Evidence Based Botanicals in the Treatment of Inflammation

Sponsored by Restorative Formulations
(Non-CME presentation)

Credits: Eugene R. Zampieron, ND

AARM
Association for the Advancement of Restorative Medicine

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

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

Minimum Constituent BioMarker Per Dose

Boswellic Acid	312 mg
Curcuminoids	60 mg
Piperine	6 mg

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

Boswellia

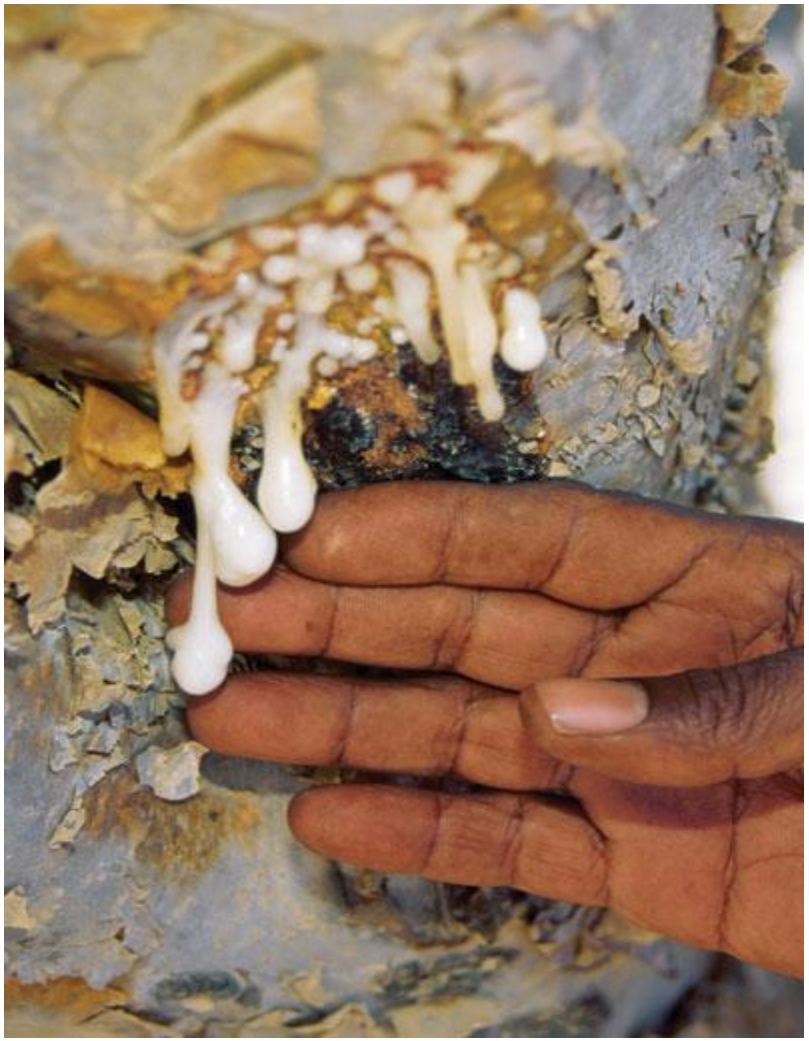
literature review

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.

http://i.telegraph.co.uk/multimedia/archive/02433/Frankinsense1_2433367b.jpg

http://www.nature.com/nature/journal/v444/n7121/images/444529a-i1.0.jpg



Boswellia in **Oman**

http://cdni.wired.co.uk/620x413/d_f/frankin.jpg

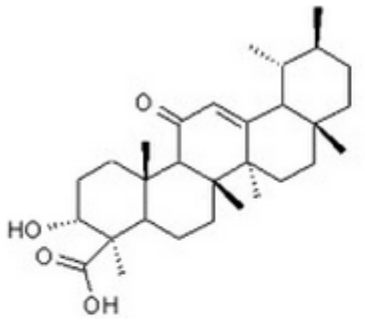
Boswellia serrata (*Salai/Salai guggul*)

- 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.

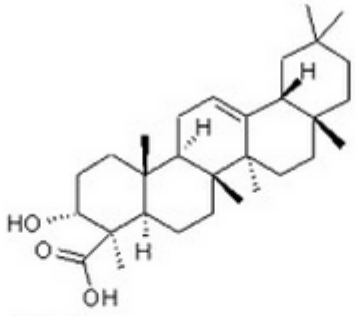
Boswellia serrata (*Salai/Salai guggul*)

- 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.

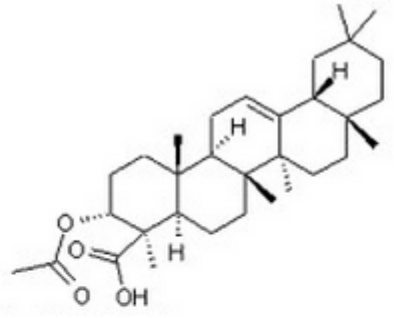
Penta{5} cyclic rings
Steroidal in nature



