# Therapeutic Advantages of highly standardized Boswellia Extracts

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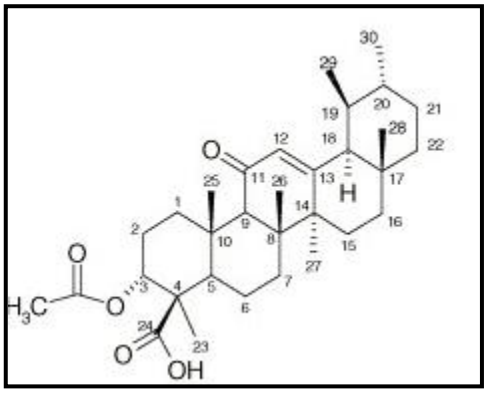
## Summary

Gum resin extracts of frankincense (*Boswellia serrata*) have been used for centuries for the treatment of chronic inflammatory diseases. AKBA (3-O-acetyl-11-keto-β- boswellic acid), a pentacyclic triterpene, is the most potent anti-inflammatory fraction of the boswellic acids. Principally among its many effects is the inhibition of the 5-LO enzyme and thus the suppression of its down stream pro-inflammatory leukotriene by-products. It is becoming increasingly clear that 5-LO metabolites are up-regulated in virtually all significant major chronic illnesses. Recent findings show that the 5-LO is expressed in practically all underlying inflammatory pathogenesis, in classical conditions like asthma, colitis or joints diseases but also in atherosclerosis and other cardiovascular diseases; bone resorption and osteoporosis; skin illnesses such as atopic dermatitis, psoriasis, acne and contact dermatitis; cancers such as pancreatic, bladder, breast, brain and prostate; neurological degenerative ailments and migraine; venous stasis; allergies and allergic sinusitis, etc. More conditions are regularly added. Inhibition of the 5-LO pro-inflammatory lipid mediators will be increasingly seen as part of the standard-of-care. The necessity of appropriately suppressing the 5-LO originating inflammation has been tackled largely unsuccessfully by the pharmaceutical industry up to now. Besides boswellic acids (BA's) there are currently no other comparably potent and risk free natural 5-LO inhibitor on the market. Boswellic acids are 5-LO inhibitors but the use of unpurified boswellia serrata extracts (BSE's) with a low 2-3% AKBA concentration have proven to have limitations and in some conditions outright contra-indications. Newly available BSE's standardized to 90% pure pharmaceutical grade AKBA avoid the previous pitfalls and augment clinical success rates. Nutritional supplementation with pharmaceutical grade BSE containing a high percentage of the AKBA fraction avoids the necessity of simultaneous exposure to high levels of other beta boswellic acids which can actually increase platelet aggregation and other paradoxical inflammatory reactions if a hyper-coagulable state exists. A daily dosage of 100-300 mg AKBA is the minimum required intake in order to achieve the effective therapeutic plasma levels suggested by clinical and laboratory studies. Various nutritional modalities are described here that have been found to significantly increase the absorption rate and bio-availability of AKBA. Most of the current boswellia formulations have a low AKBA content that cannot achieve the required blood levels of AKBA in a practicable

manner. The new BSE purified for a maximally high concentration AKBA fraction promises a leap in the hoped for clinical response rate. The ever expanding understanding of the benefits of suppression of the 5-LO enzyme will lead to an exponential increase in the diversity of indications for the use of highly standardized BSE.

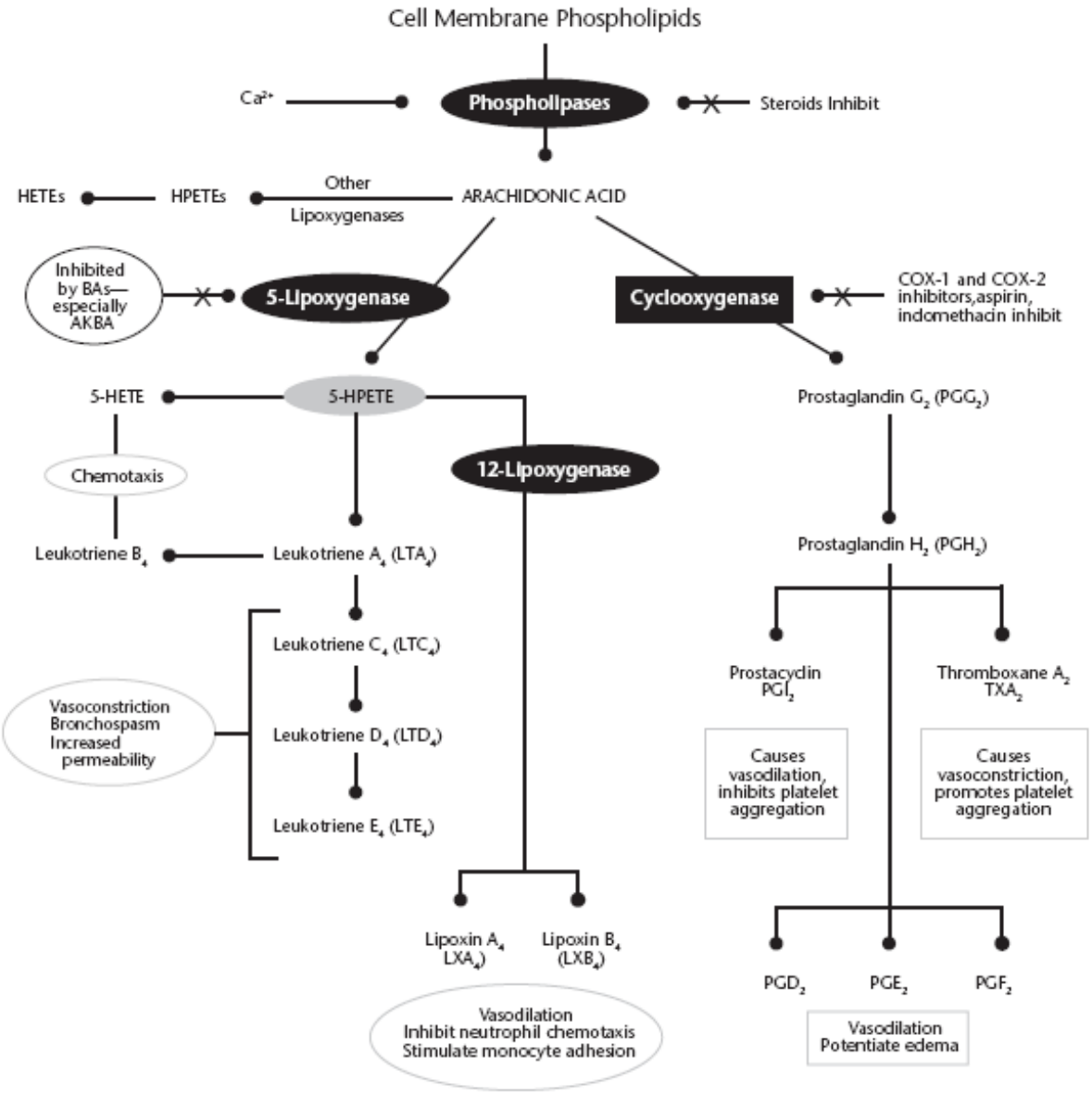
Keywords: Boswellic acids, Boswellia serrata extracts, 3-O-acetyl-11-keto-β- boswellic acid, 90% AKBA,
5-lipoxygenase, 5-LO, Leukotrienes,

**Fig.1 AKBA structure**



Abbreviations used

5 –LO = 5-Lipoxigenase
AA = Arachidonic Acid
AIA = Aspirin Induced Asthma
AKBA = Acetyl- 11-keto-β-boswellic acid
AKBBA = same as AKBA
BA = Boswellic acid
BSE = Boswellia serrata Extract
COX = Cyclooxygenase
CystLT = cystenyl leukotriene
CSCR = Central Serous Chorioretinopathy
EIA = Exercise induced Asthma
ERK = Extra-cellular signal-regulated kinase
FLAP = 5 lipoxygenase activating protein
HETEs = Hydroxyeicosatetraenoic acids
HLE = Human Leukocyte Elastase
$IC_{50}$ = Inhibitory Concentration 50%
IKK = IκB kinase
IL = Interleukin
LT = Leukotriene
MAPK = Mitogen activated protein kinase
MMP -2 = Matrix mettaloproteinase -2
NFκB = Nuclear Factor κ Beta
PAF = Platelet Activating Factor
PMNL = Polymorphonuclear Leukocytes
PT = Pentacyclic triterpenes
PUFA = Polyunsaturated fatty acid
ROS = Reactive oxygen species
RSV = Respiratory Syncitial Virus
sLT = sulphido-leukotriene
TNFα = Tumor necrosis factor α
VEGF = Vascular endothelial growth factor
WBC = White Blood Cells




Generation of arachidonic acid metabolites and their roles in inflammation.

