Evidence Based Botanicals in the Treatment of Inflammation

Sponsored by Restorative Formulations
(Non-CME presentation)

Credits: Eugene R. Zampieron, ND
Our topic and objectives...

• Inflammation is a primary factor in heart disease, arthritic disease, digestive disorders, respiratory inflammation, diabetes, and aging in general.

• Some botanical agents are shown to have broad acting anti-inflammatory effects for all these complaints
Enfla-Mend Px is an RF Phyto-Formula for Inflammation
NF-kB Support

Enfla-Mend Px is a comprehensive botanical formula that mediates activity of prostaglandins by balancing NF-kB (Nuclear Factor- Kappa B).

- Offers a full range of curcumin bio-constituents for optimal potency and activity.
- Provides powerful antioxidant activity.
- Boswellia extract offers unique properties that balance NF-kB.
- Supports healthy joint and muscle function.
## Supplement Facts

**Serving Size:** 3 capsules  
**Servings per Container:** 25

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Other Ingredients: Vegetable Capsule (cellulose)  
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Boswellia

literature review
Boswellia serrata
(Salai/Salai guggul)

• *Boswellia serrata* (Salai/Salai guggul), is a moderate to large sized branching tree of family Burseraceae (Genus Boswellia), grows in dry mountainous regions of India, Northern Africa and Middle East.
Boswellia in Oman

http://cdni.wired.co.uk/620x413/d_f/frankin.jpg
**Boswellia serrata**  
*(Salai/Salai guggul)*

- The oleo gum-resins contain 30-60% resin, 5-10% essential oils, which are soluble in the organic solvents, and the rest is made up of polysaccharides.
Boswellia serrata
(Salai/Salai guggul)

• The resinous part of *Boswellia serrata* possesses monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and four major pentacyclic triterpenic acids i.e. β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, responsible for inhibition of pro-inflammatory enzymes.
Penta\{5\} cyclic rings
Steroidal in nature
Fractions of Boswellic acid and inhibition of NFkB
Fractions of boswelliiic acids

Fig. 1. Results of chromatographic analysis of boswellic acids in hexane and methanolic fractions (fraction 1 and fraction 2, respectively) of *Boswellia serrata* used in this study.
AKBA Demonstrates Multifacted Bioactivities

Acetyl-11-Keto-β-Boswellic Acid demonstrates multifaceted bioactivities such as:

- Human leukocyte elastase inhibition
- Topoisomerase inhibition
- Calcium mobilization
- 5-Lipoxygenase inhibition
- IKK inhibition leading to inhibition of constitutively activated NFκB
- Caspase activation
- MAP kinase activation

Figure 2
Effects of Boswellia triterpenoids

- Decrease nitric oxide (a free radical) concentrations
- Decrease in lipoxygenase and leukotrienes
- Decrease tumour necrosis factor (TNF)
- Decrease release of anticatabolic factors from peripheral blood
- Improved microcirculation
- Inhibition of histamine, serotonin and kinin systems
- Release of free radical scavenging enzyme-superoxide dismutase
- Decrease humoral mediator of inflammation
- Anti-complement activity
- Vascular endothelial stabilization
- Decrease neutrophil extravasation (chemotaxis)
Boswellia is not inferior to NSAID mesalazine
Summary of Major trials on Boswellia and inflammation of Asthma, RA, and Crohn’s respectively