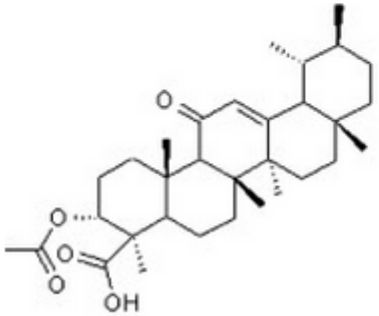
11-keto-β-Boswellic Acid



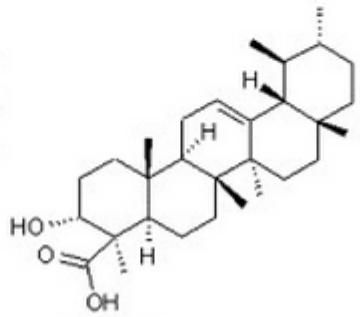
α-Boswellic Acid



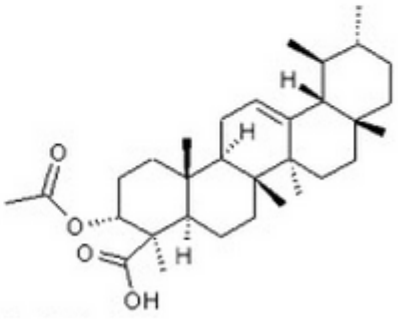
Acetyl-α-Boswellic Acid



3-O-Acetyl-11-keto-β-Boswellic Acid

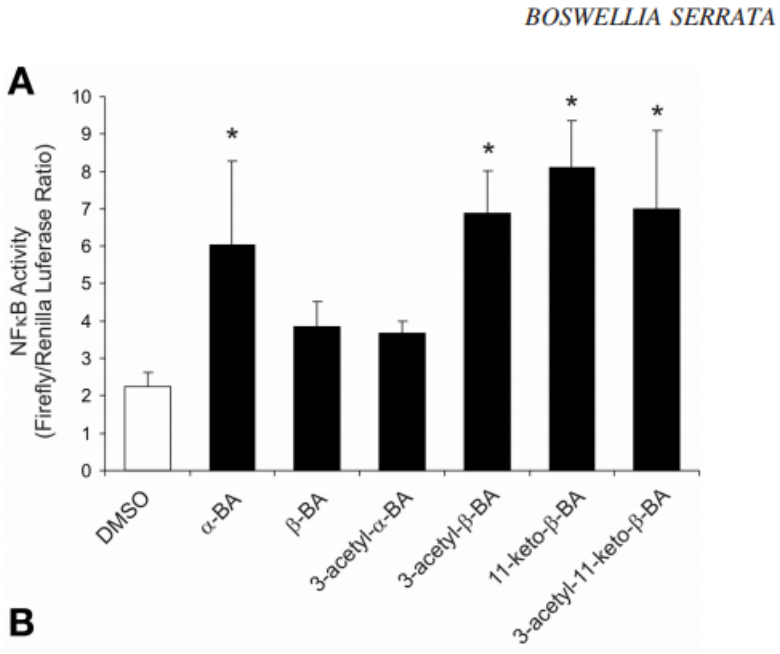


β-Boswellic Acid



Acetyl-β-Boswellic Acid

Fractions of Boswellic acid and inhibition of NFkB



Fractions of boswelliic acids

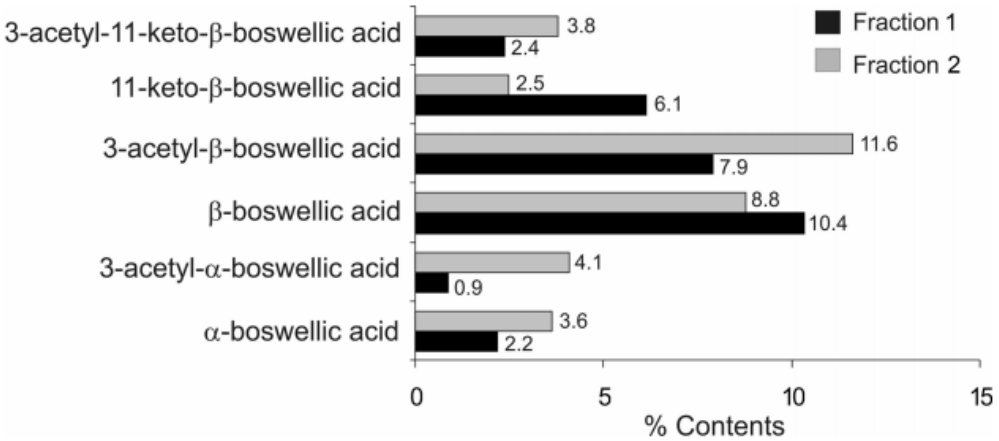


Fig. 1. Results of chromatographic analysis of boswellic acids in hexane and methanolic fractions (*fraction 1* and *fraction 2*, respectively) of *Boswellia serrata* used in this study.

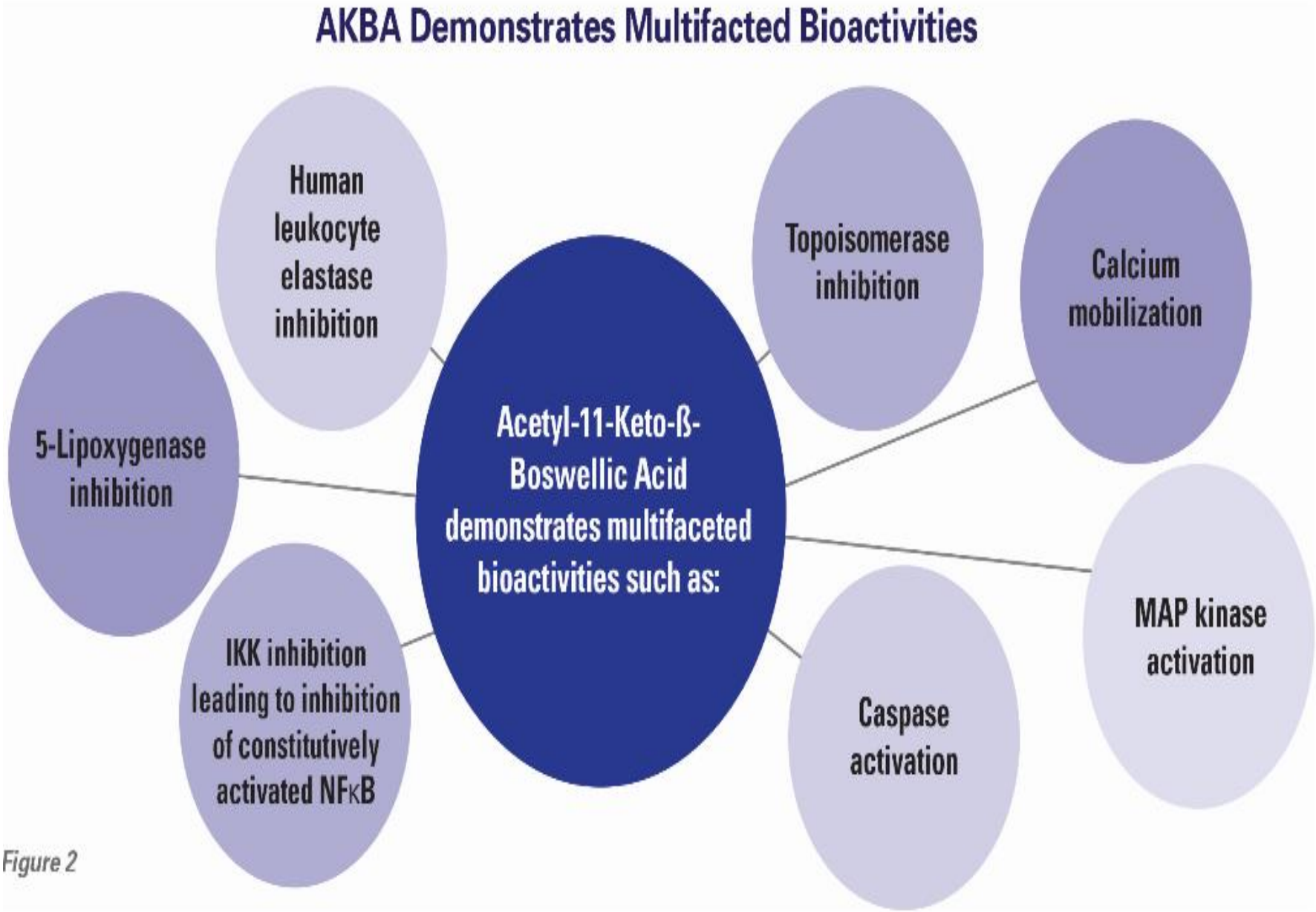
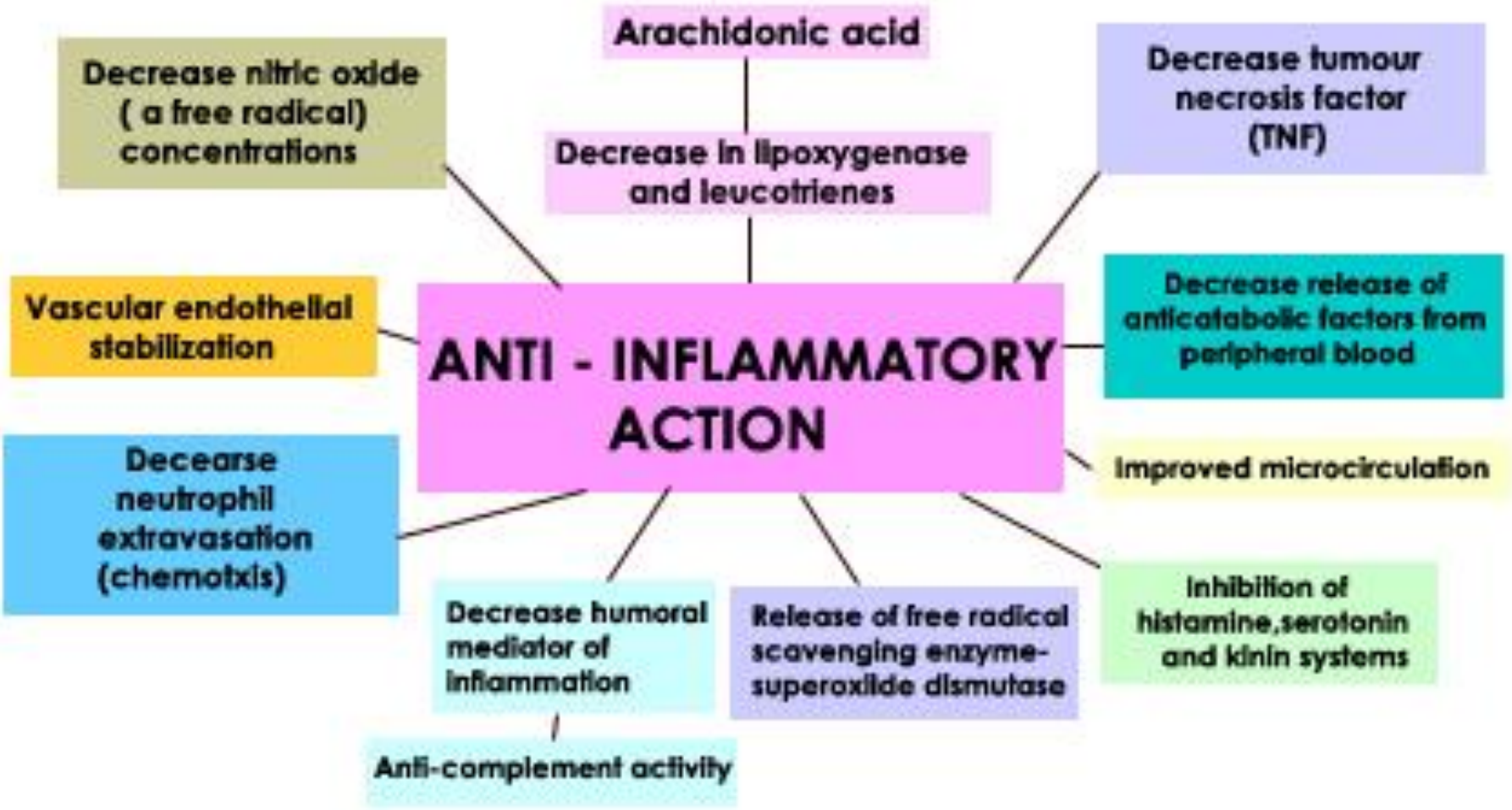

