Modulation of the immune system by *Boswellia serrata* extracts and boswellic acids

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**Article info**

Dedicated to Prof. Dr. hc mult. Wagner for his 80th birthday.

**Keywords:**

*Boswellia serrata* extracts  
Boswellic acids  
Immune system

**Abstract**

Extracts from the gum resin of *Boswellia serrata* and some of its constituents including boswellic acids affect the immune system in different ways. Among the various boswellic acids 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid have been observed to be active. However, also other boswellic acids may exhibit actions in the immune system.

In the humoral defence system a mixture of boswellic acids at higher doses reduced primary antibody titres; on the other hand lower doses enhanced secondary antibody titres following treatment with sheep erythrocytes.

In the cellular defence boswellic acids appear to increase lymphocyte proliferation whereas higher concentrations are even inhibitory. Moreover, BAs increase phagocytosis of macrophages.

BAs affect the cellular defence system by interaction with production/release of cytokines. Thus, BAs inhibit activation of NFkB which is a product of neutrophile granulocytes. Consequently a down regulation of TNF-α and decrease of IL-1, IL-2, IL-4, IL-6 and IFN-γ, which are proinflammatory cytokines by BEs and BAs has been reported.

Suppressions of the classic way of the complement system was found to be due to inhibition of the conversion of C3 into C3a and C3b. However, which of these pharmacological actions contribute to the therapeutic effects and which is finally the best dosage of a standardized extract needs further examination. And it is also a question whether or not a single BA will have the same therapeutic effect as a standardized extract.

Among the mediators of inflammatory reaction, mast cell stabilisation has been described by a BE. Inhibition of prostaglandin synthesis appears to play only a minor role as far as the anti-inflammatory effect is concerned.

On the other hand the inhibitory action of BAs on 5-LO leading to a decreased production of leukotrienes has received high attention by the scientific community since a variety of chronic inflammatory diseases is associated with increased leukotriene activity.

At the end of the cascade of events in the cellular immune system as far as it directs to various tissues of the body – i.e. autoimmune diseases – formation of oxygen radicals and proteases (for example elastase) play an important destructive role. Here, BEs as well as BAs have been found to be inhibitory.

From the pharmacological properties of BEs and BAs it is not surprising that positive effects of BEs in some chronic inflammatory diseases including rheumatoid arthritis, bronchial asthma, osteoarthritis, ulcerative colitis and Crohn’s disease have been reported.

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Introduction

Extracts from oleo gum resin of *Boswellia serrata*, in India called salai guggal, have been described in Ayurvedic text books (Charaka Samhita, 1st–2nd century AD and Astangahrdraya Samhita 7th century AD) as a remedy for the treatment of a variety of inflammatory diseases. In 1986 Singh and Atal reported anti-inflammatory activity of an extract of the gum resin of *B. serrata* in animal experiments. Wagner et al. (1987) observed inhibition of guinea pig complement system by α- and β-boswellic acids and in 1992 anti-complementary activity of a mixture of boswellic acids was described by Kapil and Moza (1991).

Any inflammation is the response of the body to damages of tissues. Its final target is healing and restauration. There are three kinds of inflammations:

- Acute inflammations are mostly related to infections or injuries.
- Chronic inflammations are the consequence of continuation of acute inflammations due to inadequate immune defence.
- Primary chronic inflammations which develop chronically just from the begin of the disease. They are mostly caused through derangements of the immune system i.e. auto-immune diseases.

The organisation of any inflammation includes a variety of factors deriving from the immune systems i.e., immune cells, complements, cytokines, mediators of inflammation, enzymes etc.

In the last decades extracts from the oleo gum resin of *B. serrata* (BEs), some boswellic acids (BAs) and other compounds have been studied for their effects on different steps/factors of the immune system and on the cascades of events finally leading to inflammation.

This review deals with the effects of BEs and active constituents on factors related to the immune system and mediators of inflammation.