## Fig. 2

**The role of the 5-LO pathway in the generation of leukotrienes (LT's).**

(after, Robbins and Cotran, Pathologic Basis of Disease, 2005, 7th Edition)

## Introduction to Boswellic Acids

The gum resin of Boswellia serrata, frankincense, has a number of components including oils, (α-Thujene), terpenols, monosaccharides and most importantly terpenes. Major research has centered on the components belonging to the pentacyclic triterpene group of compounds considered to be most bio- active. PT's are mainly synthesized in higher plants, due to the highly complex requirements for their synthesis. They exhibit a variety of profound effects such as being anti-inflammatory, anti-nociceptive, anti-oxidant, anti-bacterial, cancer drug sensitizing, cardio-protective and insulin resistance lowering.(1-5)
HPLC procedures have shown over fifteen specific PT compounds in boswellia species, such as α - and β-boswellic acid, 3-O-acetyl-β-boswellic acid, 3-O-acetyl-11-keto-β-boswellic acid, α-amyrin, β-amyrin, lupeol, 3-epi-α-amyrin, 3-epi-β-amyrin, 3-epi-lupeol, α-amyrenone, β-amyrenone, lupenone, lupeolic acid and 3-O-acetyl-lupeolic acid, tirucallic acid, and others. (2)
The general composition of the dry Boswellia serrata extract of the gum resin shows approximately 50-60% various α -and β-boswellic acids, of which roughly 1-3% of the total are the most bio-active AKBA fraction.(6, 7)
The lipophilic fraction AKBA, with a beta configuration, has been shown, by various pharmacological studies, to possess superior anti inflammatory properties over the α configured isomers. (3)
With the current commercial availability of a BSE purified to 90-99% AKBA, the work done to more fully understand this fraction is steadily gaining in importance.

## Traditional and Non-Conventional Views on the Use of BA's

Boswellia serrata is indigenous to Africa, India and the Arabian Peninsula. The fragrant resins have been used since Antiquity in incense and embalming liquids. In ancient Ayurvedic texts the gum resin is noted for its healing properties on fever, skin diseases, rheumatism, respiratory diseases including laryngitis and cough with copious amounts of sputum, liver disorders, ringworm, boils, strengthening of teeth, healing eye inflammations, enhancing the growth of hair, improving appetite, wound healing, soothing mouth sores, improving diarrhea, general restorative, tonic effects and more.
In more recent times Rudolf Steiner PhD has pointed out the significant energetic healing properties of these resins in both adults as well as in the developing infant. He especially emphasizes the beneficial effects of these resins on breast milk quality, the developing brain of the young child and their overall ability to maintain "a healthy spirit in a healthy body." (Cosmic Workings in Earth and Man, R. Steiner, R. Steiner Publishing Co., London, 1952.)

## Review of Human Clinical and Animal Studies with BA's and specifically the AKBA fraction

Multiple studies from the 1990's to the early 2000's show generally very positive results with BA's. (8) (9-11, 11-27) The main areas of study-- arthritis, cancer, asthma/allergies and inflammatory bowel disease will be briefly reviewed.

**Arthritis**

Specific findings

Poeckel (28) reviews in detail many human and animal studies done with a variety of boswellia preparations. His main findings are summarized briefly here.

The first scientific reports on the analgetic properties of BA's came out more then 35 years ago. Animal studies demonstrated the anti-inflammatory activity of BA's and the prevention of progressive joint collagen destruction due to the finding of decreased levels of inflammatory markers. More recent animal studies demonstrated reduced carrageenan or dextran induced edema, reduced papaya latex- induced rat paw inflammation, reduced intermittent lameness, local pain and stiff gait in osteoarthritic dogs, etc. A study of 2005(10) proved that strong anti-arthritic changes were accompanied by significantly suppressed TNFα and IL-1β.

In human studies the results were equally encouraging. Kulkarni(17) evaluated 42 patients with osteoarthritis recording increased walking distance, less knee stiffness, etc. However, in one multi center study no demonstrable statistically relevant clinical improvements were noted. (29) It should be noted, however, that patients received only a low BSE dose. No comments were offered whether a higher dose may have changed the outcome.

General conclusions:

- BA's lessened severity of pain in joints;
- BA's diminished knee swelling and knee flexion;
- BA's increased duration of walking distance.

**Inflammatory bowel disease**

Specific findings

Poeckel (28) reviews in detail the human and animal studies done with a variety of boswellia preparations in the IBD model. His main findings are summarized briefly here.

Animal studies showed protective effects specifically of AKBA in toxin induced hepatitis and ileitis. AKBA also significantly blunted experimental mouse colitis and prevented typical inflammatory cell reactions like recruitment of adherent leukocytes and platelets into inflamed colonic venules. AKBA also largely prevented the P-selectin up-regulation. These effects were similar to those in mice treated with corticosteroids.(30)

Recently, BA's were shown to prevent experimental diarrhea and to normalize intestinal motility without slowing down the rate of transit when given to control animals. (8)

In a human study patients with colitis, grade II and III, had an 82% remission rate when treated with BA's as opposed to 75% of those in the control sulfasalazine group.

In another study 14 BA's treated patients, out of a total of 20 patients, went into remission, as opposed to 4 out of 10 patients in the control sulfasalazine group.

General conclusions:

- BA's improved clinical well being in patients with IBD;
- BA's improved stool properties, microscopy of rectal biopsies, hemoglobin and other blood parameters, serum iron, calcium, phosphorus, proteins, total leukocytes and eosinophils, and the Crohn's disease activity index.

**Cancer**

Specific findings

Poeckel (28) reviews in detail human and animal studies done with a variety of boswellia preparations in cancer model set ups. Some of his findings are summarized briefly here.
Topical application of BA's prevented or slowed tumor cell promotion when animals were fed a diet containing 0.2% by weight AKBA, clearly showing anti-neoplastic qualities of BA's. (31)
Another study showed that BSE's influenced glioma cell growth. AKBA could still be detected in the brain 3 hours after oral administration of a 240mg/kg of BSE to rats. (32)
In a human study, 19 children with intra-cranial tumors received palliative therapy with BSE. Although no anti-neoplastic effects were seen, 8/19 children experienced some significant clinical improvement.
In 2002, the European Agency for the Evaluation of Medicinal products (EMEA) released a positive opinion for orphan designation of BSE for the treatment of peritumoral edema derived from brain tumors.

General conclusions:

- BA's improved general health status, muscular strength, weight gain in cancer patients;
- BA's decreased neurological symptoms in patients with intra-cranial tumors;
- BA's decreased edema of brain tumor patients.

**Allergy and Asthma**

Specific findings

Poeckel (28) reviews in detail human and animal studies done with a variety of boswellia preparations. His findings are summarized briefly here.
In several studies animal passive paw anaphylaxis reaction and mast cell degranulation was reduced.
A human clinical double blind study was done on forty patients with chronic asthma. They were given 300 mg three times daily of a BSE for 6 weeks. 70% of patients showed improvement by the lowering of attack frequency, lowered eosinophilic counts, disappearance of dyspnea, rhonchi and an increase in pulmonary function, such as increase of FEV 1 and FVC. In the control group only 27% of patients showed improvement.

General conclusions:

- BA's improved general status in chronic asthma patients;

## AKBA Activity at the Cellular/Molecular Level

The majority of the most recent studies and reviews have been highlighting the pre-eminent role of the AKBA fraction over the other β-boswellic acids. (27, 33, 33-42) (43-48) (24, 25, 30, 49, 50) (26, 27) (51) (52) .(3, 53) ;(54, 55) (56) (57)

AKBA has been shown to:

- impair leukocyte infiltration and antagonize humoral immune response;
- suppress the classical and alternative immune complement pathway;
- inhibit mast cell degranulation;
- suppress LPS-induced NO production in peritoneal macrophages, effects that confer a reduced risk of anaphylaxis;
- suppress LPS mediated TNFα induction in monocytes;
- inhibit TH1 cytokines (IL-2), typically elevated in rheumatoid arthritis;
- inhibit interleukin IL-1β;
- inhibit in a non-redox, non-competitive fashion the 5-Lipoxigenase enzyme (discussed in more detail below), and thus its LT's producing pathway;
- decrease intracellular basal $Ca^{2+}$ in monocytic cells, and suppress the activation of p38 MAPK , both of which being pro-inflammatory signal transducers
- inhibit the NFκB pathway and NFκB regulated gene expression leading to TNFα suppression apparently by direct inhibition of IKK's;
- inhibit the expression of the pro-inflammatory effectors (matrix metalloproteinases) and adhesion receptors;
- inhibit the human leukocyte elastase;
- suppression the P-selectin up-regulation and leukocyte platelet adherence in colitis models;
- inhibit topoisomerase I and II, thus leading to blocked proliferation and cell differentiation;
- inhibit DNA, RNA and protein synthesis in HL-60 cells;
- induce apoptosis in selected cancer cell lines through the central mediation of caspase-8 which in turn activates the "executor" enzyme caspase -3;
- inhibit PKB/Akt phosphorylation and p38 MAPK as well as ERK ½ phosphorylation and cell motility in meningioma cells;
- non- selectively inhibit the drug metabolizing CYP enzyme family;
- inhibit the activity of P-glycoprotein in leukemia cell lines (only AKBA, but not BA's lacking the 11-keto group);
- significantly reduce PAF in $CCl_4$ induced hepatic liver fibrosis.

