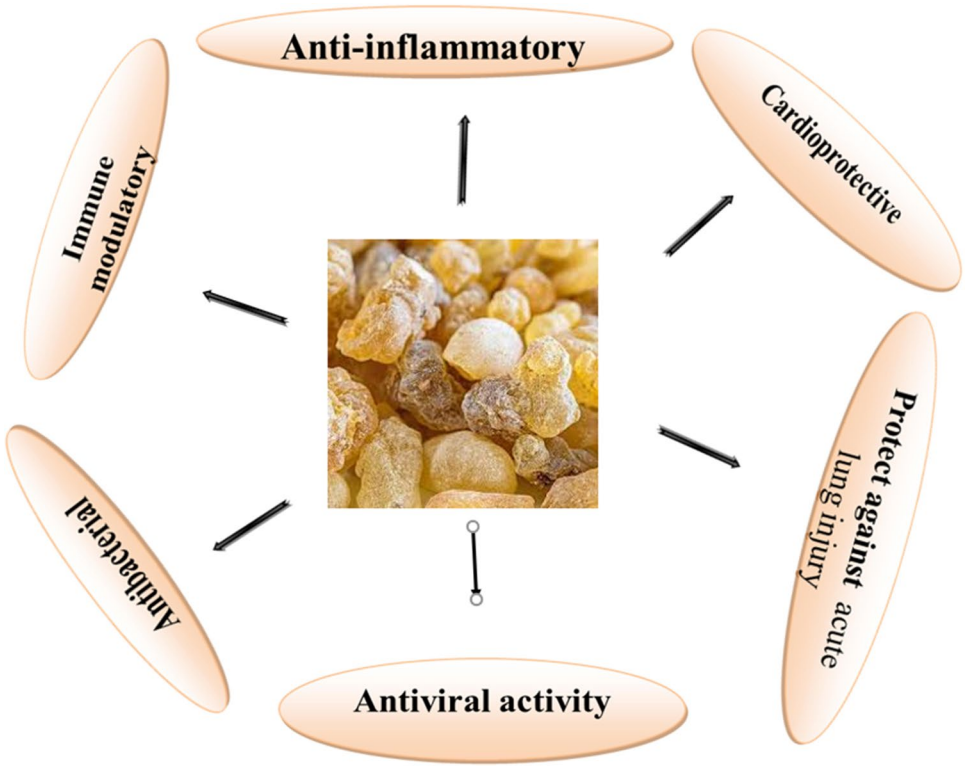

Fig. 2 Potential therapeutic effects of *B. serrata* gum, *B. serrata* extract, and boswellic acids in treating similar symptoms experienced by patients with COVID-19

Potential therapeutic effects of boswellic acids/*B. serrata* extract against SARS-CoV-2-induced pulmonary lesions

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.

Moreover, *B. serrata* extract could combat bleomycin-induced injury, collagen accumulation, airway dysfunction, and pulmonary fibrosis in rats (Ali and Mansour 2011). Additionally, *B. serrata* extract showed a direct concentration-dependent relaxant effect on rat trachea precontracted with either ACh or KCl in vitro. These results may partly contribute to validating the traditional use of *B. serrata* in treating lung diseases (Hewedy 2020).

The anti-asthmatic activity of *B. serrata* was confirmed early, in a double-blind placebo controlled clinical study with 300 mg thrice daily dose for 6 weeks (Gupta et al. 1998). In other clinical studies by Houssen et al. (2010) and Al-Jawad et al. (2012) *B. serrata* extract was effective in the management of bronchial asthma owing to its natural anti-inflammatory and leukotriene inhibitory actions. It reduces the need for inhalation therapy with corticosteroids and long-acting beta-agonists (Ferrara et al. 2015). Moreover, Liu et al. (2015) and Zhou et al. (2015) demonstrated that boswellic acid attenuates asthma phenotypes by downregulation of GATA3 via pSTAT6 inhibition. These results suggest that *B. serrata* might be effective in controlling the inflammation process in asthmatic conditions by inhibiting the production of pro-inflammatory mediators (Rashan et al. 2019). A more recent study suggested that *B. serrata* ethanolic

extracts possess significant anti-inflammatory activities in HL-60 cell lines and in BALB/c mice. This study is further support for use of *B. serrata* in the treatment of allergy, asthma, and other lung disorders (Soni et al. 2020). These therapeutic effects of *B. serrata* against induction of pulmonary lesions may be beneficial for the prevention of pulmonary lesions caused by COVID-19.