AKBA Demonstrates Multifacted Bioactivities
Human leukocyte elastase inhibition
Topoisomerase inhibition
Calcium mobilization
5-Lipoxygenase inhibition
Acetyl-11-Keto-ß-Boswellic Acid demonstrates multifaceted bioactivities such as:
MAP kinase activation
IKK inhibition leading to inhibition of constitutively activated NFκB
Caspase activation

Figure 2

Effects of Boswellia triterpenoids



Z Gastroenterol. 2001 Jan;39(1):11-7.

[Therapy of active Crohn disease with Boswellia serrata extract H 15].

[Article in German]
Gerhardt H[1], Seifert F, Buvari P, Vogelsang H, Repges R.

Author information

Boswellia is not inferior to NSAID mesalazine

Abstract

BACKGROUND: The purpose of this clinical trial was to compare efficacy and safety of the Boswellia serrata extract H15 with mesalazine for the treatment of active Crohn's disease.

PATIENTS AND METHODS: Randomised, double-blind, verum-controlled, parallel group comparison for which 102 Patients were randomised. The per protocol population included 44 patients treated with H15 and 39 patients treated with mesalazine. As primary outcome measure the change of the Crohn Disease Activity Index (CDAI) between the status of enrolment and end of therapy was chosen. H 15 was tested on non-inferiority compared to standard treatment with mesalazine.

RESULTS: The CDAI between the status of enrolment and end of therapy after treatment with H15 was reduced by 90 and after therapy with mesalazine by 53 scores in the mean. In this non-inferiority-trial the test hypothesis was confirmed by the statistical analysis. The difference between both treatments could not be proven to be statistically significant in favor to H15 for the primary outcome measure. The secondary efficacy endpoints confirm the assessment of the comparison of H15 and mesalazine. The proven tolerability of H15 completes the results of the shown clinical efficacy.

CONCLUSIONS: The study confirms that therapy with H15 is not inferior to mesalazine. This can be interpreted as evidence for the efficacy of H15 according to the state of art in the treatment of active Crohn's disease with Boswellia serrata extract, since the efficacy of mesalazine for this indication has been approved by the health authorities. Considering both safety and efficacy of Boswellia serrata extract H15 it appears to be superior over mesalazine in terms of a benefit-risk-evaluation.

Summary of Major trials on Boswellia and inflammation of Asthma, RA, and Crohn's respectively

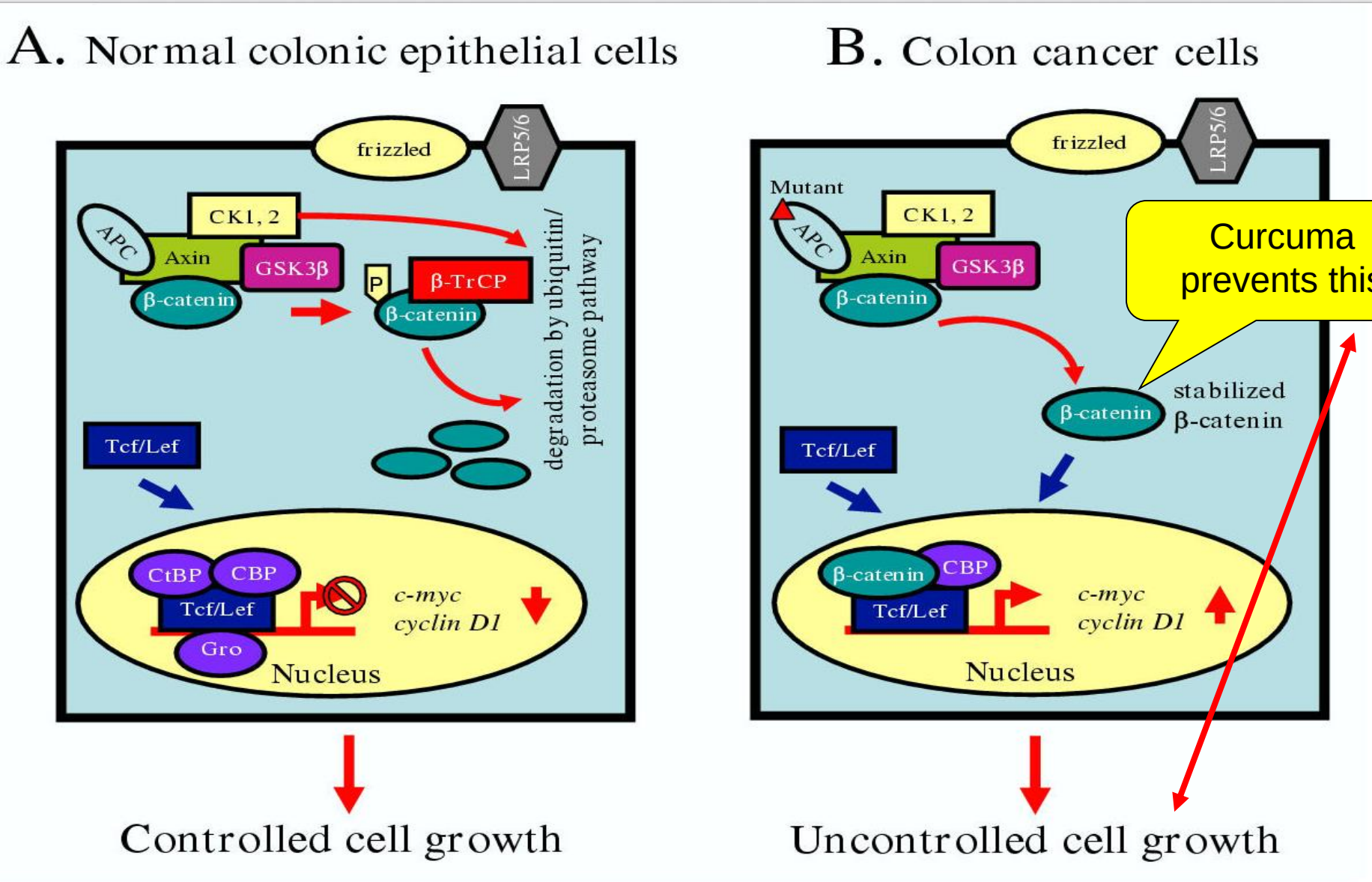
Key data from randomised clinical trials included in systematic review

First author (year), country	Condition (sample size)	Design (Jadad score)*	Interventions	Nature of extract†	Primary outcome measure	Main results/effect size‡	Adverse effects of BSE (A) and control intervention (B)	Comment
Gupta (1998), India/ Germany[7]	Asthma (80)	DB, PC, 2 PG (3)	(A) BSE (350 mg 3×day) for 6 weeks; (B) placebo	"Boswelic acid containing drug 300 mg"	Percentage of patients showing clinical improvement	(A) 70% remission; (B) 27% remission§	(A) 2 patients experienced stomach pain, hyperacidity, nausea; (B) no information	Group (A) had more severe asthma than group (B); other endpoints also suggested efficacy of BSE
Sander (1998), Germany[8]	Rheumatoid arthritis (37)	DB PC, 2 PG (2)	A) BSE (3600 mg 9×day) for 12 weeks; (B) placebo; both groups also received conventional drugs	H15§	Ritchie Index	Non-significant trend in favour of BSE§	(A) Stomatitis (1 patient); (B) eczema (1 patient), nausea (1 patient), increase of joint pain (1 patient)	Report only relates to subset of patients from larger unpublished study
Gerhardt (2001), Germany/ Austria[9]	Crohn's disease (102)	DB, 2PG, non-inferiority (3)	(A) BSE (3.6 g per day) for 8 weeks; (B) mesalazine (4.5 per day)	H15‡	Crohn's Activity Index (CAI)	Non-inferiority of BSE confirmed: (A) CAI from 301 (63) to 192 (114); (B) from 282 (72) to 163 (96)	(A) No causally related adverse effects; (B) 13 causally related adverse effects	Data refer to intention to treat analysis

