Evidence Based Botanicals in the Treatment of Inflammation

Sponsored by Restorative Formulations (Non-CME presentation)

Eugene R. Zampieron, ND,AHG
DrZ teaching at the University of Bridgeport College of Naturopathic Medicine, CT

- Licensed Naturopathic physician
  - Connecticut since 1990
- Dr. Friedman’s mentor
- Registered Professional, Herbalist, AHG
- Author/Radio host
- Academic and clinical faculty member and Founding Presidential advisors Board Member
  - University of Bridgeport College of Naturopathic Medicine, Connecticut
- Caribbean Ethnobotany researcher
  - EcoToursforCures.com
Why do I choose/use Enfla-Mend Px & T-Cell balance Px & other RF products??

Why do I choose/use Enfla-Mend Px & T-Cell balance Px & other RF products??

CAREFUL CAPSULE CREATION
Research and clinical experience are central to the development of Restorative Formulations. Our Product Development Team of physicians is led by Michael Friedman, ND. Our team combines their experience with a knowledge of the traditional and modern uses of herbs to develop new products and improve upon existing ones.

Certified Organic ingredients
Free of gluten, wheat, saturated fats, sugar, dairy, soy and yeast
Free of heavy metal toxicity
No excipients, binders, fillers or magnesium stearate
Zero tolerance for pesticide residues for certified extracts
Zero tolerance for toxic solvent residues
Zero tolerance for irradiation
Capsule filled to the max

EXTRACTION METHODS
To realize our products' greatest potential, Restorative Formulations strives to use full-spectrum botanical extracts that represent the whole herb. To create a Certified Organic Extract, the only solvents that are allowed are certified organic alcohol, water and supercritical carbon dioxide. We standardize herbal extracts when specific constituents and active ingredients from the herbs are indicated. We utilize several methods to extract and concentrate botanical ingredients. Each herb is custom-extracted based on its unique physical characteristics and the plant's chemical constituents.

WHAT IS Px?
Some Restorative Formulations products you will see in this catalog have a “Px” as part of the product name. We created the Px designation as a flag to indicate that these products are highly concentrated. Restorative Formulations’ Px products are often far more potent than other herbal supplements that healthcare practitioners may be used to administering. When you see a Px product, keep this higher concentration in mind to ensure optimal results for your patients.
Our topic and objectives...

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

• Some botanical agents are shown to have broad acting anti-inflammatory effects for all these complaints

• I use the term INFLAM-aging with patients
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

<table>
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<tr>
<th>Serving Size: 3 capsules</th>
<th>Servings per Container: 25</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td><strong>Amount per Serving</strong></td>
<td><strong>%Daily Value</strong></td>
</tr>
<tr>
<td><strong>Boswellia extract, 65% boswellic acid (Boswellia serrata)</strong></td>
<td>600 mg</td>
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<tr>
<td><strong>California Poppy (Eschscholzia californica)</strong></td>
<td>375 mg</td>
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<tr>
<td><strong>Organic Turmeric Root, 4% curcuminoid, volatile oil</strong></td>
<td>300 mg</td>
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<tr>
<td><strong>Turmeric (Meriva®)Phytosome™, 95% curcuminoids</strong></td>
<td>300 mg</td>
</tr>
<tr>
<td><strong>Bromelain 2000 GDU (Ananas comosus)</strong></td>
<td>225 mg</td>
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<tr>
<td><strong>Quercetin</strong></td>
<td>75 mg</td>
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<tr>
<td><strong>Resveratrol</strong></td>
<td>75 mg</td>
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<tr>
<td><strong>Black Pepper extract, 95% Piperine</strong></td>
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**Minimum Constituent BioMarker Per Dose**

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<td>6 mg</td>
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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
MECHANISM (Activated):
1. TNFα & TNFα-R bind as trimers.
2. TNFα alters the TNFα-R-tails.
3. **Signaling protein** docks on altered tail.
4. The signaling proteins activates an STK.
5. STK phosphorylates IkB kinase kinase (P-IKK).
6. P-IKK phosphorylates Ikβ/NFκB
7. Ikβ is marked for proteolysis & releases NFκ-B
8. NFκ-B in the nucleus, binds co-activator & stimulates inflammatory gene expression.
CURCUMIN health benefits:

- Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease)
- Epilepsy
- Cerebral injury
- Lung fibrosis
- Gall-stone formation
- Acquired Immune Deficiency Syndrome (AIDS)
- Nephrotoxicity
- Colitis
- Renal Ischemia
- Cataract formation
- Metabolic disease
- Multiple sclerosis
- Psoriasis
- Scleroderma
- Diabetes
- Asthma
- Arthritis
- Bronchitis
- Allergy
- Inflammatory bowel disease
- Wound healing
- Cardiotoxicity
- Cardiovascular disease
- Cancer
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 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 boswelliic 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 Multifaceted Bioactivities

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

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

Figure 2
Effects of Boswellia triterpenoids

- Decrease nitric oxide (a free radical) concentrations
- Decrease in lipooxygenase and leukotrienes
- Arachidonic acid
- Decrease tumour necrosis factor (TNF)
- Decrease release of anticatabolic factors from peripheral blood
- Improved microcirculation
- Inhibition of histamine, serotonin and kinin systems
- Anti-complement activity
- Decrease neutrophil extravasation (chemoattract)
- Vascular endothelial stabilization
- Decrease humoral mediator of inflammation
- Release of free radical scavenging enzyme-superoxide dismutase

**ANTI-INFLAMMATORY ACTION**
Boswellia is not inferior to NSAID mesalazine
Boswellia serrata extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial.


Abstract

BACKGROUND AND AIMS: The objective of this study was to investigate the effect of Boswellia serrata extract (BSE) on symptoms, quality of life, and histology in patients with collagenous colitis.

MATERIALS AND METHODS: Patients with chronic diarrhea and histologically proven collagenous colitis were randomized to receive either oral BSE 400 mg three times daily for 6 weeks or placebo. Complete colonoscopy and histology were performed before and after treatment. Clinical symptoms and quality of life were assessed by standardized questionnaires and SF-36. The primary endpoint was the percentage of patients with clinical remission after 6 weeks (stool frequency < or = 3 soft/solid stools per day on average during the last week). Patients of the placebo group with persistent diarrhea received open-label BSE therapy for a further 6 weeks.

RESULTS: Thirty-one patients were randomized; 26 patients were available for per-protocol-analysis. After 6 weeks, the proportion of patients in clinical remission was higher in the BSE group than in the placebo group (per protocol 63.6%; 95%CI, 30.8-89.1 vs 26.7%, 95%CI, 7.7-55.1; p=0.04; intention-to-treat 43.8% vs 26.7%, p=0.25). Compared to placebo, BSE treatment had no effect on histology and quality of life. Five patients discontinued BSE treatment prematurely. Discontinuation was due to adverse events (n=1), unwillingness to continue (n=3), or loss to follow-up for unknown reasons (n=1). Seven patients received open-label BSE therapy, five of whom achieved complete remission.

CONCLUSIONS: Our study suggests that BSE might be clinically effective in patients with collagenous colitis. Larger trials are clearly necessary to establish the clinical efficacy of BSE.
Blocking Smad7 restores TGF-beta1 signaling in chronic inflammatory bowel disease.

Monteleone G1, Kumberova A, Croft NM, McKenzie C, Steer HW, MacDonald TT.

Abstract
TGF-beta1 functions as a negative regulator of T cell immune responses, signaling to target cells using the Smad family of proteins. We show here that Smad7, an inhibitor of TGF-beta1 signaling, is overexpressed in inflammatory bowel disease (IBD) mucosa and purified mucosal T cells. Both whole tissue and isolated cells exhibit defective signaling through this pathway, as measured by phospho-Smad3 immunoreactivity. Specific antisense oligonucleotides for Smad7 reduce Smad7 protein expression in cells isolated from patients with IBD, permitting the cells to respond to exogenous TGF-beta1. TGF-beta1 cannot inhibit proinflammatory cytokine production in isolated lamina propria mononuclear cells from patients with Crohn disease (CD), but inhibition of Smad7 restores TGF-beta1 signaling and enables TGF-beta1 to inhibit cytokine production. In inflamed mucosal tissue explants from patients with CD, inhibition of Smad7 also restores p-Smad3 and decreases proinflammatory cytokine production, an effect that is partially blocked by anti-TGF-beta1. These results show that Smad7 blockade of TGF-beta1 signaling helps maintain the chronic production of proinflammatory cytokines that drives the inflammatory process in IBD and that inhibition of Smad7 enables endogenous TGF-beta to downregulate this response.