Potential therapeutic effects of boswellic acids/*B. serrata* extract against SARS-CoV-2-induced modification of cellular redox, inflammation, tissue injury, and severe hypercoagulability

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).

Several investigations indicate that the antioxidant, anti-inflammatory, and immunomodulatory effects are not limited to one specific type of *Boswellia* (Efferth and Oesch 2020). Boswellia species showed 5-lipoxygenase and cyclooxygenase (COX-1, 2) inhibitory activity (Siddiqui 2011). In addition, boswellic acids and other derivatives have been demonstrated to reduce the production of inflammatory cytokines, including IL-1, IL-2, IL-6, IFNγ, and TNFα that are ultimately directed to tissue destruction such as lung, cartilage, and insulin-producing cells. The mechanism of the anti-inflammatory therapeutic effects may be through direct interaction with IκB kinases and inhibiting nuclear factor-κB-regulated gene expression (Ammon 2016). The main mechanism of *B. serrata* may also be through the elimination of the senescent cells that secrete a group of pro-inflammatory cytokines, chemokines, and proteases called the senescence-associated secretory phenotype (SASP) (Xu et al. 2018). These pro-inflammatory mediators are responsible for tissue dysfunction during aging, obesity, and inflammatory diseases (Muñoz-Espín and Serrano 2014). Natural agents such as quercetin and kaempferol (components of *B. serrata*) have been reported to eliminate cellular senescence in vitro and in mice (Gohel et al. 2018; Lewinska et al. 2020). In vitro and in vivo evidence showed that AKBA significantly promotes peripheral nerve repair and Schwann cell proliferation after rat sciatic nerve injury (Jiang 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).

There are some clinical studies published in peer-reviewed scientific journals that draw conclusions about the clinical benefit of *B. serrata* and its phytochemicals in chronic inflammatory diseases. The clinically measurable improvements with *B. serrata* and its phytochemicals can be achieved in osteoarthritis, multiple sclerosis, bronchial asthma, and psoriasis (Efferth and Oesch 2020; Yu et al. 2020). Moreover, in a preliminary controlled trial in ischemic stroke, *B. serrata* could improve clinical outcomes in the early phases of stroke along with promising changes in plasma inflammatory factors. The levels of plasma inflammatory markers (TNFα, IL-1β, IL-6, IL-8, and PGE_2) were significantly decreased in the group of patients who received *B. serrata* for 7 days (Baram et al. 2019). Moreover, boswellic acid and AKBA show promising anti-platelet aggregation effect, anti-profibrotic mechanisms, and improve vascular remodeling by reducing the enhanced oxidative stress and inflammation through the TGFβ1/Smad3 pathway (Tawfik 2016; Shang et al. 2016). These data demonstrate that *B. serrata* extract and boswellic acids may have beneficial effects against COVID-19-induced oxidative stress, inflammation, clotting formation, and microthrombus, the main cause of the risk of damage to major organs.

Potential therapeutic effects of boswellic acids and *B. serrata* extract against SARS-CoV-2-induced immune dysregulation

Autoimmune diseases are characterized by an uncontrolled overwhelming immune system reaction with enhanced T cell proliferation. *B. serrata* extracts and their active ingredients including boswellic acids affect the immune system in different ways (Table 1). Boswellic acids have two different actions on cellular defense: they promoted lymphocyte proliferation in small doses while higher concentrations are inhibitory. In terms of the humoral defense system, boswellic acids also reduced primary antibody titers at higher doses; however, lower doses increased secondary antibody titers. Moreover, boswellic acids enhance the phagocytosis of macrophages (Mikhaeil et al. 2003; Pungle et al. 2003; Ammon 2011; Siddiqui 2011). Beghelli et al. (2017) suggested that *B. serrata* has a promising potential to modulate not only inflammation/oxidative stress but also immune dysregulation.