<table>
<thead>
<tr>
<th>First author (year, country)</th>
<th>Condition (sample size)</th>
<th>Design (Jadad score)*</th>
<th>Interventions</th>
<th>Nature of extract†</th>
<th>Primary outcome measure</th>
<th>Main results/effect size‡</th>
<th>Adverse effects of BSE (A) and control intervention (B)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta (1998), India/Germany⁷</td>
<td>Asthma (80) DB, PC, 2 PG (3)</td>
<td>(A) BSE (350 mg 3×day) for 6 weeks; (B) placebo</td>
<td>Percentage of patients showing clinical improvement</td>
<td>(A) 70% remission; (B) 27% remission§</td>
<td>(A) 2 patients experienced stomach pain, hyperacidity, nausea; (B) no information</td>
<td>Group (A) had more severe asthma than group (B); other endpoints also suggested efficacy of BSE</td>
<td></td>
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<tr>
<td>Sander (1998), Germany⁸</td>
<td>Rheumatoid arthritis (37) DB PC, 2 PG (2)</td>
<td>A) BSE (3600 mg 9×day) for 12 weeks; (B) placebo; both groups also received conventional drugs</td>
<td>H15§</td>
<td>Non-significant trend in favour of BSE§</td>
<td>(A) Stomatitis (1 patient); (B) eczema (1 patient), increase of joint pain (1 patient)</td>
<td>Report only relates to subset of patients from larger unpublished study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gerhardt (2001), Germany/Austria⁹</td>
<td>Crohn’s disease (102) DB, 2PG, non-inferiority (3)</td>
<td>(A) BSE (3.6 g per day) for 8 weeks; (B) mesalazine (4.5 per day)</td>
<td>Crohn's Activity Index (CAI)</td>
<td>Non-inferiority of BSE confirmed: (A) CAI from 301 (63) to 192 (114); (B) from 282 (72) to 163 (96)</td>
<td>(A) No causally related adverse effects; (B) 13 causally related adverse effects</td>
<td>Data refer to intention to treat analysis</td>
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Summary of Major trials on Boswellia & pain/inflammation of OA and Colitis respectively

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<th>Outcome Measures</th>
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<tr>
<td>Kimmatar (2003), India</td>
<td>Osteoarthritis of the knee (30)</td>
<td>DB, PC, crossover (5)</td>
<td>(A) BSE (333 mg per day) for 8 weeks; (B) placebo</td>
<td>Pain, function (VAS)</td>
<td>Significant intergroups differences in favour of BSE; intergroup difference for pain 2.3 (0.61)</td>
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<td>Authors state that the differences are clinically relevant</td>
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<td>Madisch (2007), Germany</td>
<td>Collagenous colitis (31)</td>
<td>RCT, DB, PC, 2 PG (5)</td>
<td>(A) BSE (400 mg 3x/day) for 6 weeks; (B) placebo</td>
<td>Percentage of patients with remission</td>
<td>(A) 64% remission (95% CI 30.8 to 89.1, ITT 44%); (B) 27% (7.7 to 55.1, 27%)</td>
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<td>(A) Dizziness, hypoglycaemia, lack of appetite, diarrhoea (1 patient); bacterial enteritis (1 patient); (B) no information</td>
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<td>Sontakke (2007), India</td>
<td>Osteoarthritis of the knee (66)</td>
<td>RCT, open, active control, 2PG (2)</td>
<td>(A) BSE (333 mg 3x/day) for 6 months; (B) valdecoxib (10 mg, 1x/day)</td>
<td>WOMAC scale</td>
<td>Pain: (A) from 245.3 (77.6) to 82.9 (62.3) at 6 months; (B) from 246.0 (71.4) to 85.4 (68.9)</td>
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<td>(A) Diarrhoea (1 patient); (B) no adverse effects</td>
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Authors state that the differences are clinically relevant.
A. Normal colonic epithelial cells

B. Colon cancer cells

Curcuma prevents this

Controlled cell growth

Uncontrolled cell growth
Boswellia may inhibit ulcers; this is critical in treating rheumatic dz, as NSAIDS can cause ulcers & Leaky gut.
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California Poppy
Eschscholzia is a fast acting herb in EnFlamend known to reduce pain and anxiety

- California Poppy (*Eschscholzia californica*) is the official state flower of California.
- The plant grows to 60 cm, has feathery foliage and velvety, golden-orange flower petals.
- It is a member of the Papaveraceae.
Ethnobotany of *Eschscholzia*

- Western coastal Indians used the seed as a general pain killer, especially as a toothache remedy.

- Also used externally for its antimicrobial properties as a poultice for sores and other skin disorders, its extract has been shown to be a very effective antispasmodic aiding in muscle spasms, cramps, convulsions and chronic coughs, which are a type of spasm.
History of *Eschscholzia*

- California Poppy was a commonly used herb in native American and Hispanic societies, and gained considerable interest from medical practitioners in the late 1800’s, when it was added to the Park-Davis drug catalog as “an excellent soporific and analgesic, above all harmless.”
The Eclectics on California Poppy....

- *Eschscholzia* was stated to be an “...analgesic and soporific without the dangers attending opiates, quieting pain and producing (a) calm sleep” (1893).

- Externally, the various Poppies can be used to treat pain and arrest local inflammation, used as a lotion, liniment, or plaster
Eschscholzia Constituents

- Like the Opium Poppy, California Poppy contains a variety of isoquinoline alkaloids including very small amounts of morphine and codeine.