## Specific Inhibition of the 5-LO by AKBA

**The Inflammatory Cascade**

In answer to specific external stimuli, and after the appropriate signal transductions, the cell membrane lipid AA – a 20 carbon PUFA- is rapidly formed in order to generate lipid mediators that lead to functional inflammatory processes. As seen in Fig.2 an increase in intra cellular $Ca^{2+}$ and various kinases is necessary for the activation of the inflammatory cascade. Two enzymes – the 5LO and the COX (1 and 2) – synthesize the eicosanoids, principally prostaglandins and leukotrienes, both of which are involved in virtually all inflammatory responses. Of main interest

here is the lipoxygenase pathway whose products lead to vascular permeability, chemotaxis and leukocyte adhesion, as well as bronchoconstriction. Particularly LTB4 is a powerful chemotactic agent that leads to activation of functional neutrophil responses, release of lysosomal enzymes, generation of ROS and platelet aggregation. LT's are several orders of magnitude more potent than histamine in increasing vascular permeability and causing bronchospasm.
When a variety of WBC's are activated, (principally among them macrophages and lymphocytes, but also endothelium, epithelium and connective tissue cells), cytokine proteins (such as TNFα, IL-1, etc) are produced and lead to the augmentation of the inflammatory reactions (fever, loss of appetite, etc.) A further consequence of the activation of inflammatory cells is the enhanced production of NO, a potent vasodilator with multiple pro-inflammatory activities. (Robbins and Cotran, Pathologic Basis of Disease, 2005, 7th Edition)

**How is 5-LO bio-regulated?**
The enzyme is mainly restricted to myeloid cells, like macrophages, granulocytes, etc but can also be expressed in human skin keratinocytes, Langerhans cells or brain cells. A number of intermediates like phospholipase A, membrane bound FLAP, and others are needed for biosynthesis. Higher intracellular Ca2+ levels increase the affinity of 5-LO toward AA. Similarly oxidative and genotoxic stress results in a higher level 5-LO activation. Of great interest should be the fact that 'priming' agents such as cytokines, Epstein-Barr virus (!) and others do not in themselves lead to activation of 5-LO and its resultant LT's, but subsequent stimulation of the cells with pro-inflammatory agonists leads to a strongly increased production of LTs! (58-60)

## 5-LO Inhibition

In general pharmacological inhibition of 5-LO and LTs can be achieved by the following main strategies:

1. Inhibition of PLA2 enzymes, leading to a lesser AA substrate availability;
2. Inhibition of FLAP.
3. Direct inhibition of 5-LO;

Inhibition of PLA2 enzymes would theoretically prevent formation of all eicosanoids. In clinical studies, however, glucocorticoids, known inhibitors of PLA2, are ineffective in suppression of LTs.
FLAP inhibitors have also proven not to be a viable solution. There are a number of synthetic FLAP inhibitors that have been tested, but they have shown to be 50 to 200 times less potent in clinical situations then in the *in vitro* isolated leukocytes.
The direct 5-LO inhibition can be categorized into three modes of action:

1. Redox-active 5-LO inhibitors, which act by reducing the iron at the active site. 5-LO is a di-oxygenase that catalyzes the incorporation of molecular oxygen into liberated AA. 5-LO contains a non-heme iron at the active site in the ferric form (Fe3+). This forms the basis for the inhibitory action of some 5-LO inhibitors which convert the ferric to the ferrous form (Fe2+). (61-64) Agents discovered in this direction are not currently used due to their severe side effects. (65)
2. Iron ligand inhibitors chelate the active site iron. An example in this category would be the drug zileuton which has been shown to improve asthma but has demonstrated only a small benefit in allergic rhinitis, arthritis and inflammatory bowel disease and no effect in ulcerative colitis. (66)
3. AKBA belongs to the third group of so called non-redox inhibitors of 5-LO. It has a unique mechanism of action that is gradually being better understood. It acts directly on 5-LO at a site that is different from the catalytic AA binding cleft. Its lack of any significant side effects, high safety level and favorable toxicological studies, as well

extensive traditional and modern clinical use across many divergent pathologies make this an ideal 5-LO inhibitor.

AKBA was confirmed as the most active boswellic acid fraction to inhibit the 5-LO with an $IC_{50}$ value in the range of 1.5-8 μM. (67) (68-72)
The AKBA concentrations needed for complete 5LO inhibition vary greatly depending on the experimental set up and type of cells studied. In some intact animal cell studies the IC50 was around 8μM while in cell free assays it could go up to 50μM! This suggests that the potent LT suppression is due also to interference of AKBA with other cellular events required for the activation of 5LO. (28)
AKBA interferes with the activity of the 5-LO by acting at a selective binding site for PTs on the 5-LO. This site is different from the AA-binding site of the 5-LO. The PT ring system is crucial for binding to the selective effector site, whereas functional groups like the 11-keto moiety are essential for the 5-LO inhibitory activity. (71-73)

Several unexpected findings point to an even more complex picture of 5-LO inhibition by AKBA. In several studies, contrary to expectations, after BA's were given to stimulated PMNL cells there occurred an increase in Ca2+ mobilization, activation of ERK2 and MAP kinases, as well as an up-regulation of 5LO activity instead of a down regulation.(68, 69)
Poeckel (28) suggests the following as explanation for these observations that run contrary to the predominant body of findings. He postulates that the mentioned events potentially lead to a temporary elevation of reactive oxygen species (ROS) production which in turn irreversibly inactivated the redox-sensitive 5LO.
It is becoming increasingly clear that the interference of BA's with the inflammatory cascade and the 5-LO is strongly dependent on the biological situation involved, the structure of the BA's- i.e. the presence of the keto moiety or not- etc. AKBA may lead to cell stimulation in un-stimulated cells but on the other hand may prevent subsequent activation of cells in inflammatory conditions such as when challenged by an additional ligand like TNFα .(28, 50, 53, 74, 75) .(69)

## Recent Insights into the Therapeutic Applications of 5-LO Inhibition

**General observations**
5-LO is the key enzyme in the biosynthesis of LT's. These pro-inflammatory mediators are potent chemotactic and chemokinetic mediators stimulating the immigration and activation of granulocytes, leading to adherence of granulocytes to the vessel walls, degranulation of mast cells, and the release of superoxide. They are connected to increased interleukin production and neutrophil dependent hyperalgesia, cause vascular permeability and smooth muscle contraction. Cys-LTs lead to smooth muscle contraction, plasma extravasation, recruitment of neutrophils, and vasoconstriction. They are up to 1000-fold more potent than histamine. Animal studies with genetically disrupted 5-LO genes showed significantly reduced inflammatory responses to a number of noxious stimuli especially arachidonic acid caused inflammation. In view of the high AA containing modern Western diets, these results are epidemiologically very significant. (76)
Multiple other studies have established a significant role for LT's in inflammatory diseases such as arthritis, inflammatory bowel diseases and asthma. (77-79)
In another comprehensive review Rubin(80) points to the central role that 5-LO and its leukotriene metabolites play in chronic severe exercise and in the aspirin induced forms of asthma, COPD, allergic rhinitis, idiopathic pulmonary fibrosis, ischemia related organ injury, and atopic dermatitis.
Recent studies have implicated LT's and other 5-LO products in unexpected pathophysiological illnesses such as the bone resorptive metabolism of osteoporosis, the atherogenic processes of the

cardiovascular system, atopic and hyperproliferative skin diseases such as dermatitis and psoriasis, and the proliferation as well as survival of tumor cells, and multiple other conditions. Studies confirm the role of 5-LO products in ear inflammation and peritonitis. (81)
Interestingly, the global inhibition of 5-LO has proven to be more efficacious than the partial inhibition of the 5-LO pathway through either LT antagonists, LT receptor antagonists or LT competitors.
Examples of the LT's induced cellular changes leading to pathological disease manifestations are given in Table 1. Not surprisingly a consensus is emerging that pharmacological inhibition of 5-LO and its metabolites represents an important potential for the treatment of a host of conditions. The broad range of applications is obvious from Table 2.