It is noteworthy that *B. serrata* gum resin extract decreased IA(2)-antibody in a patient with late-onset autoimmune diabetes of the adult (Schrott et al. 2014). Recently, Franic et al. (2020) confirmed that *B. serrata* gum resin extract inhibits the production of autoantibodies, GAD65 and IA2, markers of autoimmunity, and prevents autoimmune diabetes. Moreover, Aldahlawi et al. (2020) suggested that *B. serrata* essential oil (BSEO) has immunomodulatory effects on T cells and dendritic cells. It deflects the differentiation of monocytes into immature dendritic cells (DCs). Stimulation of immature DCs using BSEO was not able to generate full DC maturity. These results can be used to generate DCs with properties capable of inducing tolerance in hypersensitivity and autoimmune diseases (Aldahlawi et al. 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).

The immunomodulatory effects of *B. serrata* extract/boswellic acids have a wide range of clinical applications. AKBA enhances osteoblast differentiation in rheumatoid arthritis (RA)-related bone loss disease by inhibiting TNFα and NF-κB where TNFα suppresses osteoblast differentiation by activating NF-κB (Bai et al. 2018). A standardized *B. serrata* extract reduces disease activity in patients with relapsing–remitting multiple sclerosis by a significant increase in regulatory $CD4^+$ T cell markers, and a significant reduction in IL-17A-producing $CD8^+$ T cells and bioactive 5-LOX-derived lipid mediators (Stürner et al. 2018; Stürner et al. 2020). It is evident from previous results that *B. serrata* exracct and boswellic acids may have the potential to enhance the adaptive immune response, and suppress the uncontrolled activation of the innate immune response that leads to cytokine release syndrome and tissue damage in elderly people with COVID-19.

Broad antiviral effect of boswellic acids and *B. serrata* extract

Although there is no currently published study showing *B. serrata* activity against SARS-CoV-2, several investigators have shown that *B. serrata* possesses broad antiviral activity. The antiviral effect of *B. serrata* was investigated by Goswami et al. (2018). They reported that *B. serrata* and BA potently inhibited wild-type and a clinical isolate of HSV-1. The inhibitory effect was significant at 1 h post-infection and effective up to 4 h. The mechanism of the antiviral effect of *B. serrata* extract and BAs was through blocking of NF-κB, necessary for virus replication. *B. serrata* gum resin extract also has antiviral activity against Chikungunya virus (CHIKV). It blocks the entry of Chikungunya virus Env-pseudotyped lentiviral vectors and inhibited CHIKV infection in vitro. Moreover, *B. serrata* gum resin extract exhibits antiviral activity against vesicular stomatitis virus, vector particles, and viral infections to the same extent, indicating a broad antiviral activity (Von Rhein et al. 2016).

The strong antiviral activity of the total extract of *B. serrata* gum resin against the herpes virus was confirmed by Badria et al. (2003a, b). They reported that the activity of the total extract is much greater than that of the individual components. Furthermore, pentacyclic triterpenoids have been documented to have a potential therapeutic role in the treatment of virus infections. For example, research groups have investigated the activity against HIV, HCV, influenza, and other viruses of natural pentacyclic triterpenoids and their semisynthetic derivatives (Xiao et al. 2018). The mechanism of antiviral activity of triterpenoids may be through inhibiting the entry of viruses such as Ebola, Marburg, HIV, and influenza A virus. This action is achieved by wrapping the HR2 domain prevalent in viral envelopes (Si et al. 2018). In

Table 1 Immunomodulatory effects of *Boswellia* extract and boswellic acids in articles published from 1991 to 2020