- Large varieties of other isoquinolines, including: californidine, californinec helerythrine, chelilutin ch elirubine, coptisine, crypt ocavine, cryptopine, escho lidine, escholine, scholinine, eschscholtzidine, protopine and sanguinarine.
Clinical Studies

• California Poppy (CP) extract inhibits degradation of catecholamines and synthesis of epinephrine (adrenaline) in vitro.

• Preserving high levels of catecholamines may explain the sedative and antidepressant activity of CP.

• Alkaloids from CP enhance (GABA) binding to receptors, which may indicate a benzodiazapine-like activity.
Eschscholtzia

Neurophysiological effects of an extract of Eschscholzia californica Cham. (Papaveraceae).

Rolland A¹, Fleurentin J, Lanher MC, Misslin R, Mortier F.

Abstract

An aqueous alcohol extract of Eschscholzia californica (Ec) has been evaluated for benzodiazepine, neuroleptic, antidepressant, antihistaminic and analgesic properties, in order to complete the study of the sedative and anxiolytic effects previously demonstrated. The plant extract did not protect mice against the convulsant effects of pentylentetrazol, and did not cause muscle relaxant effects but appeared to possess an affinity for the benzodiazepine receptor; thus, flumazenil, an antagonist of these receptors, suppressed the sedative and anxiolytic effects of the extract. The Ec extract induced peripheral analgesic effects in mice but did not possess antidepressant, neuroleptic or antihistaminic effects.
Eschscholzia binds to GABA Receptors

GABA A receptor

benzodiazapine (BDZ) binding site

benzodiazapine

gamma sub-unit

alpha

post-synaptic membrane

cytoplasm

synaptic cleft

GABA

Cl-

alpha

Cl-

alpha

alpha
Sedative action of extract combinations of Eschscholtzia californica and Corydalis cava.

Schäfer HL, Schäfer H, Schneider W, Elstner EF.

Abstract

The herbal drug Phytonoxon N (abbreviated as PN) is indicated in nervousness induced insomnia, agitation and/or anxiety. It is composed of alcoholic drug extracts of the plants Corydalis cava (20%) and Eschscholtzia californica (80%). Both plants are rich in isoquinoline alkaloids derived from tyrosine metabolism. Recent research shows that they may influence the neurotransmitter metabolism.
Double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of a fixed combination containing two plant extracts (Crataegus oxyacantha and Eschscholtzia californica) and magnesium in mild-to-moderate anxiety disorders.

Hanus M¹, Lafon J, Mathieu M.

Abstract

OBJECTIVE: To assess the clinical efficacy of a neurotonic component containing fixed quantities of two plant extracts (Crataegus oxyacantha and Eschscholtzia californica) and magnesium versus placebo in mild-to-moderate anxiety disorders with associated functional disturbances, under usual general practice prescription conditions.

RESEARCH DESIGN AND METHODS: A total of 264 patients (81% female; mean age: 44.6 years) presenting with generalised anxiety (DSM-III-R) of mild-to-moderate intensity (total Hamilton anxiety scale score between 16 and 28) were randomised in a double-blind, randomised, placebo-controlled trial. Patients were randomly assigned to two groups: 130 received the study drug and 134 a placebo (two tablets twice daily for 3 months). Efficacy and safety data were recorded before first administration and 7, 14, 30, 60 and 90 days after start of treatment.

MAIN OUTCOME MEASURES: Efficacy was assessed by (a) change in Hamilton anxiety scale total and somatic scores; (b) change in patient self-assessment; (c) number and percentage of responsive subjects (reduction of at least 50% in Hamilton or self-assessment score); and (d) the physician's clinical global impression. Tolerance was assessed by undesirable events spontaneously reported by the patients over the study period.

RESULTS: Total and somatic Hamilton scale scores and subjective patient-rated anxiety fell during treatment, indicating clinical improvement. The decrease was greater in the study drug than in the placebo group. End of treatment clinical improvement, as measured by the mean difference between final and pre-treatment scores, was, for the study drug and placebo groups respectively: -10.6 and -8.9 on the total anxiety score \( (p = 0.005) \); -6.5 and -5.7 on the somatic score \( (p = 0.054) \); and -38.5 and -29.2 for subjectively assessed anxiety \( (p = 0.005) \). The risk/benefit ratio as judged by the investigating physicians was also significantly greater in the study drug than in the placebo group. In all, 15 patients (11.5%) in the study drug group and 13 patients (9.7%) in the placebo group experienced 22 and 15 adverse events, respectively. Undesirable events were mainly mild or moderate digestive or psychopathological disorders.