Effects of *B. serrata* extracts (BEs), boswellic acids (BAs) and other compounds of BEs on parameters of immune defence

Humoral defence

Antibody titres

Humoral defence is related to the activation of B-cells. After contact with antigens B-cells differentiate to plasma cells. These cells produce antibodies which belong to the family of immunoglobulins.

Humoral antibody synthesis was tested by Sharma et al. (1996) in the serum from mice treated with sheep erythrocytes by determining the hemagglutinating antibody titres. It was found that a single oral dose of a mixture of BAs (50–200 mg/kg) on the day of sensitisation produced a dose related reduction (10.4–32.8%) in primary hemagglutinating antibody titres on day 4. A significant reduction in antibody production was obtained with 100 and 200 mg/kg doses. On the other hand the secondary antibody titres were significantly enhanced at lower doses, the effect being more prominent at 50 mg/kg. Azathioprine as a reference compound (200 mg/kg p.o.) administered following the same schedule resulted in only 10.4% inhibition of primary antibody synthesis and had no effect on the secondary antibody production.

Using the technique of complement fixing, a method for analyzing antigen and antibody titres, oral administration of a mixture containing BAs (25, 50, 100 mg/kg) for 5 days around the time of immunization resulted in a significant decrease in primary and secondary complement fixing antibody titres at 100 mg/kg (Sharma et al. 1996).

A marked increase (15.38–26.92%) in antibody production on day +7 was observed when a BA mixture (25–100 mg/kg) was given orally for 5 days around immunization. The effect was more pronounced at a dose of 25 mg/kg than at 50 or 100 mg/kg. The secondary antibody titres were only marginally increased. Azathioprine treatment (100 mg/kg) had no significant effects on primary as well as on secondary antibody titres.

In mice in which treatment was initiated 7 days prior to immunization, BAs (25–100 mg/kg) elicited a dose related increase (37.93–63.79%) in the primary humoral response without significantly affecting the expression of the secondary response. Levamisole (2.5 mg/kg, p.o.), an immunopotentiating agent, displayed only a 25% increase in primary and a 6.66% increase in secondary antibody titres.

Immunglobulines

Previously it was shown by Khajuria et al. (2008) that oral administration of a biopolymeric fraction (BOS 2000) from *B. serrata* (1–10 mg/kg) elicited a dose related increase in the delayed hypersensitivity reaction (early 24h and delayed 48h) in mice. It also stimulated the IgM and IgG titre expressed in the form of plaques (PFC) and complement fixing antibody titre.

From these studies where either a mixture of different boswellic acids or a biopolymeric extract of BS has been employed, it appears that lower doses exhibit a humoral immunostimulating action, whereas this effect is attenuated or even reversed with increasing the dose.

Cellular defence

Cellular defence includes proliferation and activation of lymphocytes as well as induction of phagocytosis of macrophages and neutrophile granulocytes.

From the lymphocytes T1-lymphocytes cause cytotoxic actions to living cells (i.e. microorganisms and tumor cells). In case of autoimmune diseases T1-cells also attack and damage a variety of single tissues in the body, leading among others to allergic reactions, rheumatoid arthritis, psoriasis, type 1-diabetes, bronchial asthma, multiple sclerosis, neutrophilic, lupus erythematosides, Huntington thyreoiditis and others. In most cases the autoimmune diseases concentrate on specific cells/tissues inducing a chronic inflammatory process which ends with the destruction of the cells/tissues in question.

The treatment of these diseases at present consists in the applications of glucocorticoids, nonsteroidal anti-inflammatory drugs, immunosuppressives and others, their disadvantages being in part severe side effects.

Lymphocyte proliferation

Two studies investigated the effect of an extract of *Boswellia carterii* Birdw. and of BAs in the lymphocyte proliferation assay. This *in vitro* test utilizes sensitized lymphocytes, especially T-lymphocytes and is used to establish immunomodulatory activity.

In 1996 Sharma et al. reported that, if spleen cells from non-immunized mice were used, a mixture of various BAs in the range of 1.95–125.0 μg/ml showed no spontaneous mitogenic activity and the cell viability was comparable to controls. When the test was performed in the presence of mitogen stimulating lipopolysaccharides (LPS), phytohaemagglutinin (PHA), concanavalin A (ConA) and alloantigen, a concentration dependent inhibition of lymphocyte proliferation was observed.