Summary of Major trials on Boswellia & pain/inflammation of OA and Colitis respectively

Kimmatkar (2003), India[10]	Osteoarthritis of the knee (30)	DB, PC, crossover (5)	(A) BSE (333 mg per day) for 8 weeks; (B) placebo	"Standardized extract of *Boswellia serrata* gum: minimum 65% organic acids or min 40% total BA. Main components of BA: 11-keto-β BA—6.44%, 3-O-Acetyl-11-ketoβ BA—2%, β-BA—18.51%, 3-O-Acetylβ BA—8.58%, α-BA—6.93%, 3-O-Acetyl-α-BA—1.853%."	Pain, function (VAS)	Significant intergroups differences in favour of BSE; intergroup difference for pain 2.3 (0.61)	(A) Diarrhoea (1 patient), epigastric pain, nausea (1 patient); (B) no information	Authors state that the differences are clinically relevant
Madisch (2007), Germany[11]	Collagenous colitis (31)	RCT, DB, PC, 2 PG (5)	(A) BSE (400 mg 3×day) for 6 weeks; (B) placebo	"High performance liquid chromatography analysis... 21.2 mg 11-keto-β-boswellia acid, 27.3 mg α-boswellia acid, 50.9 mg β-boswellia acid, 11.3 mg acetyl-11-keto-β-boswellia acid, 9.8 mg acetyl-α-boswellia acid, 28.7 mg acetyl-β-boswellia acid."	Percentage of patients with remission	(A) 64% remission (95% CI 30.8 to 89.1, ITT 44%); (B) 27% (7.7 to 55.1, 27%)	(A) Dizziness, hypoglycaemia, lack of appetite, diarrhoea (1 patient), bacterial enteritis (1 patient); (B) no information	Other outcome measures (such as stool frequency) also suggest efficacy of BSE
Sontakke (2007), India[12]	Osteoarthritis of the knee (66)	RCT, open, active control, 2PG (2)	(A) BSE (333 mg 3×day) for 6 months; (B) valdecoxib (10 mg, 1×day)¶	"Standardized extract of BSE having minimum 40% total BA. Main components of BA: 11-keto-β BA—6.44%, 3-O-Acetyl-β BA—8.58%, alpha BA—6.93% and 3-O-acetyl α BA—1.853%."	WOMAC scale	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)	(A) Diarrhoea (1 patient); (B) no adverse effects	1 month after discontinuation of therapy, patients in group (A) maintained benefit while those in (B) deteriorated

http://www.molecular-cancer.com/content/figures/1476-4598-2-41-3-l.jpg



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

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Phytomedicine. 2008 Jun;15(6-7):408-15. doi: 10.1016/j.phymed.2008.02.017. Epub 2008 Apr 18.

The gastric ulcer protective effect of boswellic acids, a leukotriene inhibitor from Boswellia serrata, in rats.

Singh S[1], Khajuria A, Taneja SC, Khajuria RK, Singh J, Johri RK, Qazi GN.

Author information

Abstract

Aim of the study is to evaluate the anti-ulcer efficacy of the boswellic acids (BA), a triterpen
arthritic agent, which is in clinical use. The reason for the study is that, the known non-steroi
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-HCl, acetylsalicylic acid, indomethacin and cold restrained stress-induced ulceration in rats. Results of the present study revealed that BA possess a dose dependent antiulcer 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

Supplement Facts

Serving Size: 3 capsules | Servings per Container: 25

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

Minimum Constituent BioMarker Per Dose

Boswellic Acid	312 mg
Curcuminoids	60 mg
Piperine	6 mg

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

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 lat 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

Benzodiazepine receptors

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Phytother Res. 2001 Aug;15(5):377-81.

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

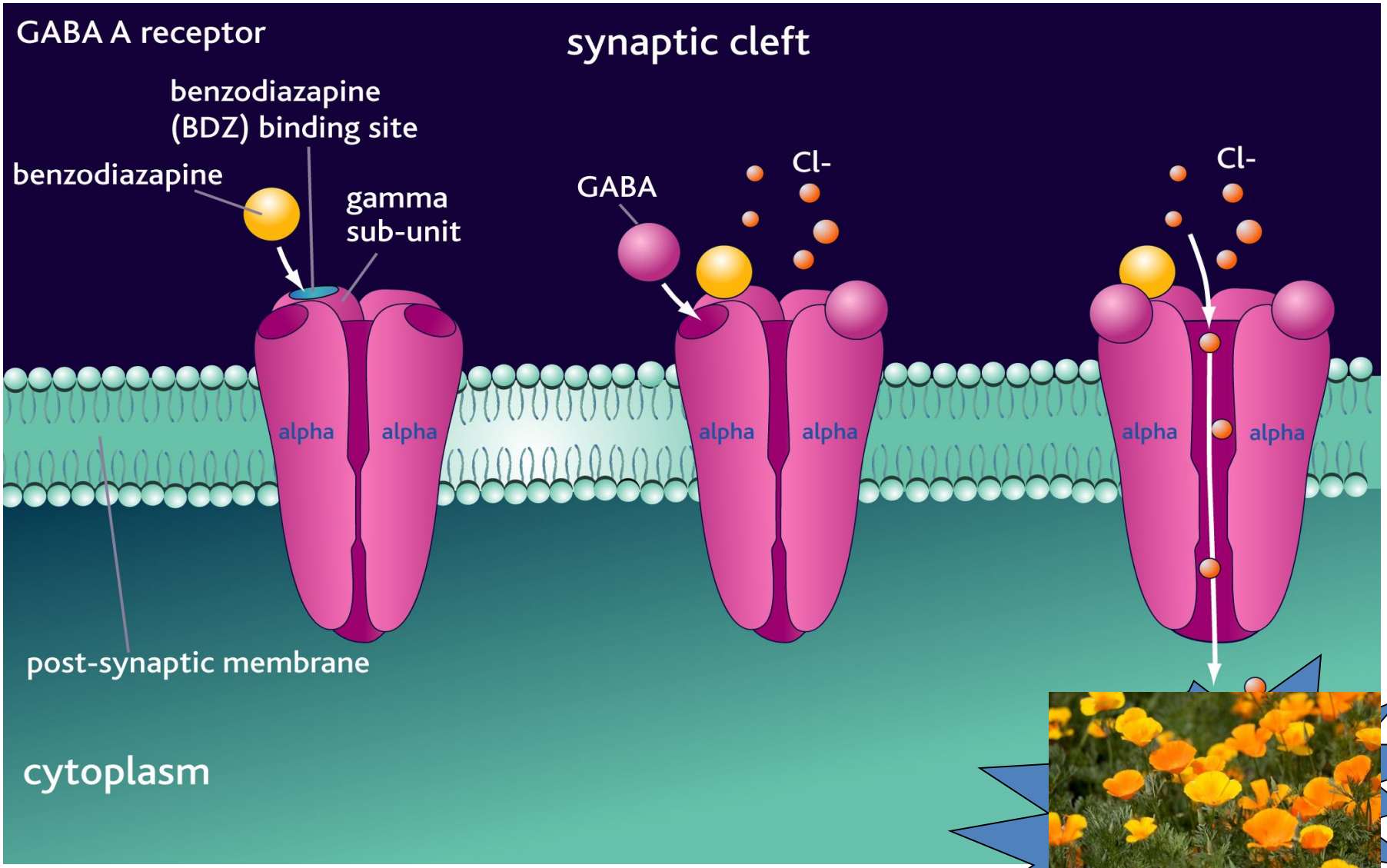
Rolland A[1], Fleurentin J, Lanhers MC, Misslin R, Mortier F.

Author information

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 pentylenetetrazol, 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



Arzneimittelforschung. 1995 Feb;45(2):124-6.

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

Schäfer HL[1], Schäfer H, Schneider W, Elstner EF.