**Cardio-vascular Diseases**
The role of the 5-LO in atherosclerosis is particularly interesting.
Atherosclerosis, a major cause of morbidity and mortality, is now seen as an inflammatory fibro-proliferative disease. LT receptors are abundantly expressed in atherosclerotic lesions in the aorta, heart and carotid artery. In fact the presence of high expression of 5-LO, FLAP, and leukotriene hydrolases correlate well with high plaque instability. (82) Review of animal and human data suggest that 5-LO and its metabolites are up regulated in vessel walls, macrophages, dendritic cells, foam cells, mast cells, and neutrophils. Recent studies clearly have identified the 5-LO and/or FLAP gene as a risk factor in such as cardio vascular diseases as stroke and myocardial infarction. (82-87)
A survey of 470 subjects identified to have a gene variant leading to an increased expression of 5-LO demonstrated a significant increase in carotid artery intima-media thickness. Dietary intake of fish oils, which reduce the production of LTs blunted the genotype effect. Another recent survey of subjects from Britain and Iceland, with higher than normal 5-LO expression, showed, double the usual rate of heart attacks. Mice genetically lacking the 5-LO gene showed a dramatic 26 fold reduction in aortic lesions. (88-90) These studies suggest that 5-LO inhibition would be a valuable preventative measure in CV disease.
Significantly increased urinary LT levels were found in patients following admission for acute myocardial infarction.
Elevated levels of LTs were also found in patients with unstable angina.
LTs are also involved in sickle cell disease and septic shock. Taken together these studies demonstrate that there is a significant benefit to treat patients suffering from ischemic injuries and the resulting organ damage by eliminating inflammatory events through 5-LO control. (91-94)
Recently, LT receptors have been shown to be expressed in the intimal hyperplasia of early atherosclerosis and in restenotic lesions after angioplasty. These findings emphasize the role that a 5-LO target could play in preventing restenosis after coronary interventions. (95)

**Hypertension**
The 5-LO derived products cystLT and 12-HETE are vasomotor mediators with increased biosynthesis in various models of hypertension. LT's are involved in glomerular inflammatory injury. In addition it has been suggested that they might contribute to the vasoconstrictor, hypertrophic and mitogenic effects of angiotensin II. This might explain at least in part the vascular inflammatory complications associated with hypertension. (96-101)

**Cancers**
Aberrant functioning and over-expression of 5-LO pathway products may contribute to cell proliferation, evoke angiogenesis and effect survival of particularly prostate and pancreatic cancers. Making these cellular signals part of the therapeutic targets, either alone or better in

combination with other modalities has been shown to slow tumor progression, reduce tumor cell invasiveness and tumor cell motility and decrease tumor angiogenesis. (102-104)
Cigarette smoke is known to cause an inflammatory response in the colon that can lead to colon adeno-carcinoma. The mechanism seems to be via an up-regulation of 5-LO induced protein expression accompanied by up-regulation of mettaloproteinases-2 and vascular endothelial growth factor. 5-LO inhibitors reduced the incidence of adenomas, angiogenesis and MMP-2 activity and VEGF. The results strongly suggest that cigarette smoke induced 5-LO expression leading to colon adenoma formation can be reduced by 5-LO inhibitors. (105, 106)
5-LO and its metabolites have been found to have an increased expression in lung cancers and to inhibit apoptosis as well as contribute to cell proliferation. These advances in the understanding of the molecular biology of lung cancer has led to the conclusion that 5-LO pathway inhibitors should be part of the chemoprevention armamentarium in these illnesses. (107)

**Respiratory illness**
Pulmonary damage in cystic fibrosis is mediated largely by 5-LO pathway generated eicosanoids and leukotrienes released by PMNL's. A reduction in pro-inflammatory mediators was deemed to substantially lessen the damaging tissue inflammation. (108)
RSV infection causes significant morbidity both in the adult but especially in the pediatric population. By the age of three most children have been infected at least once. The typical symptoms of runny nose, copious mucous discharge, cough, progression to wheezing and potential respiratory distress can lead to hospitalization in 1-2% of all cases. The illness can last for weeks and can exacerbate asthma. The mechanism for viral damage is not well understood and no specific therapy is indicated. Interestingly, however, the 5-LO and the LT's discharged from mast cells are significantly increased in the inflammatory discharge and a potential role for 5-LO inhibition is thus given.(109) (110, 111)
Pneumoccocal otitis media is associated with the production of high levels of LT's. The presumptive mechanism seems to be that the pneumoccocus bacteria activates the 5-LO pathway by up-regulating the expression of the $_{c}$PLA2 and 5-LOX genes. This in turn may stimulate the production of proteins leading to the formation of fluid in the middle ear. (112) This may explain the anecdotally observed benefit of supplementation with BA's in children with various upper and lower respiratory illnesses.
Rhinovirus infections can cause cough, wheezing and bronchial hyper-responsiveness, in otherwise normal individuals. Bronchial aspirations in these patients demonstrated marked inflammation characterized by markedly enhanced expression of 5-LO pathway proteins. (113)
The LTs involvement in severe asthma, especially AIA and EIA, is becoming well established. 5-LO inhibition has been demonstrated to significantly increase forced expiratory volume and morning and evening peak expiratory flow rate. Because inhibition of the 5-LO pathway is so highly effective in both AIA and EIA their use has been recommended as meriting first line therapy status in both disorders. (80, 114-117) Patients with severe asthma and frequent asthma exacerbations may also be good candidates since there is a common association with neutrophil predominance and there is pronounced airway remodeling. (118-123) An additional highly significant advantage to 5-LO inhibition is that it fills the gap in anti-inflammatory coverage of inhaled glucocorticoids.(124)
Trials of 5-LO inhibitors in allergic rhinitis and sinusitis showed that 72% of participants had a positive response of symptom reduction and 50% experienced reduction of nasal polyps. (125-128)

**Osteoporosis, Bone Metabolism and Joint Diseases**
A connection between 5-LO, LTB4, other arachidonic acid derived eicosanoids and osteoporosis is becoming more apparent.(129-131, 131, 132)
Bone resorption requires cooperation between osteoclasts and mononuclear accessory cells. 5-LO metabolites have been shown to stimulate this process.(133) Among the 5-LO generated LT's especially LTB4 seems to activate osteoclasts and cause surface erosion.(129)
Various animal models using experimental inhibition of 5-LO have prevented loss of bone mass in rodents, with a concomitant increase of femur and humerus volume, density, femur calcium levels and ash weight.(134) (135) (132)

**Skin Diseases**
5-LO and its lipid metabolites, the LT's, have been increasingly recognized as having a pivotal role in dermatologic disorders like psoriasis, acne and atopic dermatitis. (59, 60) In all three conditions reducing the levels of LTs results in significant lessening of edema, pruritis, redness and reduces responses to antigens. (136-138) (139-142) (143-146)
In atopic dermatitis changes related to LT's, like an elevation of eosinophils and increased production of cytokines IL-4, IL-5, IL-13, can be controlled with means that suppress LT's. Circulating leukocytes in atopic dermatitis show an increase in LTB4 and LTC4. The characteristic erythema is probably mediated via cyst-LT's. Skin cell production of LT's was increased almost 5-fold with antigen challenge. In 5 of 7 clinical studies a significant reduction in disease activity and symptom severity was noted with the use of 5-LO inhibitors.
Considering that acne is a complex inflammatory disease, it is not surprising that LT's play an important pathological role here too. LTB4 and LTC4 have been shown to have a mitogenic effect on keratinocytes. Sebocytes also express both 5-LO and LTs. Pharmacologic studies also support the idea that 5-LO and its eicosanoid metabolites have a significant role in acne. 5-LO inhibitors have been shown to be therapeutically beneficial by reducing the severity and frequency of acne lesions, and reducing sebum production and the total output of sebum lipids and sebum free fatty acids.

**Neurological Diseases**
Clinical observations have shown that patients with migraine taking LT receptor antagonists due to concomitant asthma have a lower migraine frequency. These observations are further enhanced by reports that these patients also become less sensitive to environmental triggers such as perfumes and other noxious stimuli. In an open label study the effect of LT antagonists on migraine sufferers was tested with the following results: 53% of subjects showed a greater than 50% reduction in the frequency of severe attacks; 41% showed a reduction of more than 60% in attack frequency. This was considered to be a clear indication that the 5-LO pathway was involved in the pathogenesis of migraine. (147)
More recently the postulate was examined that cognitive decline in aged brains is due to inflammatory CNS changes. Aging rats with significant cognitive defects in comparison to younger ones were examined by observing vascular leakage into the retina. Cognitive decline paralleled the LT's mediated retinal damage. (148)

**Food Allergies**
Food allergies in both adults and children have seen an explosive increase in the last several years. As an example, in recent media news an Australian study is mentioned reporting a 12-fold (!) increase in food allergies since 1995 alone. Yet few new

therapeutic methods have been developed to effectively deal with these problems. (149)
Are 5-LO mediators involved in food allergies?
Hyper-responsiveness to histamine is a key feature of a variety of pathological conditions, including food allergies and other intestinal conditions. Cysteinyl LT's have been implicated as mediators of increased histamine responses. Cyst LT's mediate histamine hyper-responsiveness by increasing histamine receptors in immunologically relevant cell types. (150)
In a study of 40 patients with adverse reactions after food intake LT's were shown to be significantly higher after antigen stimulation in the food sensitive group than in the control group. (151) Patients with chronic urticaria challenged with aspirin showed a significantly higher urinary excretion rate of LT's as compared to controls.(152)
Considering these novel insights into the role of 5-LO and LT's in the pathophysiology of these conditions one can expect to see an increased role for BA's in the first line therapy of these common complaints.