These data are in contrast to the observations of Badria et al. (2003) who used this assay with isolated lymphocytes from venous human blood. In this study, a methylene chloride extract from the oleo gum resin of *Boswellia carterii* Birdw. at 1 mg/ml stimulated lymphocyte transformation by 90% (EC50 = 0.55 mg/ml) in
the presence of PHA or Con A. Various compounds of the essential oil were also active. The different BAs and tirconic acids (TAs) tested, including acetyl-β-boswellic acid, acetyl-α-boswellic acid, 3-oxo-BA, acetyl-11-keto-β-boswellic acid, β-boswellic acid, 3-hydroxy-BA, and 11-keto-β-boswellic acid, showed a similar activity with EC50 values from 0.001 to 0.005 μM.

From these studies it may be concluded, that in addition to BAs also other compounds of an extract from Boswellia resins are effective in stimulating lymphocyte proliferation.

Though the data of both studies as far as quantitative terms are concerned are not comparable it appears, that low concentrations of BAs increase stimulated proliferation of lymphocytes whereas higher concentrations are even inhibitory. This is in line with the observations that in vivo lower doses of BAs increase antibody titers whereas higher doses show even the opposite.

**Phagocytosis**

The effect of an undefined mixture of BAs on phagocytosis was also studied by Sharma et al. (1996). Preincubation of peritoneal macrophages with different concentrations of BAs (1.95–125 μg/ml) resulted in an enhanced phagocytic function of adherent macrophages with a maximal effect occurring at 62.25 μg/ml.

**NFκB/cytokines/chemokines**

The function of cellular defense is regulated by a variety of compounds released from leukocytes, macrophages and T-cells including NFκB, cytokines and chemokines.

**NFκB**

The transcription factor NFκB, which usually is present in the cytosol is produced by neutrophil granulocytes and activates numerous genes which are related to the defense against infectious diseases and induction of inflammatory processes. Its presence is a prerequisite for the formation/action of cytokines/chemokines and thus any inhibitor of NFκB by will result in a decrease of cellular defense and inflammatory reactions.

As far as possible effects of BEs and BAs are concerned; AKBA has turned out to be a natural inhibitor of NFκB (Czuc-Jézély et al. 2008). Thus AKBA applied in vivo in mice (100 μmol/kg) for 1 week inhibited the NFκB activation. This may be one explanation why BAs inhibit production of cytokines.

However, inhibition of NFκB is not only related to the action of BAs. Previously Moussaieff et al. (2007) reported that incensole acetate a compound isolated from Boswellia resins also inhibits NFκB activation. This action was combined with an anti-inflammatory effect in the inflamed mouse paw model.

From these studies it appears possible that the anti-inflammatory action of BAs or other constituents of BEs starts with the inhibition of NFκB activation.

**Cytokines**

Cytokines are produced by macrophages and T-cells following the recognition of a pathogen.

The cytokines studied so far in connection with the antiinflammatory action of BAs are TNFα and various interleukines. TNFα, IL-1, IL-2, IL-6 and others are involved in antibacterial and proinflammatory reactions.

**TNF-α**. TNF-α is released from macrophages. It activates vascular endothelium, increases permeability of vessels, entry of IgG, and complement into tissues. It induces fever and shock.

Inhibition of TNF-α and its signaling has been recognized as a highly successful strategy for the treatment of chronic inflammatory diseases such as rheumatoid arthritis. Previously it has been shown by Syrovets et al. (2005) that acetyl-α-Ba and AKBA inhibited the generation of TNF-α in concentrations between 1 and 10 μM in lipopolysaccharide-stimulated human monocytes. AKBA was found to be the most active compound. The effect was mediated by a direct inhibitory action on IκB kinases (IKK) conveyed inhibition of NFκB and subsequent down regulation of TNF-α expression in human monocytes. In human monocytes, Borsches and Grim (personal communication 2000) observed a concentration-dependent inhibition of TNF-α and IL-1β production in a concentration range of 5–20 μM.