CONCLUSIONS: The preparation containing fixed quantities of Crataegus oxyacantha, Eschscholtzia californica, and magnesium proved safe and more effective than placebo in treating mild-to-moderate anxiety disorders.
Enfla-mend Px has 375 Mg of Eschscholzia per 3 caps, in the range recommended by the world's leading phytotherapists.

- **Dosage for pain:**
  - 1:2, 3-6 ml  
  (Mills and Bone 2005)

- 1:5, 1-4 ml, 25% ethanol  
  (Hoffmann 2003)

- 200- 800 g dried equivalent, per day
• **Toxicity**: There have been no indications of toxicity for *Eschscholzia californica* in experimental studies or in anecdotal reports.

• **Herbal action**: sedative, anodyne, anxiolytic, antidepressant

• **Indications**: anxiety, nervousness, restless, agitation, insomnia, pain

• **Contraindications and Cautions** pregnancy; perhaps caution with concurrent use with prescription drugs and psychiatric medications.
Enfla-Mend Px has used the cutting edge technologies to provide practitioners with the best curcumin delivery systems.....

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Curcuma longa

• Curcumin (diferuloylmethane; 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione)

• Curcumin is the major bioactive component of turmeric or Curcuma longa L., a widely used natural food product in curry powder and food coloring (mustard).
Figure 1: Sources of curcumin

- **Curcuma aromatica**
  - (Wild turmeric, Vanarisha, Jangali Haldi, Aranyaharidra)
  - 0.1%

- **Curcuma longa**
  - (Haldi, Turmeric, Ukon, Woolgum, Kunyit, Oendre, Rame, Temu kuning, Temu kunyit, Goeratji, Kakojeni, Koenjet, Kondin, Tius, Kunir, Gianghuang)
  - 3-8%

- **Curcuma Phaeocaulis**
  - (Ezhu, Zedoary rhizome, Gajutsu)
  - 3%

- **Curcuma zedoaria**
  - (White turmeric, Zedoary root)
  - 1-2%

- **Curcuma mangga**
  - (Mango ginger)

- **Curcuma xanthorrhiza**
  - (Temu Lawak, Ubat Jamu, Ubat maaju)

- **Costus speciosus**
  - (Cane Reed, Crepe ginger, Wild ginger, Keokand)

- **Zingiber cassumunar**
  - (Cassumunar ginger)

- **Etlingera elatior**
  - (Torch ginger, eka, opuhi, pua vao)
Figure 4: Potential uses of curcumin based on modern technology[2]
Curcumin Targets

Multi-targeted
- Inflammatory cytokines: IL-1, IL-2, IL-5, IL-6, IL-8, IL-10, IL-8, MCP-1, MIP-1, MIP
- Enzymes: ATPase, ATPase, Desaturase, FPTase, GST, GCL, HO-1, INOS, MMP, NOG-1, ODC, PHD, TIMP-3, 5-LOX, Tetramerase
- Growth factors: TGFβ, FGF, HGF, PDGF, TF
- Receptors: AR, AHR, CXCR4, DR, EGFR, ERα, FasR, H2R, IL-8R, ITPR, IR, LD-R
- Adhesion molecules: ELAM-1, ICAM-1, VCAM-1
- Anti-apoptotic proteins: Bcl-2, Bcl-xL, IAP-1
- Protein Kinases: IKK, AAK, Ca2+PK, EGFR, ERK, FAK, IL-1R, JAK, JNK, MAPK, PI3K, PKA, PKB, PKC, pp60c-src, thk, PTK
- Transcriptional factors: AP-1, β-catenin, CBP, ERG-1, ERE, HIF-1, Notch-1, Nrf-2, NF-xB, PPARγ, STAT-1, STAT-3, STAT-4, STAT-5, WTG-1
- Others: Cyclin D1, Cyclin E, HSP 70, MDR

Mono-targeted
- COX-2: Celecoxib
- EGFR: Erbitux
- TNF: Remicade, Humira, Enbrel
- HER-2: Herceptin
- Bcr-Abl: Gleevec
- VEGF: Avastin
- Tubulin: Paclitaxel
- Topoisomerase: Camptothecin
Figure 8: Proteins, enzymes, receptors modulated by curcumin[61]
Curcumin is Poorly Absorbed