Extract or active ingredient and doses	Method of research	Major finding	Mechanism of action	Reference
Ethanolic extracts of the gum resin exudate of *B. serrata*. Range between 10 and 80 µg/ml	Suspensions of rat peritoneal polymorphonuclear leukocytes were stimulated by calcium and ionophore to produce leukotrienes and 5-HETE	A concentration-dependent inhibition of LTB4 and 5-HETE production by extract	Anti-inflammatory activity in vivo is mediated by inhibition of 5-lipoxygenase	Ammon et al. (1991)
Boswellic acids (BA) Single or prolonged oral administration of BA (25–100 mg/kg/day for 21 days)	Sheep erythrocytes SRBC in mice & rats	Single dose inhibited the expression of the 24-h delayed-type hypersensitivity (DTH) reaction and primary humoral response to SRBC in mice Multiple oral dose reduced the development of the 24-h DTH reaction and complement fixing antibody titers and slightly enhanced the humoral antibody synthesis	BA displays immunosuppressive or immunopotentiating effects depending on the dosage and timings of drug administration. BA enhanced the phagocytic function of adherent macrophages	Sharma et al. (1996)
Extract of the gum resin of *B. serrata* (BS Dosage administered to patients was normally 3×2 or 3×3 tablets of H15 as a 400 mg extract of BS for 1–6 months	Clinical study of 260 patients with rheumatoid arthritis via assessment of erythrocyte sedimentation rate (ESR), joint stiffness, etc.	Improvement of criteria for assessment such as joint swelling, pain, ESR, joint stiffness H15 is useful as an adjunct to current disease-modifying drugs	Unknown	Etzel et al. (1996)
Boswellia carterii Birdwood extract and isolated ingredients 1.00 mg/ml	Assessment of immunomodulatory activity: lymphocyte blast transformation (mitogensis) assay	Immunostimulatory activity of the total extract is much greater than that of the individual components; total alcoholic extract shows a significant immunostimulatory action on T lymphocytes (90% lymphocyte proliferation)	Unknown	Badria et al. (2003a, b)
Steam distillation of frankincense essential oil (3%) (*B. carterii* Birdwood)	Assessment of the immunomodulatory activity of the oil: lymphocyte blast transformation (mitogensis) assay	Immunostimulant activity	Unknown	Mikhaeil et al. (2003)
Extract of gum resin of *B. serrata* (doses 20, 40, and 80 mg/kg, po)	Evaluation for antianaphylactic and mast cell stabilizing activity using passive paw anaphylaxis and compound 48/80 induced degranulation of mast cell methods	Inhibited the passive paw anaphylaxis reaction in rats in dose-dependent manner. A significant inhibition in the compound 48/80 induced degranulation of mast cells in dose-dependent manner	Mast cell stabilizing activity	Pungle et al. (2003)
Mixtures of boswellic acids 10 µg/ml, 50 µg/ml, and 200 µg/ml	In vitro production of TH1 cytokines (interleukin-2 [IL-2] and gamma interferon) and TH2 cytokines (IL-4 and IL-10) by murine splenocytes	BAs from *B. carterii* plant resin exhibit carrier-dependent immunomodulatory properties in vitro	Inhibition of TH1 cytokines coupled with a dose-dependent potentiation of TH2 cytokines	Chervier et al. (2005)

Table 1 (continued)