Roy et al. (2005) tested the genetic basis of the anti-inflammatory effects of a standardized BE in a system of TNF-α-induced gene expression in human micro vascular endothelial cells. Acutely, TNFα induced 522 genes and down regulated 141. 133 genes were clearly sensitive to BE treatment. Such genes are directly related to inflammation, cell adhesion and proteolysis. DNA micro array analysis in connection with Remap, gene ontology data mining tool and others led to the recognition of primary BE-sensitive and others led to the recognition of primary BE-sensitive TNFα-inducible pathways. BE was found to prevent TNF-α-induced expression of matrix metalloproteinases and mediators of apoptosis.

In this context it is important to note that most TNFα induced genes are NFκB-dependent and it appears that down regulation of TNF-α in response to BAs may be the consequence of their inhibitory action on NFκB.

**Interleukines**. A variety of interleukines is produced by macrophages and T-cells. They are related to different actions. In brief:

- IL-1 produced from macrophages activates lymphocytes, local tissue destruction and fever.
- IL-2 from Th1-O and Th1-1 cells controls proliferation and differentiation of T-cells.
- IL-4 produced by Th2-2 cells activates B-cells and T-cells, but inhibits activation of macrophages.
- IL-6 from macrophages activates lymphocytes, antibody production and generates fever.
- IL-10 a product of Th1-2 cells reduces development of Th1-1 cells.
- IL-12 which is produced by macrophages activates natural killer cells (NK-cells).
- INF-γ from Th1-1 can prevent activation of Th1-2 cells.

As far as the actions of T-cells on other cells is concerned Th1-1 cells activate macrophages whereas Th1-2 cells activate B-cells.

The effect of an extract from Boswellia carterii on the production of Th1-1 and Th2-2 cytokines by murine splenocytes was studied by Chervier et al. (2005). In these *in vitro* experiments, application of the resin extract, using ethanol as a solvent, showed significant cell

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It binds to H1 and H2 receptors. Its effects in allergic reactions include muscle, secretion of gastric acid and interacts with nociceptors. Histamine causes vasodilatation, constriction of bronchial smooth muscle, mucus secretion and vasoconstriction (partially mediated by LTC4, LTD4 and LTE4). Finally, it may decrease the cellular activity of the immune system through inhibition of activation, proliferation and differentiation of B- and T-lymphocytes (IL-1, IL-2, IL-4, IL-6), tissue destruction (IL-1), action of NK-cells (IL-12), antibody production (IL-6) and fever (IL-1, IL-6).

That this seems to be possible is evidenced by the vivo experiments of Khajuria et al. (2008).

Complement system

The complement system consists of a variety of plasma proteins which together attack extracellular pathogens. Activation of the complement system by antigens (classic way) or by surface pathogens finally leads to taxis of inflammatory cells, opsonisation of pathogens and destroy of pathogens. Inhibition of the guinea pig complement system by α-boswellic acid and β-boswellic acid in a concentration range between 5 and 100 μM has been reported by Wagner et al. (1987). Anticomplementary activities of a mixture of BAs were also described by Kapil and Moza (1991). Here BAα and the in vitro immunochemical test of antibody-coated sheep erythrocytes by pooled guinea-pig serum. The reduced immunochemical test was found to be due to inhibition of C3-convertase of the classical complement pathway. The threshold concentration for inhibiting C3-convertase was 100 μg per 0.1 ml diluent buffer added to the assay. BAs also weakly inhibited individual components of the complement system. Thus at least in vitro BAα can suppress the conversion of C3 into C3a and C3b and therefore its proinflammatory/lytic actions.

Mediators of inflammation

Mediators of inflammation are produced and released by mast cells, granulocytes, macrophages, thrombocytes, red blood cells, endothelial cells and fibroblasts. They transport specific information to related tissues and finally produce the inflammatory symptoms. Studies with BEα and/or BAα have focused so far on histamine, prostaglandins, leukotrienes and oxygen radicals.