Comment in
TGF-beta/Smad signaling defects in inflammatory bowel disease: mechanisms and possible novel therapies for chronic inflammation. [J Clin Invest. 2001]
Boswellia blocks Smad7 and thus restores Smad 3 & TGFB, which Acts to down regulate the immune system in colitis.

Boswellia helps SMAD3
Better for autoimmunity

TGFβ \rightarrow IL-2 \rightarrow Treg

IL-4 \rightarrow Th2

IL17
Modulation of the immune system by Boswellia serrata extracts and boswellic acids.

Ammon HP.

Abstract
Extracts from the gum resin of Boswellia serrata and some of its constituents including boswellic acids affect the immune system in different ways. Among the various boswellic acids, 11-keto-beta-boswellic acid (KBA) and acetyl-11-keto-beta-boswellic acid have been observed to be active. However, other boswellic acids may exhibit actions in the immune system. In the humoral defence system, a mixture of boswellic acids at higher doses reduced primary antibody titres; on the other hand, lower doses enhanced secondary antibody titres following treatment with sheep erythrocytes. In the cellular defence, boswellic acids appear to increase lymphocyte proliferation whereas higher concentrations are even inhibitory. Moreover, BAs increase phagocytosis of macrophages. BAs affect the cellular defence system by interaction with production/release of cytokines. Thus, BAs inhibit activation of NFkappaB which is a product of neutrophil granulocytes. Consequently, a down regulation of TNF-alpha and decrease of IL-1, IL-2, IL-4, IL-6 and IFN-gamma, which are proinflammatory cytokines, by BEs and BAs has been reported. Suppressions of the classic way of the complement system was found to be due to inhibition of the conversion of C3 into C3a and C3b. However, which of these pharmacological actions contribute to the therapeutic effects and which is finally the best dosage of a standardized extract needs further examination. And it is also a question whether or not a single BA will have the same therapeutic effect as a standardized extract. Among the mediators of inflammatory reaction, mast cell stabilisation has been described by a BA. Inhibition of prostaglandin synthesis appears to play only a minor role as far as the anti-inflammatory effect is concerned. On the other hand, the inhibitory action of BAs on 5-LO leading to a decreased production of leukotrienes has received high attention by the scientific community since a variety of chronic inflammatory diseases is associated with increased leukotriene activity. At the end of the cascade of events in the cellular immune system as far as it directs to various tissues of the body - i.e. autoimmune diseases - formation of oxygen radicals and proteases (for example elastase) play an important destructive role. Here, BEs as well as BAs have been found to be inhibitory. From the pharmacological properties of BEs and BAs it is not surprising that positive effects of BEs in some chronic inflammatory diseases including rheumatoid arthritis, bronchial asthma, osteoarthritis, ulcerative colitis and Crohn's disease have been reported.
Your Cartilage & Collagen doesn't stand a chance when these pathways are activated!

- **CLASSICAL PATHWAY**
  - Antigen:antibody complexes (pathogen surfaces)
  - C1q, C1r, C1s, C4, C2

- **MB-LECTIN PATHWAY**
  - Mannose-binding lectin binds mannose on pathogen surfaces
  - MBL, MASP-1, MASP-2
  - C4, C2

- **ALTERNATIVE PATHWAY**
  - Pathogen surfaces
  - C3, B, D

**C3 convertase**

**Boswellia**

- C3a, C5a
  - Peptide mediators of inflammation, phagocyte recruitment

- C3b
  - Binds to complement receptors on phagocytes
  - Opsonization of pathogens
  - Removal of immune complexes

**Terminal complement components**
- C5b, C6, C7, C8, C9
  - Membrane-attack complex, lysis of certain pathogens and cells
Boswellia was as effective as allopathic drugs for UC and Crohn’s.
The comparative study of acetyl-11-keto-beta-boswellic acid (AKBA) and aspirin in the prevention of intestinal adenomatous polyposis in APC(Min+/-) mice.