Extract or active ingredient and doses	Method of research	Major finding	Mechanism of action	Reference
Acetyl-alpha-boswellic acid (AαBA) and acetyl-11-keto-beta-boswellic acid (AKβBA) (10 µM)	Monocyte and human embryonic kidney epithelial cell line	AαBA and AKβBA inhibited NF-κB signaling both in LPS-stimulated monocytes as detected by EMSA and in an NF-κB-dependent luciferase gene reporter assay	Selective inhibition of IκBα kinases led to NF-κB-dependent cytokine expression, and that both AαBA and AKβBA are novel selective inhibitors of IKK activity	Syrovets et al. (2005)
Methanolic extract of *B. serrata* and the isolated pure compound. 10 µg/ml, 20 µg/ml, 30 µg/ml, and 50 µg/ml	Human PBMCs (peripheral blood mononuclear cell) culture and mouse macrophages	Marked downregulation of Th1 cytokines IFNγ and IL-12 while the Th2 cytokines IL-4 and IL-10 were upregulated upon treatment with crude extract and pure compound, 12-ursene 2-diketone, inhibits the expression of pro-inflammatory cytokines and mediators	Via inhibition of phosphorylation of the MAP kinases JNK and p38 while no inhibition was seen in ERK phosphorylation in LPS-stimulated PBMCs	Gayathri et al. (2007)
Biopolymeric fraction of *B. serrata* extract Oral (1–10 mg/kg)	Male BALB/c Mice, PFC assay, HA titer, Complement fixing antibody titer	Immunostimulatory effect is dose-dependent with respect to macrophage activation	By the enhancement of TNFα and IFNγ production	Khajuria et al. (2008)
Boswellic acids Doses of BA at 100 and 250 mg/kg	Animal models viz., pyloric ligation, ethanol-HCl, acetylsalicylic acid, indomethacin and cold restrained stress-induced ulceration in rats	BA possess a dose dependent antiulcer effect against different experimental models	Acting by increasing the gastric mucosal resistance and local synthesis of cytoprotective prostaglandins and inhibiting the leukotriene synthesis	Singh et al. 2008a, b b
Boswellic acids (BA)-treated animals with doses of 1.25, 2.5, and 3.75 mg/paw	Comparative anti-inflammatory (carrageenan paw edema) and anti-arthritic (*Mycobacterium*-induced arthritis) efficacy of BA via systemic administration and topical application in rats & mice	Anti-inflammatory effect observed through topical route is in accordance with the study conducted with the systemic route	Inhibition of 5-lipoxygenase	Singh et al. (2008a)
Biopolymeric fraction BOS 2000 from *B. serrata* (10, 20, 40, and 80 µg) on days 1 and 15	BALB/c mice were immunized subcutaneously with OVA 100 µg alone or with OVA 100 µg dissolved in saline containing alum (200 µg) or BOS 2000 + spleen cell culture	BOS can enhance the immunogenicity of vaccine/OVA-specific IgG, IgG1, and IgG2a antibody levels in serum	Balanced Th1- and Th2-directing immunological adjuvant	Gupta et al. (2011)
B. serrata extract daily 2 tablets with 400 mg for 8.5 weeks	Female patient, 50 years old, diabetic No improvement with regular treatment	Additional treatment of *B. serrata* extract resulted in a drop of IA2-A to normal value	Prevention/treatment of autoimmune diabetes	Schrott et al. (2014)

Table 1 (continued)