Histamine

Histamin is a vasoactive amine stored in mast cells and is released when antigens bind to IgE molecules on the surface of mast cells. Histamine causes vasodilatation, constriction of bronchial smooth muscle, secretion of gastric acid and interacts with nociceptors. It binds to H1 and H2 receptors. Its effects in allergic reactions are well known. In addition, mast cell activation results in release of leukotrienes and platelet activating factors. In 2003, Punge et al. (2003) showed that in vitro an alcoholic extract of BS inhibited LTB4 and 5-HETE (a metabolite of the 5-LO-cascade) formation in a concentration-dependent manner in PMNs. Based on this activity, the extract inhibited passive paw anaphylaxis in rats in a dose-dependent manner (20, 40 and 80 mg/kg, p.o.). However, dexamethasone (0.27 mg/kg, p.o.) served as positive control for the extract proved to be superior. A significant, dose-dependent inhibition (20, 40 and 80 mg/kg, p.o.) in compound 48/80-induced degradation of mast cells was also observed, thus showing a mast cell stabilising activity. The positive control disodium cromoglycate (50 mg/kg, i.p.) afforded maximum protection against degradation as compared to the extract containing 60% AKBA.

The results suggest promising antianaphylactic and mast cell stabilising activity of the extract of BS.

Prostaglandins

Prostaglandins are produced from arachidonic acid (a constituent of cell membrane phospholipids) either by action of the constitutive cyclooxygenase 1 (COX-1) or the inducible cyclooxygenase 2 (COX-2) enzymes. Prostaglandin production appears to depend mainly on the COX-2 products, which are responsible for inflammatory symptoms, including vasodilatation, permeability and sensitization of nociceptors.

Two types of drugs were used to treat pains/inflammation. One type (acetylsalicylic acid) does not distinguish between COX-1 and COX-2 whereas compounds such as celecoxib preferentially inhibit COX-2. In polymorphonuclear leukocytes (PMNL) stimulated with the calcium ionophore A23187 an alcoholic extract from BS inhibited 6-keto-PGF1α formation, which was substantial at 100 μg/ml being, however, two to three times higher than the level needed for inhibition of leukotriene synthesis (Ammon et al. 1991).

Acetyl boswellic acids were tested in human platelets which contain COX1 but no 5-LO. In concentrations up to 400 μM they showed no effect on 12-HHT-COX formation (Safayhi et al. 1992; Ammon et al. 1993). This is in line with data of Gupta et al. (1992) who observed little effect of BAs in the carrageenan (aspirin) model compared to the latex papaya model in which prednisolone and levamisole were effective and in which “aspirin” compounds were not active.

On the other hand Siemoneit et al. (2008) showed that BAα, especially AKBA inhibited COX-1 formation in intact human platelets (IC50 = 6 μM) in a reversible manner which is in accordance with unpublished observations of our laboratory. In the study of Siemoneit et al. (2008) COX-2 was less efficiently inhibited by BAα.

Thus, it appears that inhibition of prostaglandin synthesis by BAs is similar as the anti-inflammatory action of asproin like drugs.

Leukotriens

Leukotriens are produced in neutrophils, eosinophils, macrophages and mast cells by 5-lipoxygenase (5-LO) after activation through the membrane protein five-lipoxygenase activating protein (FLAP). Their functions include: chemotaxis, plasma exudation (oedema), stimulation of oxygen radical formation and phagocytosis (partially mediated by LTB4) as well as bronchoconstriction, mucus secretion and vasoconstriction (partially mediated by LTC4, LTD4 and LTE4).

Based on the observations of Singh and Atal (1986), Ammon et al. (1991) studied the effect of an ethanolic extract of the oleo gum resin of BS on leukotrien B4 formation in rat PMN. After stimulation of the leukotrien synthesis in PMN with calcium and ionophore A231876 the extract inhibited LTB4 and 5-HETE (a metabolite of the 5-LO-cascade) formation in a concentration-dependent manner in the range between 10 and 80 μg/ml. In this assay, prednisolone was without any effect, suggesting that the pharmacodynamic target was not phospholipase A2.

