

The mechanism of the physiological action of bromelain

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Steven J Taussig

Abstract

The pineapple protease, bromelain, selectively inhibits the biosynthesis of proinflammatory prostaglandins, apparently by indirect action. The inhibition of endogenous proteases that accompanies trauma, or prolonged exposure to excessive stress markedly elevates the relative proportions of those prostaglandins responsible for the symptoms of inflammation. It has been demonstrated that bromelain's specificity is similar to that of the endogenous protease plasmin. Bromelain acts on fibrinogen to give products that are similar, at least in effect, to those formed by plasmin. They are small molecular weight active peptides, which regulate prostaglandin biosynthesis and create conditions existing in the healthy organism. It has been shown that a substantial portion of orally administered bromelain is absorbed intact into the bloodstream, thereby elevating the proteolytic and fibrinolytic activity of the blood for hours. The similarity between the beneficial effects of aspirin-type drugs and bromelain, while bromelain causes none of the undesirable side effects of the others, suggests that bromelain acts on the prostaglandin synthetic pathway at a site different from that affected by the non-steroidal anti-inflammatory drugs. While aspirin inhibits the cyclooxygenase and thus the biosynthesis of prostaglandins, it is postulated that bromelain acts further down the arachidonate cascade at the thromboxane synthetase step. Circumstantial evidence suggests that bromelain inhibits the synthesis of the "proinflammatory" prostaglandins without affecting that of the "anti-inflammatory" ones. Bromelain therefore tends to reestablish the balance of the two types of prostaglandins that characterizes the state of the healthy organism.

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Lymphedema of the upper extremity in patients operated for carcinoma of the breast: clinical experience with coumarinic extract from *Melilotus officinalis*.

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Abstract

The aim of this clinical study was to verify the therapeutic activity of coumarinic extract of *Melilotus officinalis* (CEMO) in patients with chronic lymphedema of the upper arm caused by lymphadenectomy for breast cancer. Coumarine, in fact, has antiedemic properties due to macrophagic action that stimulates proteolysis in the tissues affected by chronic lymphedema. In an open clinical study we enrolled 24 patients with chronic upper arm lymphedema due to post-lymphadenectomy of the axilla for breast cancer. 21 patients were eligible to receive 400 mg of CEMO containing 8 mg of coumarine in a sole daily administration for 6 months. We measure the circumference of the upper arm at 3 and 6 months from treatment. We evaluated the symptoms and tolerability through a questionnaire given to the patients at every clinical control. Of the 21 (87.5%) patients eligible, only 14 (66.6%) were treated with CEMO according to protocol. Of these 11 patients (52.3%) had a reduction of the circumference of the affected arm of 5% with respect to base values. Three patients (14.2%) had no change. In 12 patients (57.1%) symptoms improved. As for tolerability: 3 patients (14.2%) had transitory gastrointestinal side-effects. There was worsening of lymphedema and symptoms in 4 patients (19%) that did not receive CEMO and were followed as controls. Three patients (14.2%) were not evaluable because they were lost to follow-up. Coumarinic extract of *Melilotus officinalis* (CEMO) was effective in reducing lymphedema in 79% of the pts treated for a period of six months. The median reduction of the upper arm circumference was modest (5% with respect to initial values) but statistically significant ($p = 0.048$). Treatment with CEMO for lymphedema could be associated to the physiotherapy given to these patients such as manual lymph drainage (MLD).

Review Article

Horse chestnut – efficacy and safety in chronic venous insufficiency: an overview

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Abstract

The extract from horse chestnut seeds (*Aesculus hippocastanum* L., Sapindaceae), standardised for the content of aescin, is used as the treatment for chronic venous insufficiency. It has anti-inflammatory and anti-oedematous properties and indicates a positive effect on the venous tone, rheological properties, and blood coagulability. The mechanism of horse chestnut seed extract/aescin activity was proposed on the basis of in vitro and in vivo studies, and its effectiveness was documented with numerous randomised clinical trials. The results of the studies have proven that horse chestnut seed extract not only significantly improves subjective symptoms in patients with chronic venous insufficiency like calf spasm, leg pain, pruritus, fatigue, but it also reduced leg volume, the ankle and calf circumference. The preparations containing horse chestnut seed extract are very popular and they have similar effectiveness as compression therapy and a preparation with O-(β -hydroxyethyl)-rutosides. Moreover, horse chestnut seed extract has been proven to be safe and very well tolerated. The study was to present the results of the studies that have been conducted so far and that have confirmed the effectiveness of use of horse chestnut seed extract or aescin as the treatment for chronic venous insufficiency.