Author information

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.

Curr Med Res Opin. 2004 Jan;20(1):63-71.

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 M[1], Lafon J, Mathieu M.

Author information

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) [redacted]d in a double-blind, randomised, placebo-controlled trial. Patients were randomly assigned to two groups: 130 received the study drug [redacted] 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. [redacted]al, Arcueil, France.

Enfla-mend Px has 375 Mg of Eschscholzia per 3 caps, in the range recommended by the worlds leading phytotherapists

- <u>Dosage for pain:</u>
- 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…..

Supplement Facts

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Piperine	6 mg

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 1: Sources of curcumin[5]

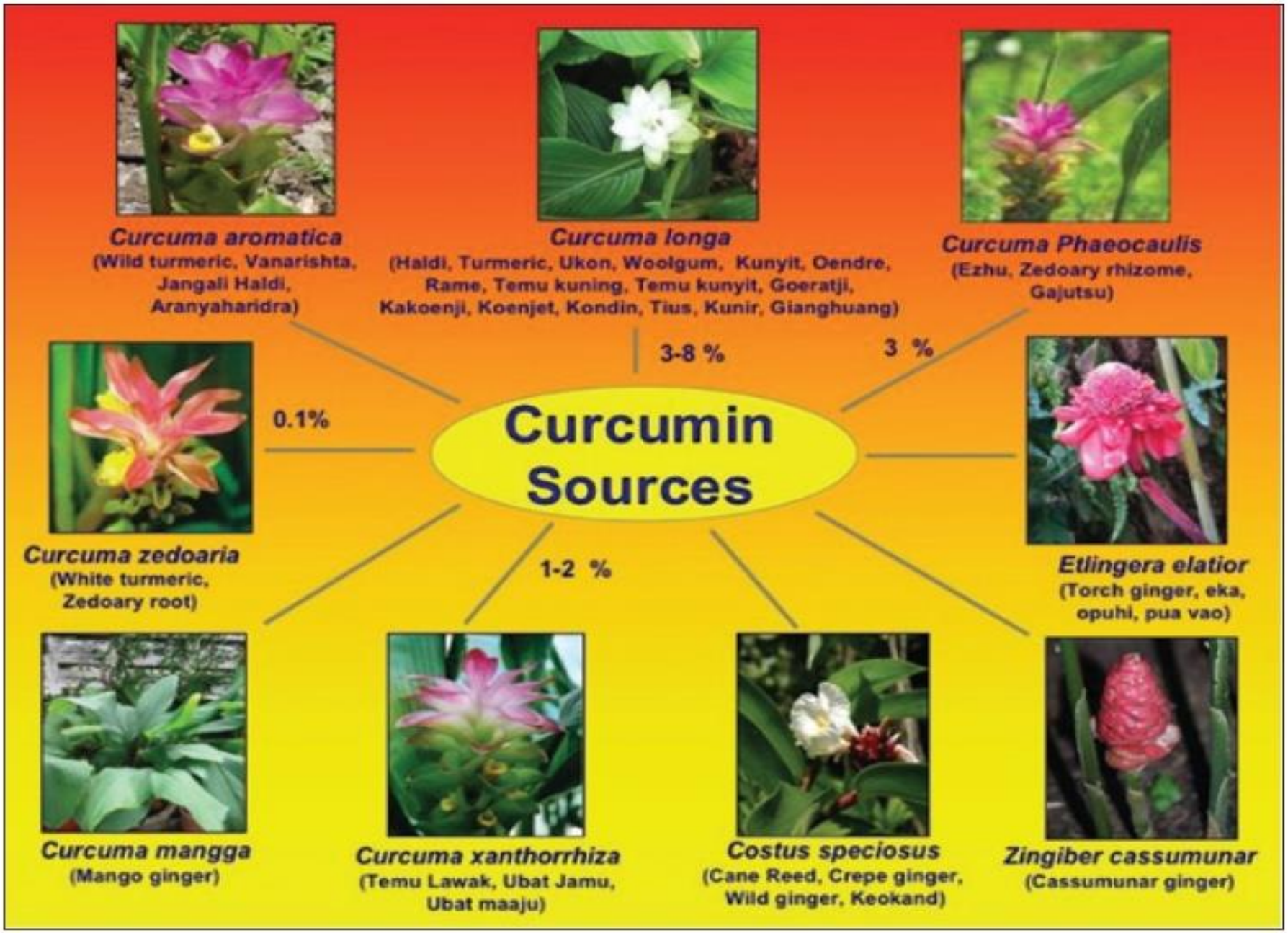


Figure 4: Potential uses of curcumin based on modern technology[2]