In 1992, BAs were reported to be specific, non-redox inhibitors of 5-LO (Safayhi et al. 1992). In this study, isomers (α- and β-) of BAs, i.e., 11-keto-β-boswellic acid and their acetyl derivatives were isolated from the oleo gum resin of BS. BAs and derivatives decreased the formation of LTB4 in calcium-stimulated PMN in a concentration-dependent manner. Acetyl-11-keto-β-boswellic acid (AKBA) was most effective with an IC50 value of 1.5 μM (Safayhi et al. 1992). To find out whether or not the inhibitory action of BAs depends on specific chemical structures, Sailer et al. (1996) studied the effect

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of a variety of derivatives of BAs on leukotrien synthesis in Ca-
ionophore-stimulated PMN. From the IC50 value, it was obvious
that not all of the compounds tested inhibited leukotrien synthesis
and that some exhibited only a partial effect. The findings revealed
that a hydrophilic function at C-4 in combination with an 11-keto
group is essential for the inhibition of leukotrien synthesis by BAs.

These data are in favour that as far as mediators of inflammation
deriving from the arachidonic acid cascade are concerned the inhibi-
tion of leukotrien synthesis by BEs and/or BAs plays the major role
in their anti-inflammatory action. As far as the clinical relevance of the
in vitro data showing inhibition of leukotrien synthesis by BE and
BAs is concerned, Siemion et al. (2009) denied such a possibility,
since they could not find a decrease of leukotriens in the plasma
of healthy subjects after oral administration of 800 mg of an extract
of the gum resins. On the other hand Th. Simmeth (personal com-
munication) observed inhibition of cystein-leucotrien formation in
granulocytes ex vivo stimulated with Ca2+ and calcium ionophore
from healthy subjects who have taken 1200 mg of the commercial
product H 15 (Gufic, Ltd. Mumbai). The inhibitor effect was more
than 90% with a maximum 6 h after intake which corresponds to
pharmacokinetic data received from humans treated orally with a
BE showing maximal blood levels of KBA after 4 h, (Sterk et al.,
2004), suggesting that BE/BAs exert their therapeutic useful effect
mainly during stimulation of leukotrien synthesis.

Oxygen radicals. Oxygen radicals are also factors involved in tis-
 sue destruction, for instance in rheumatoid arthritis. Heil et al.
(2001) studied the effects of BEs and AKBA on SOD-quenchable O2-
radical formation in intact PMNs and in a cell-free system. AKBA
(IC50 = 10 μM) and extracts (IC50 = 13 μg/ml) consistently inhibited
the phorbolester PMA-stimulated NADPH oxidase activity in rat
peritoneal PMNs and reduced FMLP and PMA-induced oxidative
burst in stimulator-sensitive human blood PMN preparations, but
failed to block the NADPH-oxidase activity in the membrane frac-
tion of PMA-prestimulated PMNs.

These data suggest direct inhibitory effects of BEs and AKBA on
oxygen radical formation in PMNs.

Human leukocyte elastase (HLE). HLE is a serine protease produced
and released by PMN, and because of its aggressive destructive
properties, some investigators have suggested that HLE may play
a role in several diseases, such as pulmonary emphysema, cystic
fibrosis, chronic bronchitis, acute respiratory distress syndrome,
glomerulonephritis and rheumatic arthritis. In 1995, it was demon-
strated that granulocyte-mediated hepatotoxicity after endotoxin
stimulation depends on elastase release (Sauer et al. 1995).

Using pure HLE Safayhi et al. (1997) screened several pentacyc-
tric triterpenes for inhibitory actions on HLE. This is of therapeutic
interest, since leukotrien formation and HLE release are increased
simultaneously during neutrophil stimulation in a variety of inflam-
antory and hypersensitivity based human diseases. Thus, decrease of chemotaxis together with inhibition of this enzyme,
would lower the destructing actions of HLE, especially at the locus
of diseases.

