REVIEW ARTICLE

Salai Guggal-Boswellia Serrata Leukotriene Antagonist & Inhibitor:Clinical Applications

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Inflammation is the hall mark of various diseases and is characterized by five symptoms; redness, heat, pain, swelling and decreased function. These symptoms are caused by a variety of inflammatory mediators which are listed in table 1.

So far only two major principles of antiphlogistic drug activity are available in therapy. First compounds inhibiting the synthesis of prostaglandin's by interfering with the cyclo-oxygenase system (salicylic acid, etc.). Second the gluco- corticosteroids, which finally inhibit both the cyclo-oxygenase pathway & the lipoxygenase pathway by interfering with the phospholipase. A2 -reaction (Fig.1). However, there are number of inflammatory diseases where increased production of leukotrienes seems to be a reason for keeping the inflammatory process running. Among these diseases are: bronchial asthma, chronic inflammatory arthritis, hepatitis, psoriasis, ulcerative colitis and crohn's disease. In these diseases leukotriene antagonists are the target point as far as therapy is concerned. We briefly review the role of Salai Guggal as anti leukotriene and its applications in different diseases.

Table. 1 Mediators of Inflammation

Mediator	Origin	Appearance after	Inflammation sumptoms
Bradykinin	Plasma	seconds	Vasodilatation, increased vascular permeability, pain
Histamine	Mast Cells	Seconds	Vasodilatation, increased vascular permeability, pain
Prostaglandins	Ubiquitous	Seconds	Vasodilatation, pain, sensitization against Bradykinin and histamine
Thromboxane	Thrombocytes other cells	Seconds	Platelet activation
Hydroxy-fatty acids	Ubiquitous	Seconds	Chemotactic for leucocytes, pain
Leucotrienes	Leucocytes	minutes	Chemotactic for leucocytes, increased vascular permeability
Lysosomal enzymes	Leucocytes synovial cells	minutes	Necrotic, chemotactic for leucocytes
Lymphokines	Lymphocytes	hours	Necrotic

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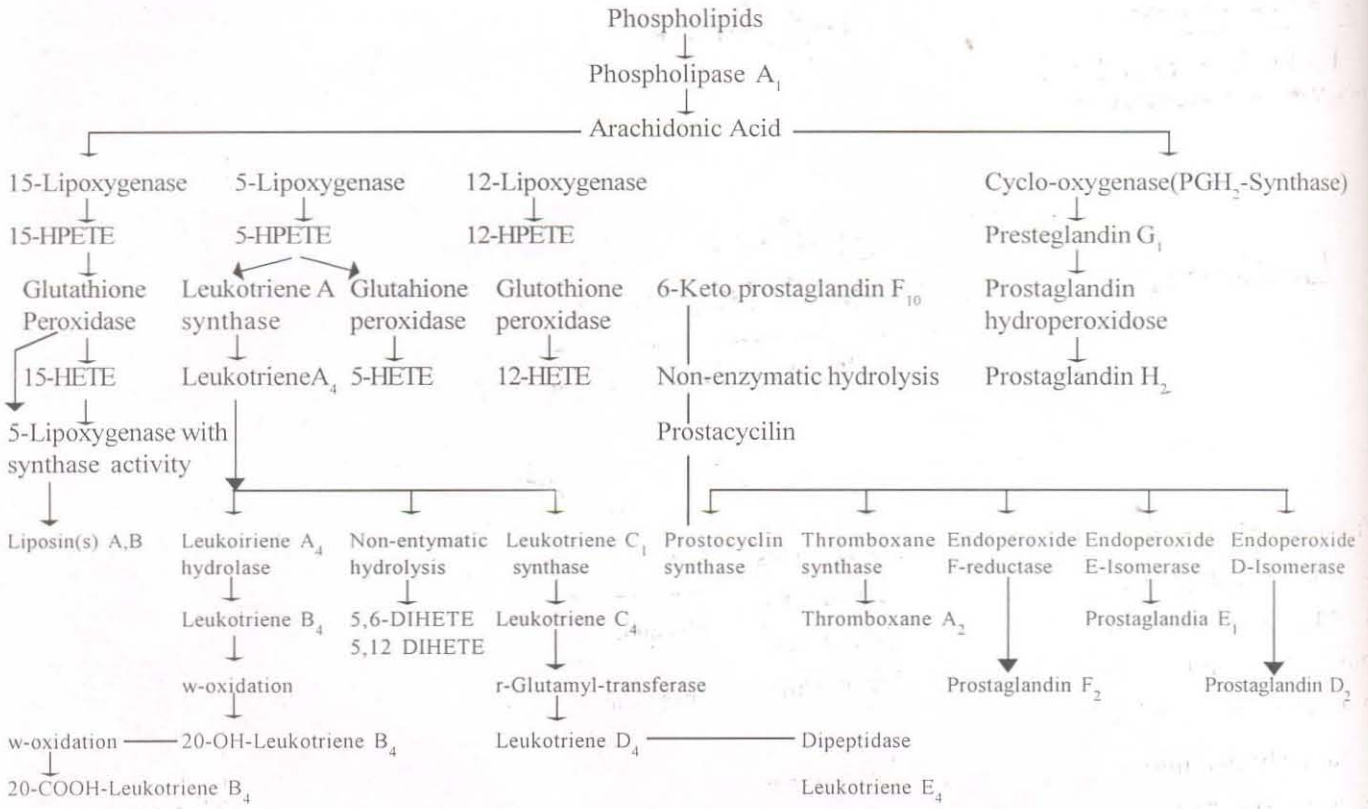