**Venous Stasis**
The formation of varicose veins is more than a cosmetic disease. Venous blood stasis, vessel wall injury and a hyper-coagulable plasma state can lead to deep vein thrombosis and thromboembolism. Neutrophils are known to promote vascular injury and thrombosis following venous stasis. LT's are potent mediators of vascular injury and neutrophil chemotaxis. Animal studies demonstrated that 5-LO inhibition reduces deleterious neutrophil/vessel wall interactions. (153)

**Gastric Diseases**
AA metabolites via the 5-LO pathway have been found to be pivotal mediators in Helicobacter pylori-induced inflammatory response. H. pylori stimulated the translocation of $cPLA_2$ from cytoplasm to nucleus and increased the biosynthesis of HETEs in the gastric epithelium. The administration of LOX inhibitors resulted in down-regulation of pro-inflammatory mediators such as IL-8 and TNFα in both H. pylori-infected gastric epithelial cells and macrophage cells. 5-LO inhibition could impose significant anti-inflammatory responses after H. pylori infection, based on the fact that H. pylori infection provoked gastric inflammation through metabolizing arachidonic acid by the 5-LO pathway.(154-156)

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## Table 1.
## Role of the 5-LO and its metabolites in creating pathological conditions

Asthma
- Reversible airway narrowing
- Hyper-responsiveness
- Eosinophil influx
- TH2 lymphocyte influx
- Basophil influx
- Neutrophil influx

Edema
Increased mucous production
Decreased mucociliary clearance
Goblet cell metaplasia
Increased mast cell cytokines
Collagen deposition
Epithelial hypertrophy
Myofibroblast hyperplasia

Allergic rhinitis
Nasal congestion
TH2 lymphocyte influx
Edema
Collagen deposition
Subepithelial fibrosis
Increased mast cell cytokines

COPD
Neutrophil influx
Macrophage influx
Increased mucous production
Goblet cell hyperplasia
Collagen deposition
Subepithilial fibrosis

Idiopathic pulmonary fibrosis
Collagen deposition
Subepithelial fibrosis
Smooth muscle hyperplasia

Atherosclerosis
Monocyte/macrophage influx
Foam cell conversion
Dendritic cell influx
Mast cell influx
T cell influx
Intimal edema
Smooth muscle cell hyperplasia

Ischemia reperfusion injury
Edema
Increased endothelial adhesion molecules
Neutrophil influx

Atopic dermatitis
Erythema
TH2 lymphocyte influx
Monocyte/macrophage influx
Eosinophil/neutrophil influx
Edema
Collagen deposition

Fibrosis

Acne vulgaris
- Seborrhea
- Keratinocyte prolipheration
- Erythema
- T cell influx
- Mocyte/neutrophil/macrophage influx

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## Table 2.

**Conditions in which 5-LO and leukotrienes are excessively expressed.**
**The use of AKBA is indicated here due to its potent inhibition of these pro-inflammatory metabolites.**

**Acne**
**Allergies**
**Allergic conjunctivitis**
**Allergic rhinitis**
**Arthritis**
**Asthma**
**Atherosclerosis**
**Bronchospasms**
**Cancer**
**Cellulites**
**Cystic Fibrosis**
**Dermatitis**
**Ear inflammation**
**Eczema**
**Exercise induced shortness of breath**
**Gastric ulcers/ H. pylori infection**
**Gout**
**Hepatitis**
**Hyperlipedemia**
**Inflammatory Bowel Disease**
**Ischemic organ injuries**
**Liver Cirrhosis**
**Lupus Erythematosus**
**Migraines**
**Multiple Sclerosis**
**Myocardial Infarction**
**Neuro-degenerative Diseases**
**Osteoarthritis**
**Osteoporosis**
**Pain syndrome**
**Perennial Rhinitis**

**Psoriasis**
**Sinusitis**
**Smoking**
**Stroke**
**Urticaria**
**Venous Stasis/ Thrombosis**

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## Problems with boswellic acids

Kiela reports of three studies with negative results. In one animal study BSE's were found to be ineffective in ameliorating murine colitis. He also reports that in a different in vitro set up, individual BA's rather increased the basal and IL 1-β stimulated NFκB activity in the intestinal endothelial cells. In a third sturdy BSE's showed hepatotoxic effects. (157)

Of the beta boswellic acids primarily BA's without the 11-keto moiety induced the pro-inflammatory ERK phosphorylation connected to substantial mobilization of $Ca^{2+}$. They also triggered liberation of endogenous AA, formation of p12-LO products, generation of thrombin and caused moderate aggregation of platelets. On the other hand AKBA suppressed survival signals along the ERK route in meningioma cells which could explain the anti-proliferative activities of AKBA . Inhibition of the classical and alternative complement pathway was reported only for high concentrations of BA's , for example β-BA's at $IC_{50}$ >50 μM(45, 47)

BA's overcome the problems of other 5-LO inhibitors most of whom, while identified as being active in vitro, have thus far not been suitable for clinical application, either because of poor bioavailability, specific side effects or loss of potency under oxidative conditions.
This naturally increases the importance of BA's which have been shown to be of considerable value in human conditions.
Nevertheless not all BA fractions act in identical fashion.
For example, LT biosynthesis in intact cells was shown to be only weakly inhibited by BA's in the range of 15 to 40μg/ml. On the other hand, AKBA already inhibited 5-LO in the range of IC50 of about 0.75μg/ml (1.5 μM). (71, 72)
Moreover, very low concentrations of BA's – up to 10μg/ml- increased the 5-LO product formation to about 155% over controls (!) but reverted to the expected inhibition of 5-LO at higher concentrations of 20-40μg/ml, decreasing LT product synthesis by about 19%.
In contrast to the crude extracts, AKBA exerted no 5-LO increasing activity in low concentrations up to 0.25μg/ml, and starting with concentrations of 0.5μg/ml acted in an inhibitory manner.
Again in contrast to the simple crude extracts, AKBA inhibited the 5-LO completely with an IC50 of about 2μM whereas the action of the extracts was only 80-85% complete.
It seems that the action of crude extract BA's is biphasic in nature with both inflammatory and anti-inflammatory results depending on the concentration, while AKBA has a purely inhibitory property. These findings underlie the necessity of standardization of boswellia extracts if consistent results are hoped to be obtained. (158)
Poeckel (159) presents data in his paper on the influence of BA's on human platelets. He reports that β-boswellic acids caused a pronounced mobilization of Ca2+ from internal stores and induced the phosphorylation of p38 MAPK, ERK2 and Akt. These pro inflammatory changes were concentration dependent and the magnitude of the responses was comparable to those

obtained after platelet stimulation with thrombin or collagen. In higher concentrations, > 10μM , liberation of AA and platelet aggregation can occur. In contrast to β-BA's the 11-keto-β-boswellic acids, AKBA, evoke only moderate Ca 2+ mobilization, but fail to induce phosphorylation of ERK2 or Akt, and do not cause platelet aggregation or significant generation of thrombin. Since β-BA's induce the changes at concentrations comparable to those seen in human plasma levels the findings might raise the concern that under the right hypercoagulatory circumstances thrombus formation may occur. Nevertheless, while certain signaling components are induced, others are not, so that the process must not lead necessarily to the induction of a full platelet aggregation function. Still the advantage of using purified AKBA fractions when higher concentrations are desired for clinical purposes becomes evident.

## Dosage questions in the Administration of AKBA

**Bioavailability**
To be effective a product must be demonstrated to be bioavailable. Several studies have looked at the plasma levels of BA's and AKBA following single or multiple oral intakes.
On a rudimentary basis this was proven in rats (32) where measurable levels of AKBA were found in the brain after 3 hours following a single oral administration dose of 240 mg/kg of dry BA's extract.
In a human study the plasma level of AKBA was 0.1μM after oral intake of 4x786mg unpurified B. serrata extract. (28)

**$IC_{50}$ values**
Inhibition of the classical and alternative complement pathway was reported only for high concentrations of BA's f.ex. β-BA's at $IC_{50}$ >50 μM (45, 47)
AKBA, a non-redox inhibitor of 5LO, was found to have an $IC_{50}$ value determined at 1.5μM. (70) up to 8μM (68-71, 73)
AKBA potently suppressed p12-LO product formation ($IC_{50}$=15μM), with higher potency for p12-LO in cell free assays as compared to crude 5-LO. (28, 74)
AKBA inhibits the HLE at levels of $IC_{50}$ = 0.9-15μM. (19)
In monocytic cells AKBA reduced the phosphorylation of ERK2 at a concentration of 3μM. (28, 53, 74)
Different BAs, with AKBA being the most potent derivative, were found to inhibit DNA and RNA in HL-60 cells with $IC_{50}$ values ranging from 0.5 – 7.1μM. Apoptosis of various cancer cell lines could be achieved with AKBA concentration > 10 μM. (31, 35, 54, 55, 160-167)

**Pharmacokinetics**
A basic pharmacokinetic study was done by Sharma et. al. (168) on BA's and AKBA. This was helpful in order to begin elucidating the behavior of BA's, their bioavailability and optimal dosing. Twelve healthy volunteers were given a one time dose of 333mg of a BSE containing 65% organic acids, minimum 40% boswellic acids, and 2% AKBA.
The plasma levels were assessed prior to and hourly after drug administration. The peak plasma levels of BSE (2.72x10-3 ± 0.18μmoles/ml) were reached at 4.5 ± 0.55 hours. The apparent volume of distribution was very large at 142.87 ± 22.78 L. The elimination time was 4.5 ± 0.55 hours. This elimination time suggests that the drug should be given at an interval of approx. 6 hours. They calculated that the steady state would be achieved in approximately 30 hours.