Extract or active ingredient and doses	Method of research	Major finding	Mechanism of action	Reference
B. serrata (BS) extracts. BS extracts (0.1 µg/ml). AKBA concentration of 3.8–6 ng/ml	Proliferation assay Human peripheral blood mononuclear cells (PBMCs) of seven healthy donors	In vitro lymphocyte proliferation when cells were activated by PWM, the addition of BS extracts induced a significantly higher lymphocyte response BS extract led to a significant increase of $FOXP3^+$ cells. BS modulates not only inflammation/oxidative stress but also immune dysregulation	Ability to influence the regulatory and effector T cell compartments	Beghelli et al. (2017)
Standardized *B. serrata* extract 400–4800 mg/day)	Enrolled 38 patients with relapsing–remitting multiple sclerosis (RRMS)	Oral SFE was safe, tolerated well, and exhibited beneficial effects on RRMS disease activity	Significant increase in regulatory $CD4^+$ T cell markers and a significant decrease in IL-17A-producing $CD8^+$ T cells indicating a distinct mechanism	Stürner et al. (2018)
Standardized *B. serrata* extract containing boswellic and lupeolic acid 6–44 µg/ml	LPS-stimulated peripheral blood mononuclear cells (PBMC) and whole blood	Nutraceuticals exhibited toxicity against the human triple-negative breast cancer cell and inhibited the release of pro-inflammatory cytokines, such as TNFα, IL-6, and IL-8	Inhibited growth of cancer xenografts in vivo, and released pro-inflammatory cytokines	Schmiech et al. (2019)
Standardized *B. serrata* extract 3600–4800 mg/day	Plasma samples from 28 patients with RRMS who took a standardized frankincense extract (SFE) daily for 8 months	Oral treatment with an SFE significantly reduces 5-LO-derived lipid mediators in patients with RRMS during an 8-month treatment period	Inhibition of 12-,15-LO and cyclooxygenase product levels	Stürner et al. (2020)
B. serrata (BS) extract for 9 months	Case study of male patient diagnosed with latent autoimmune diabetes with positive GAD65 autoantibodies	Prevent insulitis in patients with latent autoimmune diabetes in adults (LADA)	Suppression of autoimmune diabetes markers, i.e., GAD65 and IA2 autoantibodies	Franic et al. (2020)
Boswellia sacra essential oil (BSEO)	Normal human skin dermis cell line (HSD) + PBMCs	BSEO exerts suppression effects by inhibition of differentiation, expression of maturation markers, cytokine production, and monocyte-derived DCs stimulated with LPS	Immune suppressor of human peripheral blood monocyte-derived DCs, which may promote the Treg permissive environment	Aldahlawi et al. (2020)
B. carterii extract and 3-*O*-acetyl-alpha-boswellic acid	Cultured cells, lymphocytes were isolated from the blood of healthy adult donors obtained from a blood transfusion center	Inhibited 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 range	Immunosuppressive effects of the extract are based on specific NFAT-conditioned suppression within T cell signaling	Zimmermann-Klemd et al. (2020)

addition to the antiviral activity of boswellic acids, flavonoids of *B. serrata* possess inhibitory activity against many viruses (Zakaryan et al. 2017). On the basis of these studies, it is clear that *B. serrata* extract and boswellic acids have a broad antiviral activity that may be beneficial in the fight against SARS-CoV-2.

Potential therapeutic effects of boswellic acids and *B. serrata* extract against COVID-19-induced secondary microbial infections

COVID-19 infection results in significant and persistent lymphopenia in 85% of patients. Furthermore, a person taking immunosuppressants, such as corticosteroids and monoclonal antibodies, may experience severe lymphocytopenia. Because lymphocytes play an important role in the immune defense function against infection, patients with COVID-19 are highly susceptible to bacterial and fungal secondary infections causing a high mortality rate in patients with COVID-19 (Bhatt et al. 2021). About 3.6–13% of patients with COVID-19 developed a secondary bacterial or fungal infection and the mortality rate among these patients was about 33.3–56.7% (Khurana et al. 2021; Vijay et al. 2021). Also, it has been verified that major anaerobic pathogens *Tannerella forsythia* and *Porphyromonas gingivalis* in periodontitis are associated with a higher risk of developing a severe secondary infection in patients with COVID-19 (Aquino-Martinez et al. 2021; Marouf et al. 2021; Şehirli et al. 2021), and importantly that patients with COVID-19 have a high probability of suffering from an invasive fungal infection such as mucormycosis, cryptococcosis, aspergillosis, or candidiasis as secondary infection (Song et al. 2020).