Fig. 1 Eicosanoid metablic pathways

Salai Guggal is a traditional remedy in Ayurvedic medicine used in India for a variety of inflammatory diseases including rheumatoid arthritis, osteoarthritis & cervical spondylosis. Salai guggal is the gumresin of Boswellia serrata Roxb. The main constituents of the gum resin are boswellic acids and other compounds such as volatile oils, terpinols, arabinosa, xylose, galactose, uronic acids, β-sicosterin and phlobaphenes. Boswellic acids are also a constituent of the gum resin of Boswellia carterti Birdw, also known as Olibanum. The known pharmacological effects of Olibanum are anti-inflammatory, analgesic, immunosuppressive, hepatoprotective and antimicrobic (1,2). The gum resin of Boswellia serrata & Boswellia carterti is also widely used as incense for religious ceremonies. Salai guggal & boswellic acids have been shown to possess anti-inflammatory activity in a variety of animal's models (3-5).

Boswellic Acids

The resin of Boswellia serrata is used in India for the treatment of chronic inflammatory arthritis. The raw product is called 'salai guggal' when defatted ethanolic extracts of salai guggal was introduced into the 5 - lipoxygenase test system using calcium/calcium ionophore- stimulated peritoneal neutrophils of rats, it turned out that this extract significantly decreased production of LTB_4 and total 5 - lipoxygenase products, the EC 50 being about 30 ug/ml.

Boswellic acids are the main constituents of the ethanolic extract of the resin of Boswellia serrata. Different Boswellic acids have been identified including β-Boswellic acid, α-Boswellic acid and 11-keto -β- Boswellic acid and other acetyl forms (9-13).

Crude ethanolic extracts of the resin and or Boswellic acid have pharmacological actions as anti-inflammatory, inhibition of complement system and hepatoprotective. Studies of the boswellic acids possible effects on cyclo-oxygenase or 12- lipoxygenase activity showed that they affected neither prostaglandin synthesis nor 12-lipoxygenase activity suggesting that this type of pentacyclic triterpenes may inhibit only leukotriene

synthesis. Boswellic acids are specifically non-redox inhibitors of 5- lipoxygenase (14-23).

Clinical Applications

Rheumatoid Arthritis & Osteoarthritis:

In the traditional Ayurvedic medicine of India the use of Salai guggal is very common to treat inflammatory disease including chronic polyarthritis especially rheumatoid arthritis and osteoarthritis. Many preparations like S-compound Sallaki, H15 etc. are available in the market for the treatment of these inflammatory and degenerative diseases (24-28).

Inflammatory Bowel Diseases

a. Ulcerative colitis is a chronic inflammatory disease with remissions and exacerbations affecting principally the rectal mucosa, the left colon but in many instances the entire colon. It is characterized by rectal bleeding and diarrhea appearing principally.

Though the aetiology of this disease is complex, it has been reported that the inflammatory process is associated with extensive leukocyte infiltration & increased formation of leukotrienes. Drug therapy so far is mainly limited to the use of sulfasalazine or other aminosalicylates and corticosteroids but they are weak inhibitors of leukotrienes production & cellular interleukin-1 release and dose dependent modifiers of prostaglandin profile, all of which might affect the inflammatory response in inflammatory bowel diseases.

Boswellia serrata blocked leukotriene biosynthesis in neutrophilic granulocytes, being direct non-redox and non-competitive inhibitors of 5 - lipoxygenase - Gupta *et. al.* (29) have for the first time demonstrated the use of Boswellia serrata in ulcerative colitis.

b. Crohns Disease is also a chronic inflammatory disease with remission and exacerbations. Leukotrienes (LTB_4) are major chemotactic factors in such patients and large amounts of leukotrienes are found in the mucosa of patients with Crohns disease. Gerhardt *et al* (30) had confirmed in their studies that therapy with Boswellia serrata is not inferior to mesalzine in Crohns disease. Considering both safety and efficacy of Boswellia serrata extract it appears to be superior over mesalazine in terms of a benefit risk evaluation.