In the study of Safayhi et al. (1997) AKBA decreased the activity
of HLE in vitro with an IC50 value of roughly 15 μM. Among the
pentacyclic triterpenes tested in concentrations up to 20 μM, they
also observed substantial inhibition by β-boswellic acid, amyrin
and ursolic acid, but not by 18β-glycyrrhetinic acid. The data show,
that the dual inhibition of 5-lipoxygenase and HLE is unique to BAs:
other pentacyclic triterpenes with HLE inhibitory activities (e.g.,
ursolic acid and amyrin) did not inhibit 5-L0.

When an extract was employed in the enzyme test (H15TM Gufic
Ltd. Mumbai) half maximal inhibition occurred at ~7.5 μg/ml (per-
sonal observation).

In addition to the inhibitory action on oxygen radical formation
in PMNs, BEs, AKBA and some other constituents of BEs produced
direct inhibition of human leukocyte elastase, an enzyme which is
responsible for destruction of functional tissues including cartilage
in joints.

Clinical studies

There are variety of clinical studies dealing with the effects of
BEs in chronic inflammatory diseases including rheumatoid arthritis
(Etzel 1996), bronchial asthma (Gupta et al. 1998) ulcerative
colitis (Gupta et al. 1997), Crohn’s disease (Gerhardt et al.
2001), Osteoarthritis (Kimmakar et al. 2003; Sengupta et al. 2008;
Sontakke et al. 2007) suggesting improvement. It is possible that
this is due to different actions of BE/BAs on factors mediators of the
immune system.

Summary

Extracts from the gum resin of B. serrata and other Boswellia
species as well as some of its constituents including boswellic acids
and others have been shown to affect parameters of the immune
system in different ways.

As far as the humoral defence system is concerned boswellic
etracts and boswellic acids affect antibody titres and immuno-
globines. Here, it appears that in mice oral doses of 50 mg/kg and
less are stimulatory whereas higher doses tend to show the oppo-
site. The same holds for the proliferation of lymphocytes.

A further target of BEs and BAs in the immune system is the com-
plement system where inhibition of C3-convertase was reported.

Many studies deal with the effects of BEs, BAs and other con-
stituents of BEs on NFκB and cytokines. The activation of the
transcription factor NFκB was shown to be inhibited by AKBA and
probably also of other compounds including incensole acetate
and 12-ursene-2-diketone suggesting decreased transcription of
cfactors related to inflammation including a variety of cytokines.

Among the factors are proinflammatory interleukines TNF-α, IL-1β,
IL-2, INF-γ, IL-6, IL-12, but also upregulation (IL-4, IL-10) was
observed.

In addition to effects of BEs and BAs and other factors related to
the humoral and cellular immune system direct actions on periph-
eral mediators of inflammation have been reported. Thus BEs and
various BAs are inhibiting leukotrien biosynthesis by 5-LO. As far as
an action on prostaglandin synthesis is concerned BEs and a mixture
of acetyl boswellic acids showed no effect whereas prostaglandin
synthesis in human platelets which represent COX-1 was inhibited
by AKBA. On the other hand COX-2 appeared to be less sensitive to
AKBA.

Products of the inflammatory process which finally cause destruc-
tion of tissues in chronic inflammatory diseases—are oxygen
radicals and enzymes released by leukocytes and macrophages
including human leukocyte elastase (HLE). The action of both is
inhibited by BEs and AKBA.

Conclusion

Both BEs, BAs and probably also other constituents of BEs pos-
sess a variety of different actions in the immune system. Depending
on the dose they may be stimulating in formation of antibodies
(lower doses) or inhibitory in the cellular part by affecting the
action of NFκB and a variety of cytokines and finally the execu-
tors for all damages. Most of the data discussed in this review have
been obtained in in vitro experiments in a wide range of concentra-
tions. Whether or not the results obtained with BEs and BAs in every
case are relevant in the therapy of chronic inflammatory diseases
remains to be established. Nevertheless some clinical studies have shown positive results in the treatment with boswellic extracts.

References