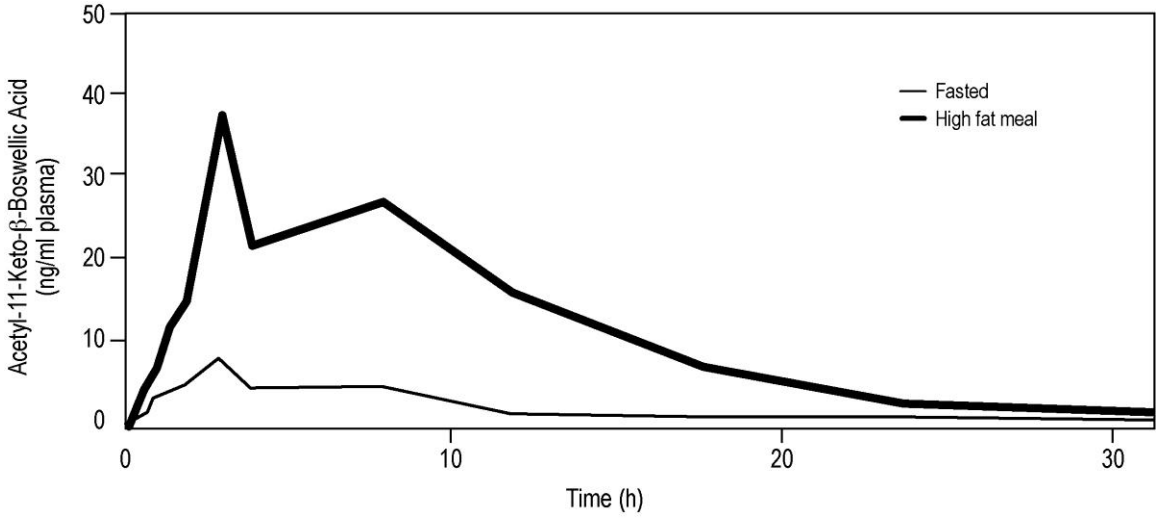
One can make some interesting observations looking at their data. At six hours post drug the maximal plasma levels of AKBA of the 12 subjects were: 1.56; 1.41; 1.84; 2.18; 1.75; 2.73; 2.39; 1.79; 1.20; 0.99; 0.86; 3.18 ( plasma concentration x 10-3(μmoles/ml). This means that no more then 50% of the subjects reached the 1.5μM concentration that all the other studies demonstrated is the minimum needed for an effective inhibitory concentration. Going above the usually given daily1g of a BSE with the customary 2-3% AKBA might help capture a lot of the so called therapeutic failures which may simply represent an under-dosing of test subjects or patients.

**What is then a desirable range for an oral dose of AKBA?**

Ideally, one would need a daily intake of at least 150 mg of pure AKBA(!) in order to be in the minimally effective concentration range of 2μM .
This sheds an interesting light on the success rate, or rather lack thereof, of studies where amounts of 3,600 mg daily of unpurified BSE's (with AKBA contents around 2-3%) were given. With the most generous assumptions this would result in a 100 mg daily pure AKBA dose, right at the border of effectiveness. In the current "real world" practice even lower daily doses of only 1,000 mg unpurified BSE's are given again with correspondingly low success rates.

## Enhancing Therapeutic Blood Levels of AKBA

The bio-available plasma levels of various BA's and especially AKBA were shown to be significantly enhanced by concomitant administration of a fat containing meal. (7)
786 mg of a dry BSE containing 28.71 mg, 3.7%, AKBA were administered to healthy volunteers and plasma levels recorded at hourly intervals post ingestion. Various boswellic acid fractions were analyzed. For AKBA, the data (as also seen in Fig. 3) shows that the mean concentration went from 6.0 to 28.8 ng/ml. Overall, the area under the concentration time curve under high fat meal conditions compared to fasted conditions was increased by 414%, and the maximal plasma concentration under fed conditions compared to fasting increased by 380%.
The meal consisted of fried eggs, bacon, milk and French fries. The authors (7) interpret the improved results accompanying this meal to suggest that the benefit was due to an increased stimulation of bile acids.




Plasma concentration of AKBBA after a single oral dose of BSE of 786mg, containing 28.71 mg AKBBA, under fasting conditions and then concomitant with a high fat meal. (after Sterk, V. et al, 2004) (7)

**Fig. 3**

Clearly there are more desirable ways to improve bile secretion then a highly atherogenic meal. Several animal studies have objectified the stimulant action of food spices on the enhanced secretion of bile acids, as well as improved function of pancreatic enzymes and the terminal digestive enzymes of the small intestine. (170-172)
In these experiments the following spices have proven to be most stimulatory on bile acid outflow, both biliary solids and bile acids: fenugreek, curcumin, coriander and particularly a mixture of coriander, pepper, turmeric, ginger and onion. The observed increase in bile acid flow and production was in the range of 50-80%.

**Further means of improving 5-LO inhibition in general**

Various nutritional manipulations have been shown to enhance the effects of 5-LO inhibitors as such. Supplying the body with high amounts of Omega-3 fish oils is known to accomplish this goal. Additionally, altering the daily diet such that foods low in AA are eaten (meat, dairy products, eggs, etc) reduces the available AA load and thus automatically lowers the output of 5-LO metabolites, such as LT's.

H1 receptor antagonists like Allegra, Benadryl, etc. or their natural equivalents are employed to fight nasal congestion, eye and ear allergic reactions. The combination of an H1 receptor antagonist with a 5-LO inhibitor was found to have synergistic beneficial effects in animal models of allergy as compared to giving either drug alone. These insights may be valuable in the management allergic disorders, including asthma, allergic conjunctivitis, and allergic rhinitis. (173-180)

## Safety and Toxicology

Boswellic acids are generally regarded as safe (GRAS). Considering that BA's have been administered for thousands of years both orally and topically not to mention their inhalation as incense this in itself is not surprising. At high concentrations, unpurified BSE's have been reported on occasion to cause headaches or bowel irritation. This was easily remedied by temporarily suspending or reducing administration of the resin. Blood tests and tissue analysis have never revealed permanent toxic effects. Boswellic acids, even in concentrated forms, have never been shown to be skin irritating.
Recently (181), purified BA's were shown to be potent non-selective inhibitors of the drug metabolizing CYP enzyme family. Although the physiologic significance of this inhibition is not known to date the influence of this phenomenon on the pharmacokinetics of the other drugs should be kept in mind. To date no serious deleterious interactions with other prescription medications have ever been noted.

## Anecdotal Case Reports and Observations

**From the Paulina Medical Clinic**
At our clinic, during the last three years, over 400 patients have received dietary supplements containing boswellia std. to 90% pure AKBA, either as sole intervention or in combination with other CAM modalities. The vast majority of cases involved fatigue, asthma, allergies, arthritis, pain syndromes, colitis and other inflammatory bowel diseases and allergic skin conditions. The results showed improved clinical outcomes in over 90% of all cases. Typical comments from patients were: "noted rapid relief response", " profound difference", or "best allergy season ever", etc. Essentially no adverse events were reported with the exception of a single case of gastric and intestinal irritation in a patient in whom very high doses were attempted (over 10 capsules /day). Incidentally, in similar cases of high dosing no such intolerance was seen. With our advancing understanding of the wide application palette of this substance we have started using boswellia std. to 90% pure AKBA in all the conditions noted in the tables above.

One particularly interesting case shall be presented here.
A 50 year old professional, male, was seen in the office presenting with visual disturbances in the left eye, hypertension of 170/100, and occasional upper abdominal "heart burn". Physical exam was unremarkable with the exception of mild obesity, BMI=28. The patient had been examined shortly before by an eye specialist who had found mild retinal changes consistent with central serous chorioretinopathy. CSCR is known to affect mainly high stress, "Alpha Type", males in the range of 30-50 years. The complaints are loss of sharpness in the eye field, distortions or trailing shadows after objects, sometimes light flashes or floaters. Some cases are quickly resolved, while others may lead to a chronic state. Hypertension, and, interestingly, gastric infection with Helicobacter pylori are frequent co-morbid conditions. Steroids given in any form can worsen the condition!
Neither conventional nor CAM therapies had been of any benefit up to this point. Surprisingly, within 24 hours of taking the first 50 mg capsule of boswellia std. to 90% pure AKBA, the patient reported a dramatic improvement in eye sight, the blood pressure lowered to 150/90 and the gastro-intestinal tract felt relieved. This improvement continued for the following observation time only to be negated again by stopping the purified AKBA supplementation. The patient is again on 50 mg x2 daily of AKBA and doing better.