Wang R, Wang Y, Gao Z, Qu X.

Boswellia induces apoptosis in the polyps

Abstract

Acetyl-11-keto-beta-BA (AKBA), a component of the gum resin of Boswellia serrata, has been recognized as a promising agent for the prevention of intestinal tumorigenesis. Aspirin, a non-steroidal anti-inflammatory drug (NSAID), has also been considered to have the activity against intestinal tumorigenesis. However, the prevention of colonic cancer is insufficient and no definitive recommendation has been made for clinic use. Herein, we compared the efficacy of AKBA with that of aspirin in an adenomatous polyposis coli intestinal neoplasia consecutive weeks. Mice were sacrificed by anesthetizing. The whole intestine was removed from each mouse. The number, size and histopathology of intestinal adenomatous polyps were examined under microscopy. The adenomatous polyps were removed for further analysis by the assays of western blotting and immunohistochemical staining. AKBA significantly prevented the formation of intestinal adenomatous polyps without toxicity to mice. Statistical analysis indicated that AKBA's activity both in the prevention of small intestinal and colonic polyps was more potently than aspirin. Histopathologic examination revealed that AKBA's effect, that is the reduction of polyp size and degree of dysplasia, was more prominent in larger sized polyps, especially those originating in colon. These effects of AKBA were associated with its role in the induction of apoptosis in carcinomas. The assays of western blotting and immunohistochemistry staining indicated that the efficacy of AKBA might arise from its activity in the modulation of the Wnt/β-catenin pathway and NF-κB/COX-2 pathway in adenomatous polyps. Conclusion, AKBA by oral application prevented intestinal tumorigenesis more potential than aspirin.
A. Normal colonic epithelial cells

B. Colon cancer cells

Curcuma prevents this
Boswellia may inhibit ulcers; this is critical in treating rheumatic dz, as NSAIDS can cause ulcers & Leaky gut.

**Abstract**

Aim of the study is to evaluate the anti-ulcer efficacy of the boswellic acids (BA), a triterpenoid known as anti-inflammatory/anti-arthritic agent, which is in clinical use. The reason for the study is that, the known non-steroidal anti-inflammatory drugs (NSAIDs) are full of side effects especially ulceration which is at the top. BA, although, used as an anti-arthritic agent yet it is not only devoid of ulcer production but protective also. The activity evaluation was done by the following universally accepted animal models viz., pyloric ligation, ethanol-\text{HCl}, acetylsalicylic acid, indomethacin and cold restrained stress-induced ulceration in rats. Results of the present study revealed that BA possess a dose dependent antulcer effect against different experimental models. It showed different degree of inhibition of the ulcer score towards different ulcerogenic agents. The ulcer score against various ulcer inducing agents viz., pyloric ligation, ethanol/HCl, (acute and chronic) acetylsalicylic acid, indomethacin and cold restraint stress, was inhibited by 39%, 38%, 51%, 31%, 37% and 42% respectively at 250mg/kg. From the data it is concluded that BA inhibited ulcer production non-specifically in all the experimental models, whereby, it is not possible to propose a single specific mechanism. Nevertheless it is possible that BA might be acting by increasing the gastric mucosal resistance and local synthesis of cytoprotective prostaglandins and inhibiting the leukotriene synthesis.

Boswellia blocks Leukotrienes and may increase protective prostaglandins.
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, eschodine, escholine, scholinine, eschoscholtzidine, protopine and sanguinarine.
Clinical Studies

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

- Preserving catecholamines may explain the Pain relieving and endorphin activity of CP.