- Traditionally people have prepared curcumin in fat – heating with butter or oil– creates “liposomes” of a sort: little spheres of fat that carry the curcumin across the intestinal wall.
Meriva™ Phosphatidyl Complex is a Patented and Evidence-based Whole intact Curcuma Wholistic, balanced with Meriva™

Bromelain acts As another Absorption synergist, and is a powerful botanical agent By it’s own right…

Volatile oils intact

Piperine for ASSIMILATION

Quercetin & resveratrol, powerful anti-inflammatory Agents by themselves… synergizes absorption kinetics with Meriva Bromelain, piperine & the volatile oils
Comparative Absorption of a Standardized Curcuminoid Mixture and Its Lecithin Formulation

John Cuomo,*† Giovanni Appendino,*‡ Adam S. Dern,† Erik Schneider,† Toni P. McKinnon,† Mark J. Brown,† Stefano Togni,§ and Brian M. Dixon†

†USANA Health Sciences, Inc., 3838 West Parkway Boulevard, Salt Lake City, Utah 84120, United States
‡Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università degli Studi del Piemonte Orientale, Via Bovio 6, 28100, Novara, Italy
§Indena S.p.A., Viale Ortles 12, 20139 Milano, Italy

ABSTRACT: The relative absorption of a standardized curcuminooid mixture and its corresponding lecithin formulation (Meriva) was investigated in a randomized, double-blind, crossover human study. Clinically validated dosages were used for both products, and plasma levels of all three major curcuminoioids [curcumin (1a), demethoxycurcumin (1b), and bisdemethoxycurcumin (1c)] were evaluated. Total curcuminooid absorption was about 29-fold higher for Meriva than for its corresponding unformulated curcuminooid mixture, but only phase-2 metabolites could be detected, and plasma concentrations were still significantly lower than those required for the inhibition of most anti-inflammatory targets of curcumin. Remarkably, phospholipid formulation increased the absorption of demethoxylated curcuminoioids much more than that of curcumin (1a), with significant differences in plasma curcuminooid profile between Meriva and its corresponding unformulated curcuminooid mixture. Thus, the major plasma curcuminooid after administration of Meriva was not curcumin (1a), but demethoxycurcumin (1b), a more potent analogue in many in vitro anti-inflammatory assays. The improved absorption, and possibly also a better plasma curcuminooid profile, might underlie the clinical efficacy of Meriva at doses significantly lower than unformulated curcuminooid mixtures.
Figure 1. Pharmacokinetic data for curcumin (1a), demethoxycurcumin (1b), bisdemethoxycurcumin (1c), and total curcuminoids for each dosage. Concentrations are expressed in ng/mL and refer to enzymatically hydrolyzed plasma samples. Circles (●) represent high dosages of Meriva; squares (■) represent low-dose Meriva; and triangles (▲) represent the reference material.Insets (A and C) show an expanded view of the original data. The data shown are baseline subtracted means ± SEM.
Adding Piperine...The science

- Curcumin bioavailability has been improved by co-administering it with piperine.
- Piperine is a piperidine alkaloid found in the fruit of the black pepper (*Piper nigrum*), and is responsible for the pungency of black pepper spice.
Piperine’s Effect on Curcumin

- Piperine improves Curcumin’s bioavailability by inhibiting Hepatic phase II glucuronidation.
- Piperine also improves intestinal absorption by inhibiting P-glycoprotein-1, a broad-acting xenobiotic efflux transporter.
Piperine inhibits liver degradation of the curcuma, supporting tissue saturation.
Curcumin piperine and Curcumin with resveratrol, quercetin and piperidine resulted in the greatest absorption thru an in vitro simulation of a human GUT versus Curcumin alone.
Quercetin and Resveratrol also offer powerful anti-inflammatory effects.