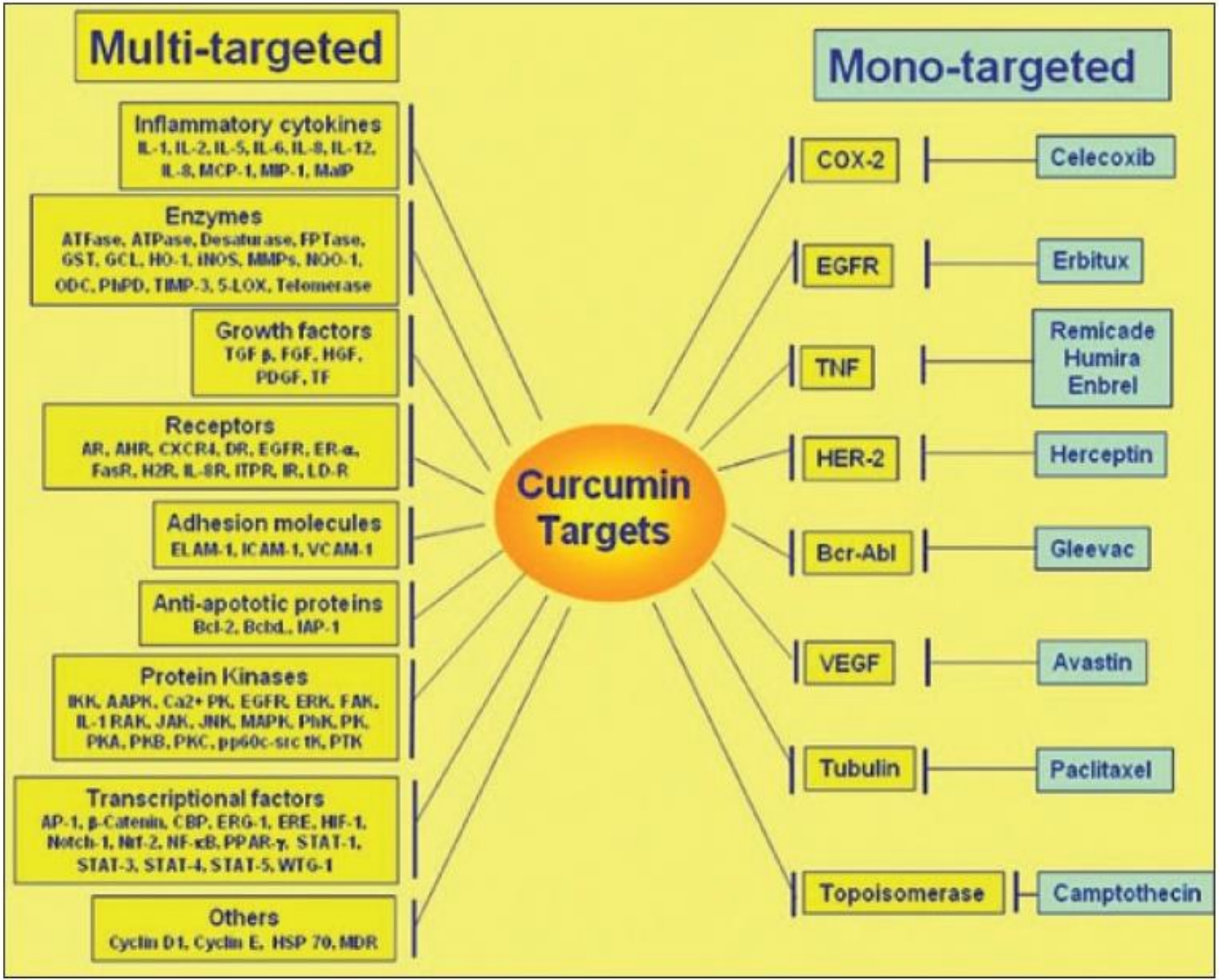
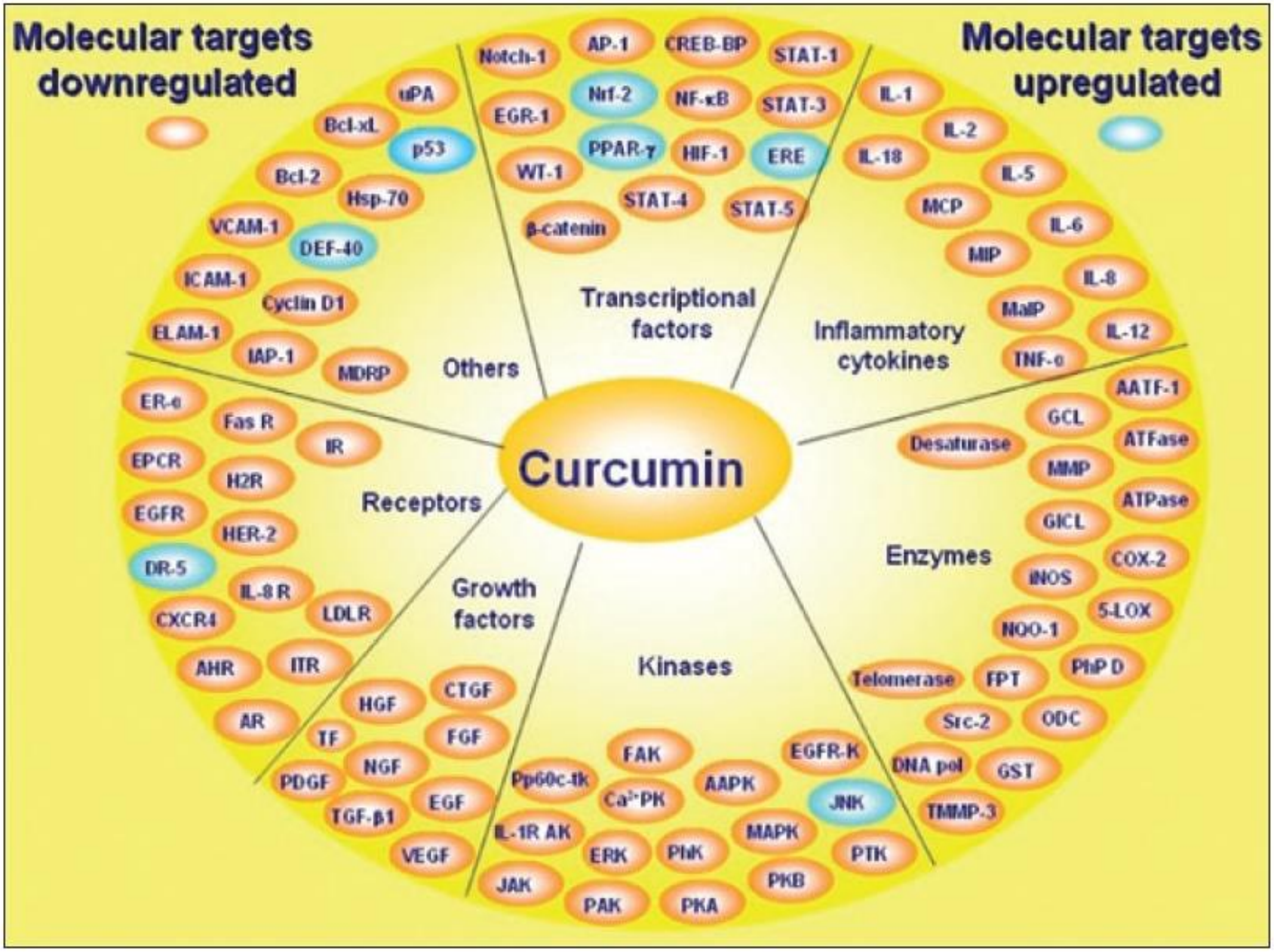
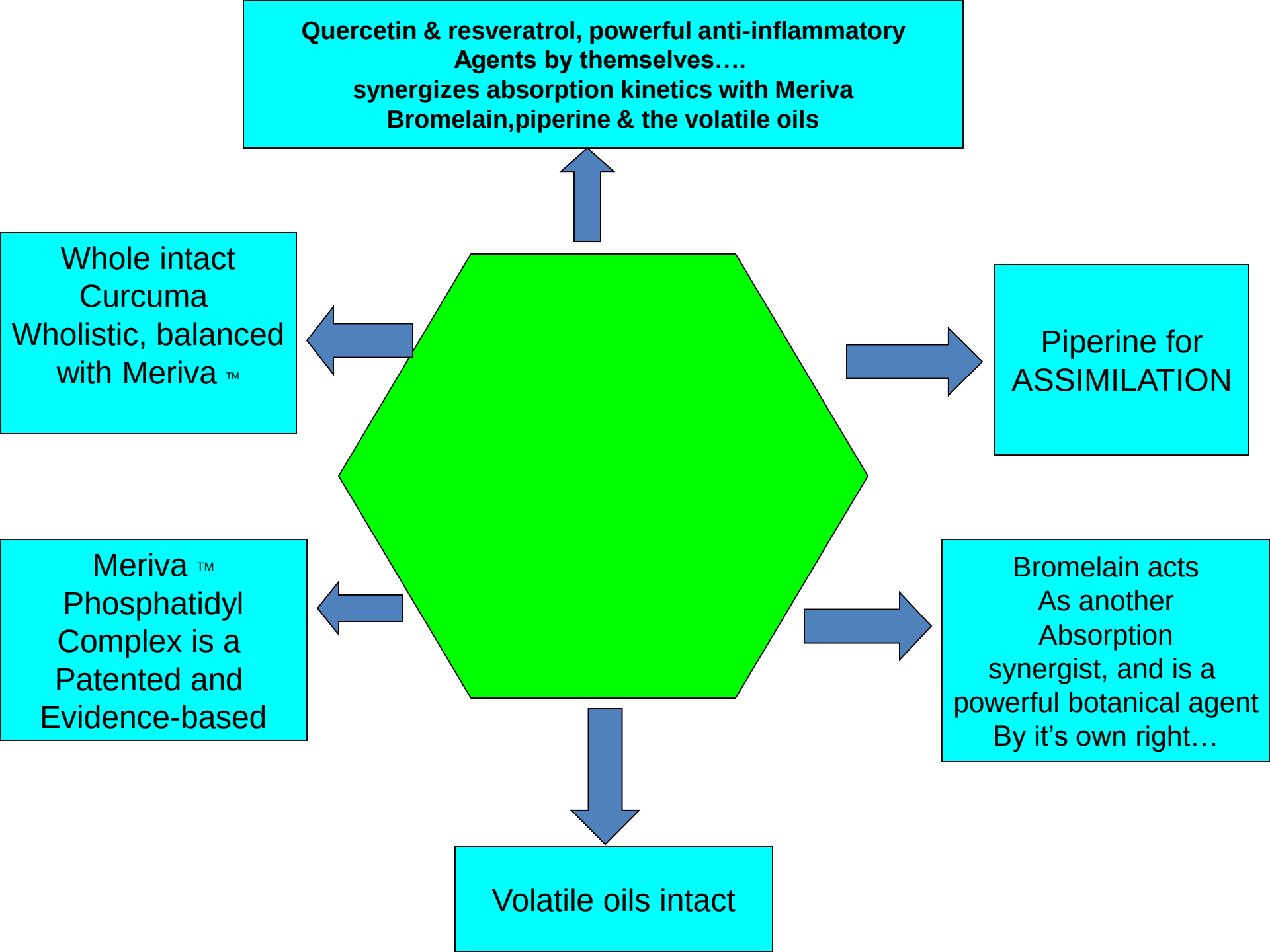

Multi-targeted
Inflammatory cytokines
IL-1, IL-2, IL-5, IL-6, IL-8, IL-12, IL-8, MCP-1, MIP-1, MaIP
Enzymes
ATFase, ATPase, Desaturase, FPTase, GST, GCL, HO-1, iNOS, MMPs, NQO-1, ODC, PNPD, TIMP-3, 5-LOX, Telomerase
Growth factors
TGF β, FGF, HGF, PDGF, TF
Receptors
AR, AHR, CXCR4, DR, EGFR, ER-α, FasR, H2R, IL-8R, ITPR, IR, LD-R
Adhesion molecules
ELAM-1, ICAM-1, VCAM-1
Anti-apototic proteins
Bcl-2, Bchd., IAP-1
Protein Kinases
IKK, AAPK, Ca2+ PK, EGFR, ERK, FAK, IL-1 RAK, JAK, JNK, MAPK, PhK, PK, PKA, PKB, PKC, pp60c-src tK, PTK
Transcriptional factors
AP-1, β-Catenin, CBP, ERG-1, ERE, HIF-1, Notch-1, Nrf-2, NF-κB, PPAR-γ, STAT-1, STAT-3, STAT-4, STAT-5, WTG-1
Others
Cyclin D1, Cyclin E, HSP 70, MDR
Curcumin Targets
Mono-targeted
COX-2
Celecoxib
EGFR
Erbitux
TNF
Remicade
Humira
Enbrel
HER-2
Herceptin
Bcr-Abl
Gleevac
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.