- Alkaloids from CP enhance (GABA) binding to receptors, which may indicate a benzodiazapine-like activity.
Pain cycle broken by EnFlamend and its herb Eschscholzia...
Neurophysiological effects of an extract of *Eschscholzia californica* Cham. (Papaveraceae).

Rolland A¹, Fleurentin J, Lanners 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<sub>A</sub> Receptor

- BzRAs are allosteric modulators of the GABA receptor complex.
- BzRA binding increases the frequency of Cl<sup>-</sup> channel openings in the presence of GABA and prolong miniature inhibitory postsynaptic currents (mIPSC).

GABA=gamma-aminobutyric acid.

Dawson, CNS Spectrums, 2005.
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.
Enfla-mend Px has 375 Mg of Eschscholtzia 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
Enfla-Mend Px has used the cutting edge technologies to provide practitioners with the best curcumin delivery systems.....

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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
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 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-12, IL-8, MCP-1, MIP-1, Maf

- Enzymes
  - ATFase, ATPase, Desaturase, FPTase, GST, GCL, HO-1, INOS, MMPs, NOO-1, ODC, PhPD, TIMP-3, 5-LOX, Tetramerase

- Growth factors
  - TGF β, FGF, HGF, PDGF, TF

- Receptors
  - AR, AHR, CXCR4, DR, EGFR, ER-α, FasR, H2R, IL-8R, ITPR, IR, LD-R

- Adhesion molecules
  - ELAM-1, ICAM-1, VCAM-1

- Anti-apoptotic proteins
  - Bcl-2, Bcl-x, IAP-1

- Protein Kinases
  - IKK, AAKP, Ca2+ PK, EGFR, ERK, FAK, IL-1 RAK, JAK, JNK, MAPK, PhK, PK, 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, PPAR-γ, 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

- HER-2
  - Humira

- Bcr-Abl
  - Enbrel

- VEGF
  - Herceptin

- Tubulin
  - Gleevec

- Topoisomerase
  - Avastin

- Paclitaxel

- Camptothecin
Figure 8: Proteins, enzymes, receptors modulated by curcumin[61]
Curcuma and its multi-effects downstream of NFkB

Curcumin inhibits NFkB, and is thus able to greatly impact cancer progression. Take a look at this CAT scan from a patient with liver cancer who had already failed chemotherapy:
New mechanism of action of curcuma in Cardiovascular disease

Molecular mechanism of curcumin on the suppression of cholesterol accumulation in macrophage foam cells and atherosclerosis.

Zhao JF, Ching LC, Huang YC, Chen CY, Chiang AN, Kou YR, Shyue SK, Lee TS.

Abstract
SCOPE: Curcumin, a potent antioxidant extracted from Curcuma longa, confers protection against atherosclerosis, yet the detailed mechanisms are not fully understood. In this study, we examined the effect of curcumin on lipid accumulation and the underlying molecular mechanisms in macrophages and apolipoprotein E-deficient (apoE−/−) mice.

METHODS AND RESULTS: Treatment with curcumin markedly ameliorated oxidized low-density lipoprotein (oxLDL)-induced cholesterol accumulation in macrophages, which was due to decreased oxLDL uptake and increased cholesterol efflux. In addition, curcumin decreased the protein expression of scavenger receptor class A (SR-A) but increased that of ATP-binding cassette transporter (ABC) A1 and had no effect on the protein expression of CD36, class B receptor type I (SR-BI), or ATP-binding cassette transporter G1 (ABCG1). The downregulation of SR-A by curcumin was via ubiquitin-proteasome-calpain-mediated proteolysis. Furthermore, the curcumin-induced upregulation of ABCA1 was mainly through calmodulin-liver X receptor α (LXRα)-dependent transcriptional regulation. Curcumin administration modulated the expression of SR-A, ABCA1, ABCG1, and SR-BI in aortas and retarded atherosclerosis in apoE−/− mice.

CONCLUSION: Our findings suggest that inhibition of SR-A-mediated oxLDL uptake and promotion of ABCA1-dependent cholesterol efflux are two crucial events in suppression of cholesterol accumulation by curcumin in the transformation of macrophage foam cells.