L'azione inibitrice sull'espressione delle metallo proteasi come meccanismo antinfiammatorio

Antioxidants & Redox Signaling

Regulation of Vascular Responses to Inflammation: Inducible Matrix Metalloproteinase-3 Expression in Human Microvascular Endothelial Cells Is Sensitive to Antiinflammatory Boswellia

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Abstract

Endothelial cells are critical elements in the pathophysiology of inflammation. Tumor necrosis factor (TNF) α potently induces inflammatory responses in endothelial cells. Recently we have examined the genetic basis of the antiinflammatory effects of Boswellia extract (BE) in a system of TNF α -induced gene expression in human microvascular endothelial cells (HMECs). Of the 522 genes induced by TNF α in HMECs, 113 genes were sensitive to BE. BE prevented the TNF α -induced expression of matrix metalloproteinases (MMPs). In the current work, we sought to test the effects of BE on TNF α -inducible MMP expression in HMECs. Acetyl-11-ketoboswellic acid (AKBA) is known to be an active principle in BE. To evaluate the significance of AKBA in the antiinflammatory properties of BE, effects of BE containing either 3% (BE3%) or 30% (BE30%, 5- Loxin®) were compared. Pretreatment of HMECs for 2 days with BE potently prevented TNF α -induced expression and activity of MMP-3, MMP-10, and MMP-12. In vivo, BE protected against experimental arthritis. In all experiments, both in vitro and in vivo, BE30% was more effective than BE3%. In sum, this work lends support to our previous report that BE has potent antiinflammatory properties both in vitro as well as in vivo.

Identificazione dei target che spiegano l'effetto antinfiammatorio della *Boswellia*, tra cui le 5-lipossigenasi e le elastasi

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Boswellic Acids: Biological Actions and Molecular Targets

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Abstract

Gum resin extracts of *Boswellia* species have been traditionally applied in folk medicine for centuries to treat various chronic inflammatory diseases, and experimental data from animal models and studies with human subjects confirmed the potential of *B. spec* extracts for the treatment of not only inflammation but also of cancer. Analysis of the ingredients of these extracts revealed that the pentacyclotriterpenes boswellic acids (BAs) possess biological activities and appear to be responsible for the respective pharmacological actions. Approaches in order to elucidate the molecular mechanisms underlying the biological effects of BAs identified 5-lipoxygenase, human leukocyte elastase, topoisomerase I and II, as well as I κ B kinases as molecular targets of BAs. Moreover, it was shown that depending on the cell type and the structure of the BAs, the compounds differentially interfere with signal transduction pathways including Ca²⁺- and MAPK signaling in various blood cells, related to functional cellular processes important for inflammatory reactions and tumor growth. This review summarizes the biological actions of BAs on the cellular and molecular level and attempts to put the data into perspective of the beneficial effects manifested in animal studies and trials with human subjects related to inflammation and cancer.

Inibizione di 5-lipossigenasi, citochine ed elastasi alla base dell'attività antinfiammatoria dell'estratto di *Boswellia*

Planta Med. 2006 Oct;72(12):1100-16.

Boswellic acids in chronic inflammatory diseases.

Ammon HP1.

Abstract

Oleogum resins from *BOSWELLIA* species are used in traditional medicine in India and African countries for the treatment of a variety of diseases. Animal experiments showed anti-inflammatory activity of the extract. The mechanism of this action is due to some boswellic acids. It is different from that of NSAID and is related to components of the immune system. The most evident action is the inhibition of 5-lipoxygenase. However, other factors such as cytokines (interleukins and TNF- α) and the complement system are also candidates. Moreover, leukocyte elastase and oxygen radicals are targets. Clinical studies, so far with pilot character, suggest efficacy in some autoimmune diseases including rheumatoid arthritis, Crohn's disease, ulcerative colitis and bronchial asthma. Side effects are not severe when compared to modern drugs used for the treatment of these diseases.