Quercetin & resveratrol, powerful anti-inflammatory Agents by themselves….
synergizes absorption kinetics with Meriva
Bromelain,piperine & the volatile oils
Whole intact Curcuma Wholistic, balanced with Meriva ™
Piperine for ASSIMILATION
Meriva ™ Phosphatidyl Complex is a Patented and Evidence-based
Bromelain acts As another Absorption synergist, and is a powerful botanical agent By it's own right…
Volatile oils intact

JOURNAL OF NATURAL PRODUCTS

ARTICLE

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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[†]

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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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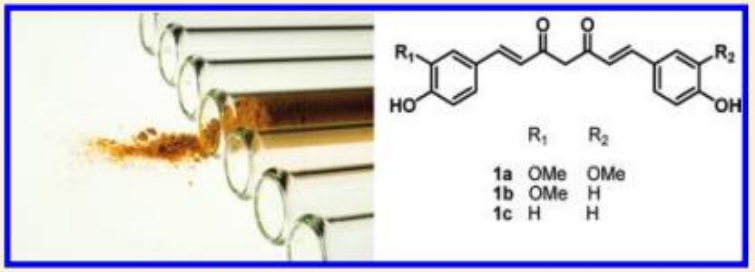
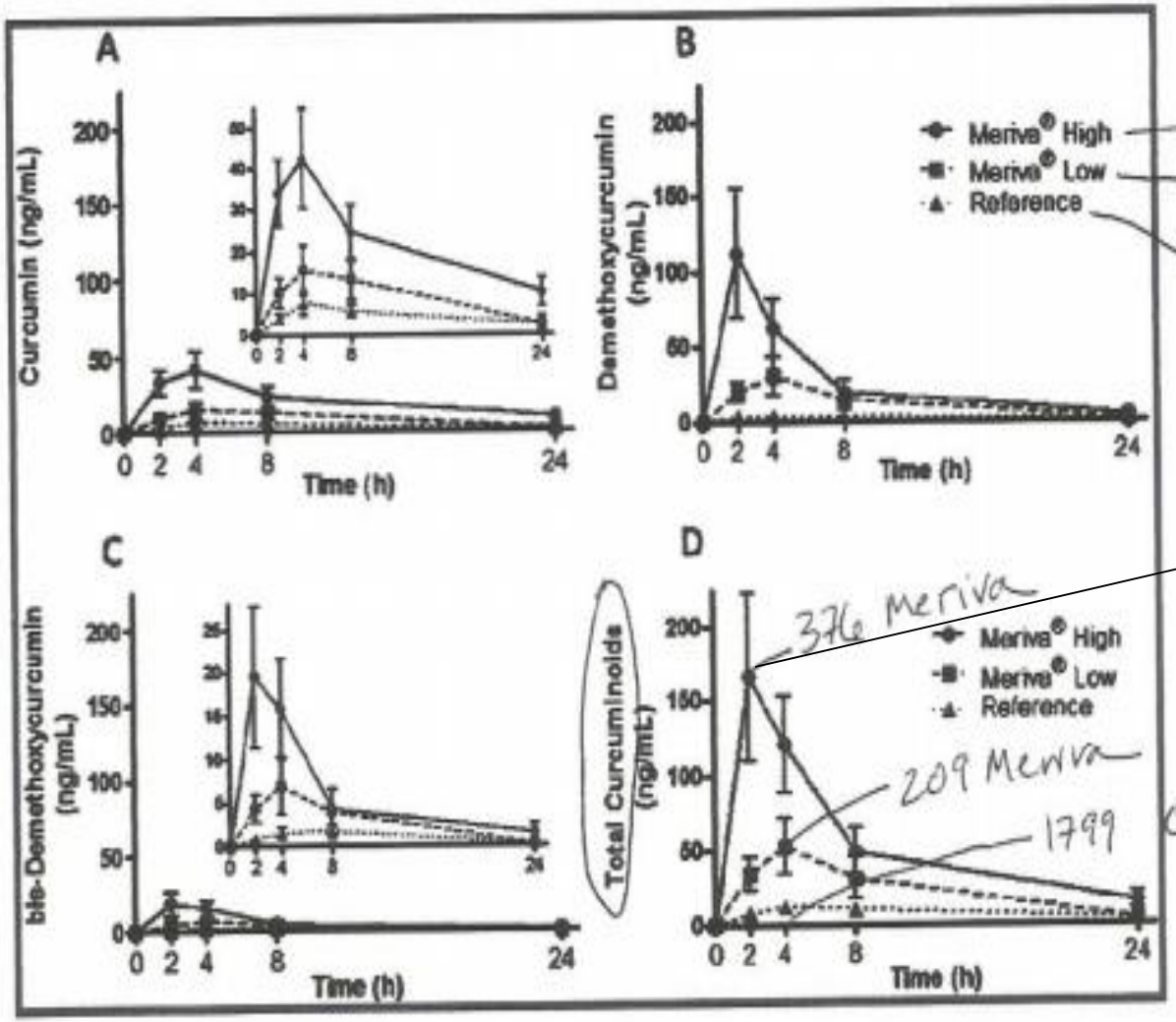
ABSTRACT: The relative absorption of a standardized curcuminoid mixture and its corresponding lecithin formulation (Meriva) was investigated in a randomized, double-blind, crossover human study. Clinically validated dosages were used for both products, and plasma levels of all three major curcuminoids [curcumin (**1a**), demethoxycurcumin (**1b**), and bisdemethoxycurcumin (**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.



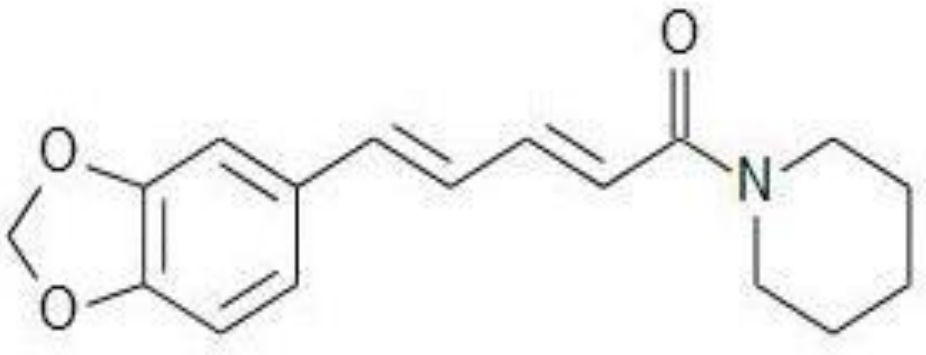


Meriva showing better absorption of curcuminoids

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).**

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Pharmazie. 2012 Jun;67(6):518-24.

Physiological barriers to the oral delivery of curcumin.

Berginc K[1], Trontelj J, Basnet NS, Kristl A.