What the heck is this?? How does it work??
ATP binding Cassette transporter?
Curcuma lowered oxyLDL
Upregulated ABCA1
Pathway for regulating reelin- and ApoE-induced ABCA1 expression. Up to now, data from our laboratory suggest that reelin and apolipoprotein E (apoE) are able to activate very low-density lipoprotein receptor (VLDLR) and apoE receptor 2 (ApoER2), and trigger a signaling cascade involving disabled-1 (Dab1), phosphatidylinositol 3-kinase (PI3K), protein kinase C-ζ (PKC-ζ) and specificity protein 1 (Sp1), which up-regulates ATP–binding cassette transporter A1 (ABCA1) expression and enhances cholesterol efflux. Increasing evidence indicates that a deficiency in ABCA1 could result in cellular cholesterol accumulation, and thus promoting abnormalities such as atherosclerosis.

A deficiency in ABCA1 may cause increased atherosclerosis

ABCA1 is ATP-Binding cassette transporter A1

Curcumin causes efflux ejection of cholesterol from foam cells which is picked up by HDL & ApoA1
Smooth muscle migration is essential in the sequence & pathogenesis of atherosclerosis.
**Figure 1.** Domain structure of the matrix metalloproteinases (MMPs). Each of the 25 vertebral MMPs is categorized by domain structure. Abbreviations used: Pre = signal sequence, Pro = propeptide with a free.

**The Metalloproteinase System**

![Diagram of the metalloproteinase system](image)

**Figure 2.** The metalloproteinase system. Matrix metalloproteinase activity is regulated at the level of transcription (1), activation (2) and regulation at the tissue level by tissue inhibitors of metalloproteinases (TIMPs; 3). Once activated and left uninhibited, MMPs can either degrade extracellular matrix (ECM) inducing classical tissue remodeling or regulate numerous biological activities through the modulation of various cell signaling mechanisms.
Curcuma spp. stopped this migration of smooth muscle cells into the plaque.
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™

Quercetin & resveratrol, powerful anti-inflammatory Agents by themselves… synergizes absorption kinetics with Meriva Bromelain, piperine & the volatile oils

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

Volatile oils intact

Piperine for ASSIMILATION

Enfla-Mend Px

Restorative Formulations

75 Vegi-Capsules
Dietary Supplement
Comparative Absorption of a Standardized Curcuminoid Mixture and Its Lecithin Formulation

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†Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università degli Studi del Piemonte Orientale, Via Bovio 6, 28100, Novara, Italy
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ABSTRACT: The relative absorption of a standardized curcuminoid 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 curcuminoids [curcumin (1a), demethoxycurcumin (1b), and bisde-methoxycurcumin (1c)] were evaluated. Total curcuminoid absorption was about 29-fold higher for Meriva than for its corresponding unformulated curcuminoid 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 curcuminoids much more than that of curcumin (1a), with significant differences in plasma curcuminoid profile between Meriva and its corresponding unformulated curcuminoid mixture. Thus, the major plasma curcuminoid 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 curcuminoid profile, might underlie the clinical efficacy of Meriva at doses significantly lower than unformulated curcuminoid 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.

Meriva showing better absorption of curcuminoids
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.
Graph of curcuma plus synergists, not even taking into account EnFlamend uses Meriva, which is superior to regular curcuma.

Enfla-Mend Px now incorporates these three key ingredients to increase curcumin absorption, plus the phospholipid-bound form of curcumin, Meriva.
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

<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>
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<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>
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</table>

**Minimum Constituent BioMarker Per Dose**

<table>
<thead>
<tr>
<th>BioMarker</th>
<th>Amount per Dose</th>
</tr>
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<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>
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</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 S, März R, Schmolz M, Drewelow B, Eschmann K, Meiser P.

**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 × 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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Bromelain blocks bradykinin, VCAM-1 and Cox 2
Bromelain modulated VCAM-1 and stops atherosclerosis.
Bromelain versus NSAIDS: an effective and healthier choice

Table 4.

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

References