Several studies have noted that *B. serrata* extract or boswellic acids are bacteriostatic at low concentration or bactericidal at high concentration for many gram-positive and gram-negative bacteria in vitro and in vivo. According to the findings of Bakhtiari et al. (2019), hydro-alcoholic extract of *B. serrata* is more effective against *Candida albicans*, *Candida glabrata*, *Candida krusei*, and *Streptococcus mutans* than organic extract. Hydro-alcoholic extract of *B. serrata* was most effective against *C. albicans* and *S. mutans*. *B. serrata* also showed antifungal effects (Camarda et al. 2007). Kasali et al.(2002) and Schillaci et al. (2008) Also observed that *B. serrata* essential oil inhibited *C. albicans*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* biofilm formation. AKBA showed an inhibitory effect on all the oral cavity microorganisms. It showed concentration-dependent killing of *S. aureus* and *S. mutans*. Moreover, AKBA blocked the formation of biofilms generated by *S. aureus S. epidermidis*, *S. mutants*, and *Actinomyces viscosus* (Raja et al. 2011a, b).

The periodontal infection is polymicrobial of different bacterial species but aggressive forms of this disease have been associated with specific Gram-negative bacteria *Aggregatibacter actinomycetemcomitans*. *B. serrata* is effective against *A. actinomycetemcomitans* which may be useful as a suitable oral health medicine and treatment of periodontal infection (Maraghehpour et al. 2016). A double-blind randomized controlled trial was conducted among high school students with moderate plaque-induced gingivitis. *B. serrata* extract has been safely used to treat and improve the gum health of students. It demonstrated satisfactory medicinal properties, which may be superior to scaling and root planing (SRP) as a conventional method for removing dental plaque (Khosravi Samani et al. 2011).

Many investigators have suggested that AKBA could be a useful agent for developing an antibacterial agent against oral pathogens and it has the potential for use in mouthwash to prevent and treat oral infection (Raja 2011a, b; Patel and Patel 2014). However, Sabra and Al-Masoudi (2014) suggested that *B. serrata* chewing gum is a safe and low-cost herbal product, which supports mouth hygiene for all ages. It improves buccal/oral cavity hygiene by antimicrobial effects which decrease the sources of microbial infection in the buccal/oral cavity as tested by counting microbial contents of the buccal/oral cavity through microbial identification of saliva.

Several researchers demonstrated the antifungal activity of *B. serrata*. Essential oil of *B. serrata* has shown broad antifungal activity against many types of fungal infections and is likely to be a good source of antifungal agents to prevent fungal infections and mycotoxin contamination (Venkatesh et al. 2017). Furthermore, the antimicrobial activity of *B. serrata* essential oil has been demonstrated against fungal infections, and it has shown synergistic antifungal activity in combination with azoles against the azole-resistant *C. albicans* (Sadhasivam et al. 2016). Acetone extract of *B. serrata* was shown to be more effective than ethanol against drug-resistant *Aspergillus fumigatus* isolated from Diyala patients and has excellent potential as an antifungal agent (Abdul Sattar et al. 2019).

Given the poor bioavailability of *B. serrata* after oral administration (Sharma et al. 2004; Siddiqui 2011; Sharma et al. 2020), chewing *B. serrata* gum may lead to better absorption of active ingredients from buccal mucosa. Moreover, the art of chewing *B. serrata* has other benefits: *B. serrata* has antibacterial, antifungal, and antiviral activities against oral pathogens and it has great potential for use in preventing and treating oral infections (Raja et al. 2011a, b; Hasson et al. 2011; Bakhtiari et al. 2019; Rad and Taherian 2020). However, chewing *B. serrata* gum may not be the most effective or easiest way to give *B. serrata*. In addition, the bioavailability of the active ingredients after conventional use of chewable *B. serrata* has not yet been published. To overcome the poor

bioavailability of the concentrated or isolated boswellic acids, attempts have been made to enhance the bioavailability by the combination of *Piper longum* (long pepper) and by producing specific compounds such as boswellic acids attached to phospholipids or incorporated into micelles (Hüsch et al. 2013; Meins et al. 2018; Vijayarani et al. 2020). On the basis of the aforementioned studies, it is clear that *B. serrata* extract and boswellic acids may have a therapeutic effect against virus-induced secondary microbial infection and may be effective in preventing COVID-19 causing secondary infection and COVID-19 causing complications.