Figure 1: Molecular structures of resveratrol, quercetin and curcumin demonstrating the relative similarities of placement of hydroxyl groups along unsaturated carbon chains and the presence of several phenolic groups.
Quercetin stops leaky gut
Resveratrol has its own effects on oxidative stress by blocking TNF alpha
Bromelain
Proteolytic Enzyme From Pineapple

Bromelain is concentrated in the core
# Supplement Facts

Serving Size: 3 capsules  
Servings per Container: 25

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boswellia extract, 65% boswellic acid (Boswellia serrata)</td>
<td>600 mg</td>
<td>†</td>
</tr>
<tr>
<td>California Poppy (Eschscholzia californica)</td>
<td>375 mg</td>
<td>†</td>
</tr>
<tr>
<td>Organic Turmeric Root, 4% curcuminoid, volatile oil</td>
<td>300 mg</td>
<td>†</td>
</tr>
<tr>
<td>Turmeric (Meriva®)Phytosome™, 95% curcuminoids</td>
<td>300 mg</td>
<td>†</td>
</tr>
<tr>
<td>Bromelain 2000 GDU (Ananas comosus)</td>
<td>225 mg</td>
<td>†</td>
</tr>
<tr>
<td>Quercetin</td>
<td>75 mg</td>
<td>†</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>75 mg</td>
<td>†</td>
</tr>
<tr>
<td>Black Pepper extract, 95% Piperine</td>
<td>7.5 mg</td>
<td>†</td>
</tr>
</tbody>
</table>

## Minimum Constituent BioMarker Per Dose

<table>
<thead>
<tr>
<th>BioMarker</th>
<th>Amount Per Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boswellic Acid</td>
<td>312 mg</td>
</tr>
<tr>
<td>Curcuminoids</td>
<td>60 mg</td>
</tr>
<tr>
<td>Piperine</td>
<td>6 mg</td>
</tr>
</tbody>
</table>

All Organic Herbs are Certified Organic  
† Daily Value not established

Other Ingredients: Vegetable Capsule (cellulose)  
To refill contact your practitioner or visit www.restorative.com
Bromelain

- Fibrinolysis
- Vascular integrity
  - Tissue drainage
- Plasmin
- Inflammatory balance*
- Proteases
- Kinins
Bromelain modulates cytokines


**Placebo-controlled randomized clinical trial on the immunomodulating activities of low- and high-dose bromelain after oral administration - new evidence on the antiinflammatory mode of action of bromelain.**

Müller S¹, März R, Schmolz M, Drewelow B, Eschmann K, Meiser P.

Author information

**Abstract**

Bromelain has been used for treatment of inflammatory diseases for decades. However, the exact mechanism of action remains poorly understood. While in vitro investigations have shown conflicting effects on the release of various cytokines, no in vivo data were available. In this study, the effects on inflammation-related cytokines of two doses of bromelain were tested in a single dose placebo-controlled 3 x crossover randomized clinical trial. Cytokine circadian profiles were used to investigate the effects of bromelain on the human immune system by using stimulated whole-blood leukocytes. The effects seen in these cultures demonstrated a significant shift in the circadian profiles of the Th1 cell mediator interferon gamma (IFNγ; p < 0.043) after bromelain 3000 FIP (Fédération Internationale Pharmaceutique) units, and trends in those of the Th2-type cytokine IL-5 as well as the immunosuppressive cytokine interleukin (IL)-10. This suggests a general effect on the antigen-specific (T cell) compartment of the human immune system. This is the first time that bromelain has been shown to modulate the cellular responses of lymphocyte after oral use. It is postulated that the immunomodulating effect of bromelain observed in this trial is part of its known antiinflammatory activities. Further investigations will be necessary to verify the relevance of these findings to a diseased immune system.

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Bradykinin stimulates PI3k and AKT which causes pain.

Bromelain inhibits Bradykinin and PI3K.
Bromelain blocks bradykinin, VCAM-1 and Cox 2
Bromelain modulated VCAM-1 and stops atherosclerosis
### Table 4

<table>
<thead>
<tr>
<th>Conditions in which Bromelain has Documented Therapeutic Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Athletic and musculoskeletal injuries</td>
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<tr>
<td>Bacterial infections</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Cellulitis</td>
</tr>
<tr>
<td>Cutaneous Staphylococcus infection</td>
</tr>
<tr>
<td>Debridement of Burns</td>
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<tr>
<td>Dysmenorrhea</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Inflammation</td>
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<tr>
<td>Maldigestion</td>
</tr>
<tr>
<td>Pancreatic insufficiency and Steatorrhea</td>
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<tr>
<td>Platelet aggregation</td>
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<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Pyelonephritis</td>
</tr>
<tr>
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<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Surgical traumas</td>
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<tr>
<td>Thrombophlebitis</td>
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</tbody>
</table>
Osteoarthritis and Sports Medicine

References