**From the Delafield Pediatrics Clinic**
Over 70,000 doses of AKBA have been dispensed from Delafield Pediatrics for a wide variety of conditions including asthma, allergic rhinitis, colitis, arthritis, RSV and acute infections, tendencies towards chronic and recurrent infections (pneumonia, sinusitis), complementary cancer support, breastfeeding support, general constitutional support for malaise and fatigue and others.

Patients have consistently reported favorable responses to therapy. Several examples follow:

M.J., a nine year old girl with a history of asthma and allergic rhinitis first came for evaluation for a history of persistent and recurrent symptoms including wheeze with intermittent respiratory distress, cough, and nasal congestion. She was on Flovent inhaler prophylactically and albuterol inhaler as needed (multiple times per week) and had required occasional rescue treatment with oral prednisolone. In addition she was taking Zyrtec syrup as needed.

After starting on 90% AKBA therapy, she was able to successfully wean off the Flovent over a 2-3 month period and her albuterol use decreased to once or twice per month. Over the last two years, she has maintained good control, sometimes going stretches of months without need for albuterol. Only once or twice has she required rescue treatment with Flovent inhaler for several days duration and has not required any subsequent oral steroid bursts. She rarely requires the addition of Zyrtec. She is in overall good health and the family is quite relieved and grateful for the changes.

D.I., a seven year old girl, presented with new onset Juvenile Rheumatoid Arthritis. Initial symptoms included severe right knee swelling and pain, varied toe swelling and pain, and hip pain. Over the initial months of the illness, affected areas included knees, hips, feet, hands, and back and she was also diagnosed with uveitis. After much of their own research, the family decided they wanted to pursue a more holistic therapy program.

Central to her therapeutic regimen has been treatment with 90% AKBA. On this therapy, she had some relief within 4-6 weeks and within 3-4 months was experiencing significant relief of symptoms with decreased swelling and increased range of motion. Over the past three years, she has had occasional mild flares, improved with increased dosage of her therapies. At baseline, the only evidence of her disease is minimal swelling and stiffness of two toes. Much to the surprise of her ophthalmologist, the uveitis is fully resolved.

A.C., a 3y4m male, with a birth history of 27 wk EGA infant in the NICU on a ventilator for one week, who then had an air embolus leading to severe CNS sequelae. He was now seen for frequent severe respiratory infections including pneumonia, croup, breathing difficulty, sinusitis and frequent otitis media. During the previous six months, he had only 3 weeks total time without illness and had been placed on multiple courses of antibiotics (approx. 5 times in 5-6 months).

After initial presentation with the above history, the 90% AKBA was the core of his treatment plan. Over the following four months, he has had no significant illness. There were two brief episodes of nasal congestion, at which time his mother increased the dosage as directed and symptoms resolved in 2-3 days. His mother came for evaluation by the referral of one of his therapists and was initially skeptical of holistic therapies. She is now very happy and surprised he has gone this long without more significant illness and continues to do quite well.

## Conclusions

Abundant scientific research shows that the AKBA fraction of Boswellic acids is ideally suited to inhibit the 5-lipoxygenase pathway and its resultant pathological inflammatory cascade. The use of boswellia over the centuries attests to therapeutic potential of the gum resin. In recent studies results have been favorable but never spectacular. Raising the level of daily doses of unpurified boswellia extracts, in order to achieve an optimal blood level is difficult from a practical compliance point of view. Even at a standardization level of 5% AKBA, which most market preparations do not have, (if they declare it on the label at all), it would take approx. 16 capsules of 250 mg BSE to achieve a daily dose of 200 mg AKBA per day. The bigger problem, however, would be the concern that concomitantly with the desired AKBA fraction high dosages of the other beta boswellic acids would be ingested. They could potentially exacerbate a hypercoagulable state, particularly in today's world where most patients are presenting with a host of co-morbid conditions.

A highly purified pharmaceutical grade BSE consisting essentially of pure AKBA avoids all the problems and increases exponentially the clinical success rate.

The safety and versatility of this nutritional product will allow its use in numerous pathological conditions that have never been approached in this manner before.

Including inhibitors of 5-LO mediated inflammations in one's routine clinical management should become an established standard of care.

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# ADDENDUM- Additional Research papers 2009-2011

## Evaluation of systemic administration of Boswellia papyrifera extracts on spatial memory retention in male rats

Abstract
Time-dependent effects of ethanolic extract of Boswellia papyrifera, administered systemically, on spatial memory retention in the Morris water maze were investigated in male rats. A total extract of Boswellia papyrifera (300 mg/kg) was administered every eight hours to three groups of rats by gavage for 1, 2 and 4 weeks. In a separate set of experiments, three doses of a fraction of the extract, called the boswellic acids (100, 200 and 300 mg/kg) were administered by gavage to three groups of rats three times a day for 2 weeks. Following these applications, animals were trained for 4 days. Behavioral testing for evaluation of spatial memory retention was performed 48 h after completion of training. Boswellia papyrifera extracts and boswellic acids caused a significant reduction in escape latency and distance traveled but had no influence on swimming speed. These findings provide evidence that Boswellia papyrifera extracts affect spatial memory retention irrespective of the treatment period. In addition our data show that systemic administration of the boswellic acids fraction enhanced spatial memory retention in a dosedependent manner. These improving effects may be due to some extent to the interactions of these products with inflammatory mediators, neurotransmitter signaling cascades or protein kinase pathways in the brain. (184)

## Acetyl-11-keto-b-boswellic acid suppresses invasion of pancreatic cancer cells through the downregulation of CXCR4 chemokine receptor expression

Abstract
Ninety percent of cancer-mediated deaths are due to metastasis of the tumor; however, the mechanisms controlling metastasis remain poorly understood. Thus, no therapy targeting this process has yet been approved. Chemokines and their receptors are mediators of chronic inflammation and have been linked to the metastasis of numerous cancers. More recently, the Cysteine X Cysteine (CXC) chemokine receptor 4 (CXCR4) has emerged as a key mediator of tumor metastasis; therefore, identification of inhibitors of this receptor has the potential to abrogate metastasis. In this report, we demonstrate that acetyl-11-keto-b-boswellic acid (AKBA), a component of the therapeutic plant Boswellia serrata, can downregulate CXCR4 expression in pancreatic cancer cells. The reduction in CXCR4 induced by this terpenoid was found to be cell-type specific, as its expression was also abrogated in leukemia, myeloma and breast cancer cell lines. Neither proteasome inhibitors nor lysosomal stabilization could prevent the AKBA-induced reduction in CXCR4 expression. This downregulation occurred at the transcriptional level. Suppression of CXCR4 by AKBA was accompanied by the inhibition of pancreatic cancer cell invasion, which is induced by CXCL12, the ligand for CXCR4. In addition, abrogation of the expression of chemokine receptor by AKBA was found in human pancreatic tissues from orthotopic animal model. AKBA also abolished breast tumor cell invasion, and this effect correlated with the disappearance of both the CXCR4 messenger RNA and CXCR4 protein. Overall, our results show that AKBA is a novel inhibitor of CXCR4 expression and, thus, has the potential to suppress the invasion and metastasis of cancer cells. (185)

## Antistaphylococcal and biofilm inhibitory activities of acetyl-11-keto-b-boswellic acid from Boswellia serrata

Abstract
Background: Boswellic acids are pentacyclic triterpenes, which are produced in plants belonging to the genus Boswellia. Boswellic acids appear in the resin exudates of the plant and it makes up 25-35% of the resin. Boswellic acid, 11-keto-b-boswellic acid and acetyl-11-keto-b-boswellic acid have been implicated in apoptosis of cancer cells, particularly that of brain tumors and cells affected by leukemia or colon cancer. These molecules are also associated with potent antimicrobial activities. The present study describes the antimicrobial activities of boswellic acid molecules against 112 pathogenic bacterial isolates including ATCC strains. Acetyl-11-keto-bboswellic acid (AKBA), which exhibited the most potent antibacterial activity, was further evaluated in time kill studies, postantibiotic effect (PAE) and biofilm susceptibility assay. The mechanism of action of AKBA was investigated by propidium iodide uptake, leakage of 260 and 280 nm absorbing material assays.
Results: AKBA was found to be the most active compound showing an MIC range of 2-8 μg/ml against the entire gram positive bacterial pathogens tested. It exhibited concentration dependent killing of Staphylococcus aureus ATCC 29213 up to 8 × MIC and also demonstrated postantibiotic effect (PAE) of 4.8 h at 2 × MIC. Furthermore, AKBA inhibited the formation of biofilms generated by S. aureus and Staphylococcus epidermidis and also reduced the preformed biofilms by these bacteria. Increased uptake of propidium iodide and leakage of 260 and 280 nm absorbing material by AKBA treated cells of S aureus indicating that the antibacterial mode of action of AKBA probably occurred via disruption of microbial embrane structure.