Toxicity and safety of *B. serrata* extract and boswellic acids

Recent studies confirmed that *B. serrata* extract and boswellic acids possess a high safety margin. Acute oral toxicity studies did not exhibit mortality or signs of toxicity in Wistar rats up to 2000 mg/kg (Alluri et al. 2019). In mice, no death was recorded following the single-dose administration of *B. serrata* extract at a dose of up to 5 g/kg (Gomaa et al. 2019). Oral administration of the extract for 28 consecutive days did not exhibit any sign of behavioral toxicity and did not show significant changes of biomarkers of hepatic and renal functions as well as the histological characters in rats (Al-Yahya et al. 2020). Moreover, Alluri et al. (2019) demonstrated that repeated oral dose of *B. serrata* extract for 28 days in Wistar rats did not show dose-related signs of toxicity on the hematology, clinical chemistry, mutagenic, and clastogenic parameters. In previous studies, it was observed that acute oral LD50 of *B. serrata* extract was greater than 5000 mg/kg in female and male Sprague Dawley rats, and repeated oral dose for 28 or 90 days in Sprague Dawley rats showed no significant adverse changes in hematology, clinical chemistry, gross necropsy, histopathology examinations, and hepatic DNA fragmentation at 30, 60, or 90 days of treatment (Krishnaraju et al. 2010; Singh et al. 2012). Boswellic acids have the same wide spectrum of safety as *B. serrata* extract. They did not exhibit any sign of toxicity up to 2 g/kg administered orally or intraperitoneally and daily oral administration of BAs in three doses (low and very high) to rats and monkeys revealed no significant changes in general behavior or clinical, hematological, biochemical, and pathological parameters (Singh et al. 1996; Lalithakumari et al. 2006).

Perspectives

We propose that *B. serrata* extract in small to moderate dose (100–200 mg/day) can be used in early stages in mild to moderate symptoms of COVID-19 to enhance the adaptive immune response. However a large dose of *B. serrata* extract or boswellic acid can be used to suppress the uncontrolled activation of the innate immune response that leads to cytokine storm. Because of the low oral bioavailability and improvement of buccal/oral cavity hygiene, traditional use by chewing *B. serrata* gum may be more beneficial in mild to moderate symptoms and as prophylactic. Also, it may be the cheapest option for a lot of poorer people; however, it may not be the most effective or easiest way of administering *B. serrata*. *B. serrata* extract or boswellic acid may be used also as a prophylactic agent in combination with other natural antiviral agents such as licorice for the prevention of progression of the COVID-19 (Gomaa and Abdel-wadood 2021). This combination can be considered as one of the best suggested natural regimens for the prevention of COVID-19. Since this regimen has a high safety margin, it is now under clinical trial to determine its therapeutic efficacy in patients with COVID-19 (ClinicalTrials.gov Identifier NCT04487964).

Conclusions

Given the pharmacological and clinical evidence, there may be a use for *B. serrata* in treating similar symptoms experienced by patients with COVID-19. The potential therapeutic effects of boswellic acids and *B. serrata* extract are attributed mainly to its anti-inflammatory, immunomodulatory, cardioprotective, anti-platelet aggregation, antibacterial, antifungal, and broad antiviral activity. Because of the low oral bioavailability and improvement of buccal/oral cavity hygiene, traditional use by chewing *B. serrata* gum may be a good, and only, option for poorer people. The main mechanism of therapeutic effects may be through direct interaction with IκB kinases and inhibiting nuclear factor-κB-regulated gene expression. However, the most recent mechanism proposed that BA not only inhibited the formation of classical 5-lipoxygenase products but also caused a switch from the production of pro-inflammatory leukotienes to formation of anti-inflammatory LOX-isoform-selective modulators. Although the non-clinical studies acknowledge the usefulness of boswellic acids and *B. serrata* extract in treating COVID-19, these data reinforce the idea that more clinical results are required to determine with certainty whether there is sufficient evidence of the benefits of *B. serrata* extract and boswellic acids against COVID-19.

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Declarations

Conflict of interest The author declares no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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