Bronchial Asthma

It is a chronic inflammatory condition characterized by bronchial hyperesponsiveness and reversible airway obstruction. A wide range of compounds mediate these processes. Leukotrienes were identified as products of arachidonic acid metabolism and as inflammatory mediators in the late 1970. Prior to this their existence was recognized as the slow-reacting substances of anaphylaxis (SRS-A) a term coined by Feldberg and kellaway in 1938. In 1940, Kellaway and Trethewie suggested a role of SRS-A in asthma but it was not until 40 years later that it became clear that SRS-A consisted of the leukotrienes. Besides causing chemotaxis, chemokinesis, synthesis of superoxide radicals and release of lysosomal enzymes by phagocytes leukotrienes cause (a) broncho-constriction (b) mucosal oedema (c) increased mucus secretion and (d) an inflammatory cellular infiltrate rich in eosinophils (31-41).

Anti-leukotriene drugs either inhibit the synthesis of leukotrienes from arachidonic acid (e.g. zileuton, MK-886, BAYX1005) or act as leukotriene receptor antagonists (e.g. zafirlukast, ICI 204, 219: montelukast, MK0476, pranlukast, iralukast). The gum resin of Boswellia seratta (salai guggal) was shown to block leukotrienes biosynthesis due to the action of genuine boswellic acids constituents. Keto-boswellic acid (i.e. AKBA-acetyl: II-Keto-β-Boswellic acid) are orally, active direct non-redox and noncompetitive inhibitors of 5-lipoxygenase (19).

Gupta *et. al.* (36) have shown that Boswellia serrata induces remission in patients with bronchial asthma. Improvement of the disease is evident by disappearance of physical symptoms and increase in FEVI, FVC and PEFR as well as decrease in eosinophilic count and ESR.

Peritumoral Brain Oedema

Boswellia seratta containing AKBA and KBA provided promising result in reducing peritumoral brain oedema in patients with malignant glioblastomas along with a decreased

urinary leukotriene excretion. Heldt *et. al.* have shown cysteinyl leukotrienes as potential mediators of the peritumoral brain oedema in astrocytoma patients while Boker *et. al.* reported wonderful effects in therapy of malignant glioma. Higher dose of drugs in grams are given in reducing intracranial pressure in head injuries (42-45).

Psoriasis

Psoriasis is another disease characterized by extensive leukocyte infiltration albeit into the skin rather than the rectal mucosa. Measurements have been made for the presence of various chemotactic agents in psoriatic lesions and the presence of LTB_4 like immunnoreactive material has been described. There have also been suggestions that existing drugs may act by inhibiting the production of leukotrienes. Clinical trials have been carried out with both zileuton (topically and systematically) and MK-886. These agents were found not to decrease the amount of LTB_4 like material found in psoriatic skin lesions indicating that this material is not derived through the action of the 5-lipoxygenase pathways(46). Many studies are showing good results of boswellic acids in the treatment of psoriasis(47).

Chronic Colits

Chronic nonspecific colitis is a common disease characterized by vague lower abdominal pain bleeding per rectum with diarrhea and palpable tender descending as well as sigmoid colon (48-50). This disease is seen in young and middle aged persons and may be a variation of ulcerative colitis. Gupta *et. al.* (24) have shown promising results with Boswellia seratta in chronic colitis.

Glomerulonephritis

Leukotrienes mediate the alterations in renal halmodynamic and glomerular filtration, which occur in a variety of nephritis including nephrotoxic serum nephritis, murine lupus and passive Heyman nephritis. A correlation between neutrophil infiltration and glomerual LTB_4 synthesis has been defined. Cysteinyl leukotrienes play a role in the pathogenesis and progression of glomerulonephritis not only through effects on renal blood flow and filtration but also through proliferative changes in response to both LTC_4 and LTD_4 and in vivo inhibition of LT biosynthesis in nephritic rats with MK-886 by preventing glomerular cell proliferation (11).Many studies are underway which show that gum resin of Boswellia serrata is very effective in nephritis patients(47).

Other Diseases

Animal studies have shown that Boswellia serrata is effective in treatment of drug induced hepatitis and lupoid hepatitis. Clinical trials are being conducted for the effects of Boswellic acid in these diseases(50,51).

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