Conclusions: This study supported the potential use of AKBA in treating S. aureus infections. AKBA can be further exploited to evolve potential lead compounds in the discovery of new anti-Gram-positive and anti-biofilm agents. (186)

## Cellular and molecular mechanisms of anti-inflammatory effect of Aflapin: a novel Boswellia serrata extract

Abstract
There is significant number of evidences suggesting the anti-inflammatory properties of gum resin extracts of Boswellia serrata containing 3-O-acetyl-11-ketob-boswellic acid (AKBA) and their promising potential as therapeutic interventions against inflammatory diseases such as osteoarthritis (OA). Unfortunately, the poor bioavailability of AKBA following oral administration might limit the anti-inflammatory efficacy of standardized Boswellia extract(s). To address this issue, we describe a novel composition called Aflapin, which contains B. serrata extract enriched in AKBA and non-volatile oil portion of B. serrata gum resin. Our observations show that the availability of AKBA in systemic circulation of experimental animals is increased by 51.78% in Aflapin-supplemented animals, in comparison with that of 30% AKBA standardized extract or BE-30 (5-Loxin_). Consistently, Aflapin confers better antiinflammatory efficacy in Freund's Complete Adjuvant (FCA)-induced inflammation model of Sprague–Dawley rats. Interestingly, in comparison with BE-30, Aflapin_ also provides significantly better protection from IL-1b-induced death of human primary chondrocytes and improves glycosaminoglycans production in human chondrocytes. In Tumor necrosis factor alpha (TNFa)-induced human synovial cells, the inhibitory potential of Aflapin (IC50 44.736 ng/ml) on matrix metalloproteinase-3 (MMP-3) production is 14.83% better than that of BE-30 (IC50 52.528 ng/ml). In summary, our observations collectively suggest that both the Boswellia products, BE-30 (5-Loxin_) and Aflapin, exhibit powerful anti-inflammatory efficacy and anti-arthritic potential. In particular, in comparison with BE-30, Aflapin provides more potential benefits in recovering articular cartilage damage or protection from proteolytic degradation due to inflammatory insult in arthritis such as osteoarthritis or rheumatoid arthritis. (187)

## Natural anti-inflammatory products and leukotriene inhibitors as complementary therapy for bronchial asthma

Abstract
Objective: To assess the efficacy of a combination of frankincense *(Boswellia serrata*), licorice root (Glycyrrhiza glabra) and Tumeric root (Curcuma longa) as natural leukotriene inhibitors, antiinflammatory and antioxidant products respectively in controlling bronchial asthma. Subjects and methods: The study comprised 63 patients with bronchial asthma that are further subdivided into two groups .Group 1 receiving oral capsule (combined herb) in a soft-gelatin capsule 3 times daily for 4 weeks and group 2 receiving placebo. Plasma leukotriene C4 (LTC4), nitric oxide (NO) and malondialdehyde (MDA) levels were measured and pulmonary function was also assessed in all patients enrolled in the study. Results: There was a statistically significant decrease in the plasma levels of LTC4, (MDA), and NO in target therapy group when compared with placebo group.
Conclusion: The used extract contained Boswellia serrata, Curcuma longa and Glycyrrhiza has a pronounced effect in the management of bronchial asthma.(191)

## The enhancement effect of beta-boswellic acid on hippocampal neurites outgrowth and branching (an in vitro study)

Abstract
Increasing evidences implicate impairment of axonal integrity in mechanisms underlying neurodegenerative disorders. Beta-boswellic acid (BBA) is the major component of Boswellia serrata gum. This resin has long been used in Ayurveda (India's traditional medicine) to prevent amnesia. In this study, the effect of BBA was examined on neurites outgrowth and branching as well as on polymerization dynamics of tubulin. The morphometric parameters (axonal length and neuritis branching) were examined microscopically after treating the hippocampal cells with BBA. Also the assembly process of tubulin was assessed using UV/V is spectrophotometer through following of absorbance at 350 nm. The results revealed that BBA could significantly enhance neurite outgrowth, branching, and tubulin polymerization dynamics. The obtained results suggest that enhancing effect of BBA on microtubule polymerization kinetics might be the origin of increasing axonal outgrowth and branching.(193)

## Inhibition of microsomal prostaglandin E2 synthase-1 as a molecular basis for the anti-inflammatory actions of boswellic acids from frankincense

Abstract
Frankincense, the gum resin derived from *Boswellia* species, showed anti-inflammatory efficacy in animal models and in pilot clinical studies. Boswellic acids (BAs) are assumed to be responsible for these effects but their anti-inflammatory efficacy *in vivo* and their molecular modes of action are incompletely understood. A protein fishing approach using immobilized BA and surface plasmon resonance (SPR) spectroscopy were used to reveal microsomal rostaglandin E2 synthase-1 (mPGES1) as a BA-interacting protein. Cell-free and cell-based assays were applied to confirm the functional interference of BAs with mPGES1. Carrageenan-induced mouse paw oedema and rat pleurisy models were utilized to demonstrate the efficacy of defined BAs *in vivo*. Human mPGES1 from A549 cells or *in vitro*-translated human enzyme selectively bound to BA affinity matrices and SPR spectroscopy confirmed these interactions. BAs reversibly uppressed the transformation of prostaglandin (PG)H2 to PGE2 mediated by mPGES1 (IC50 = 3–10 mM). Also, in intact A549 cells, BAs selectively inhibited PGE2 generation and, in human whole blood, b-BA reduced lipopolysaccharide-induced PGE2 biosynthesis without affecting formation of the COX-derived metabolites 6-keto PGF1a and thromboxane B2. Intraperitoneal or oral administration of b-BA (1 mg·kg-1) suppressed rat pleurisy, accompanied by impaired levels of PGE2 and b-BA (1 mg·kg-1, given i.p.) also reduced mouse paw oedema, both induced by carrageenan. CONCLUSIONS: Suppression of PGE2 formation by BAs via interference with mPGES1 contribute to the anti-inflammatory effectiveness of BAs and of frankincense, and may constitute a biochemical basis for their anti-inflammatory properties. (198)

## Frankincense: A Systematic Review

ABSTRACT
Objective To assess evidence from randomised clinical trials about the effectiveness of extracts of Boswellia serrata (frankincense).Design Systematic review. Data sources Electronic searches on Medline, Embase, Cinahl, Amed, and Cochrane Library. Hand searches of conference proceedings, bibliographies, and departmental files. Review methods All randomised clinical trials of B serrata extract as a treatment for any human medical condition were included and studies of B serrata preparations combinedwith other ingredients were excluded. Titles and

abstracts of all retrieved articles were read and hard copies of all relevant articles were obtained. Selection of studies, data extraction and validation were done by the author. The Jadad score was used to evaluate the methodological quality of all included trials. Results Of 47 potentially relevant studies, seven met all inclusion criteria (five placebo controlled, two with active controls). The included trials related to asthma, rheumatoid arthritis, Crohn's disease, osteoarthritis, and collagenous colitis. Results of all trials indicated that B serrata extracts were clinically effective. Three studies were of good methodological quality. No serious safety issues were noted. Conclusions: The evidence for the effectiveness of Boswellia is encouraging but not compelling. (199)

**A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin® for treatment of osteoarthritis of the knee**

Introduction 5-Loxin® is a novel Boswellia serrata extract enriched with 30% 3-O-acetyl-11-keto-beta-boswellic acid (AKBA), which exhibits potential anti-inflammatory properties by inhibiting the 5-lipoxygenase enzyme. A 90-day, double-blind, randomized, placebo-controlled study was conducted to evaluate the efficacy and safety of 5-Loxin® in the treatment of osteoarthritis (OA) of the knee. Methods Seventy-five OA patients were included in the study. The patients received either 100 mg (n = 25) or 250 mg (n =25) of 5-Loxin® daily or a placebo (n = 25) for 90 days. Each patient was evaluated for pain and physical functions by using the standard tools (visual analog scale, Lequesne's Functional Index, and Western Ontario and McMaster Universities Osteoarthritis Index) at the baseline (day 0), and at days 7, 30, 60 and 90. Additionally, the cartilage degrading enzyme matrix metalloproteinase-3 was also evaluated in synovial fluid from OA patients. Measurement of a battery of biochemical parameters in serum and haematological parameters, and urine analysis were performed to evaluate the safety of 5-Loxin® in OA patients. Results Seventy patients completed the study. At the end of the study, both doses of 5-Loxin® conferred clinically and statistically significant improvements in pain scores and physical function scores in OA patients. Interestingly, significant improvements in pain score and functional ability were recorded in the treatment group supplemented with 250 mg 5-Loxin® as early as 7 days after the start of treatment. Corroborating the improvements in pain scores in treatment groups, we also noted significant reduction in synovial fluid matrix metalloproteinase-3. In comparison with placebo, the safety parameters were almost unchanged in the treatment groups. Conclusion 5-Loxin® reduces pain and improves physical functioning significantly in OA patients; and it is safe for human consumption. 5-Loxin® may exert its beneficial effects by controlling inflammatory responses through reducing proinflammatory modulators, and it may improve joint health by reducing the enzymatic degradation of cartilage in OA patients.(201)

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