Author information

Abstract

Curcumin, a principal component from Curcuma longa, with antioxidant and anti-inflammat
preventation and/or treatment of cancer and chronic diseases. However, curcumin could not achieve its expected therapeutic outcome in clinical trials due to its low solubility and poor bioavailability. The actual intestinal physiological barriers limiting curcumin absorption after oral administration have not been fully investigated. To identify the main barriers curtailing its absorption, in vitro permeability of curcumin and flux of its glucuronide were monitored in rat jejunum and Transwell grown Caco-2 cells. Curcumin was more permeable under acidic conditions, but the permeability was substantially below the permeability of highly permeable standards. Its efflux could not be inhibited by specific Pgp and MRP inhibitors. BCRP was found to participate in curcumin transport, but the Organic Anion Transporting Polypeptide (OATP) did not. The permeability of curcumin significantly increased when the structure of mucus was compromised. The inhibitor of curcumin metabolism, piperin, failed to act as a permeability enhancer. Piperin inhibited Pgp and MRP transporters and decreased the amount of glucuronide transported back into the intestine. Inclusion of piperin in curcumin-containing formulations is highly recommended as to inhibit curcumin glucuronidation and to increase the transport of formed glucuronides into the plasma, therefore increasing the probability of glucuronide distribution into target tissue and inter-convertion to curcumin. It would also be beneficial, if curcumin delivery systems could reversibly compromise the mucous integrity to minimize the non-specific binding of curcumin to its constituents.

PMID: 22822540 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances

LinkOut - more resources

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

Curcumin with piperidine resveratrol and quercetin

Curcuma itself

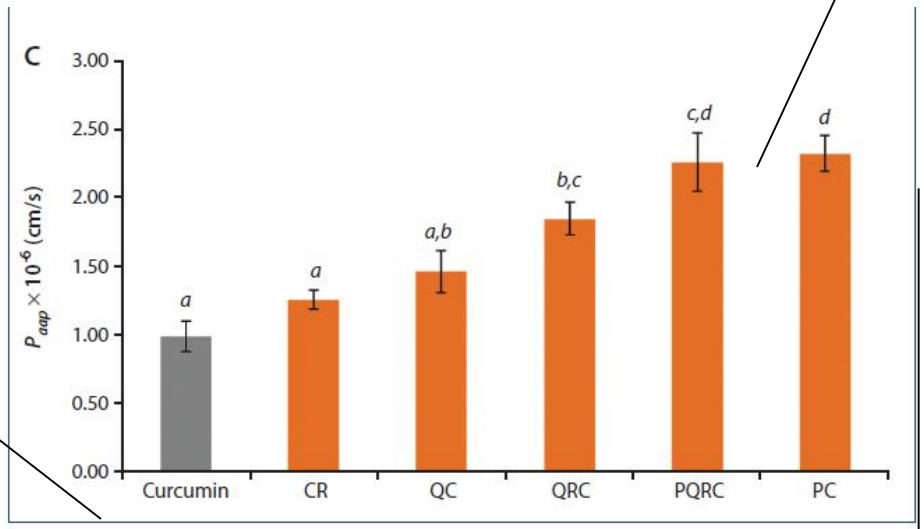


Figure 3: Apical-to-basal permeability of (A) quercetin (Q), (B) resveratrol (R) or (C) curcumin (C), alone or in combination across intact caco-2 monolayers. Compounds were applied apically at 50 μM (piperine (P) at 200 nM) and measured in the basal compartment at 30 min. Data is expressed as the average $P_{app} \times 10^{-6}$ (cm/s) of three separate experiments ± SD. Bars labeled with different letters are significantly different from each other, $P < 0.05$.

from quercetin alone was observed when combined with the other compounds. It is worth mentioning, however, that quercetin showed the lowest absorption in the PQRC combination suggesting piperine may adversely affect quercetin permeability. In contrast adding piperine a

Piperidine with the curcumin

Journal of Re

New Journal of Restorative medicine article

Quercetin and Resveratrol also offer powerful anti-inflammatory effects

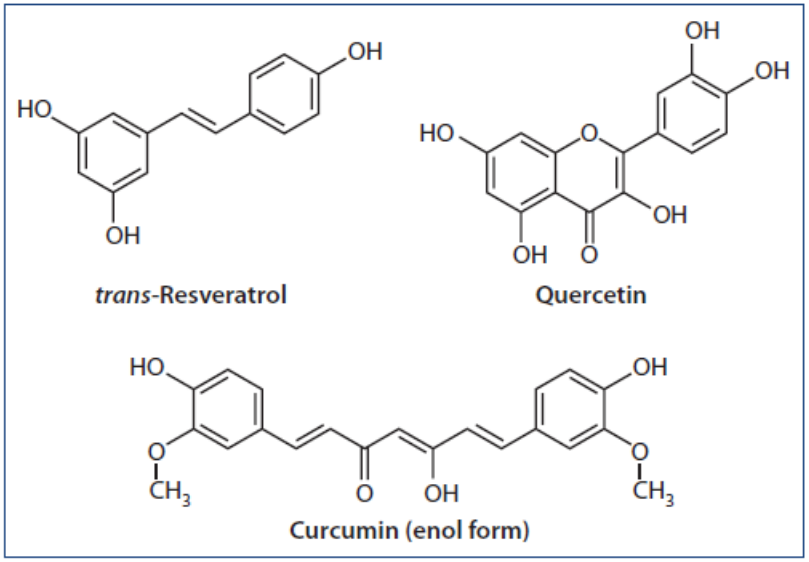
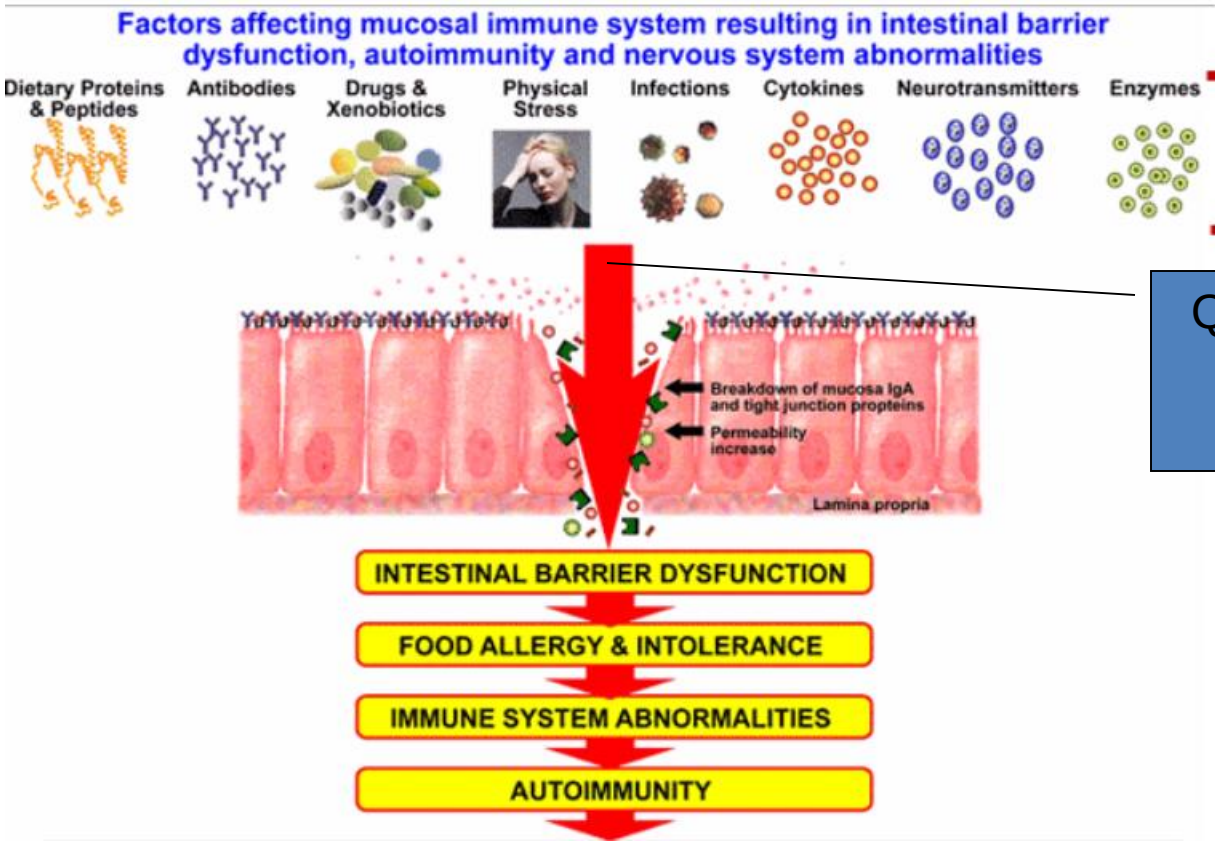


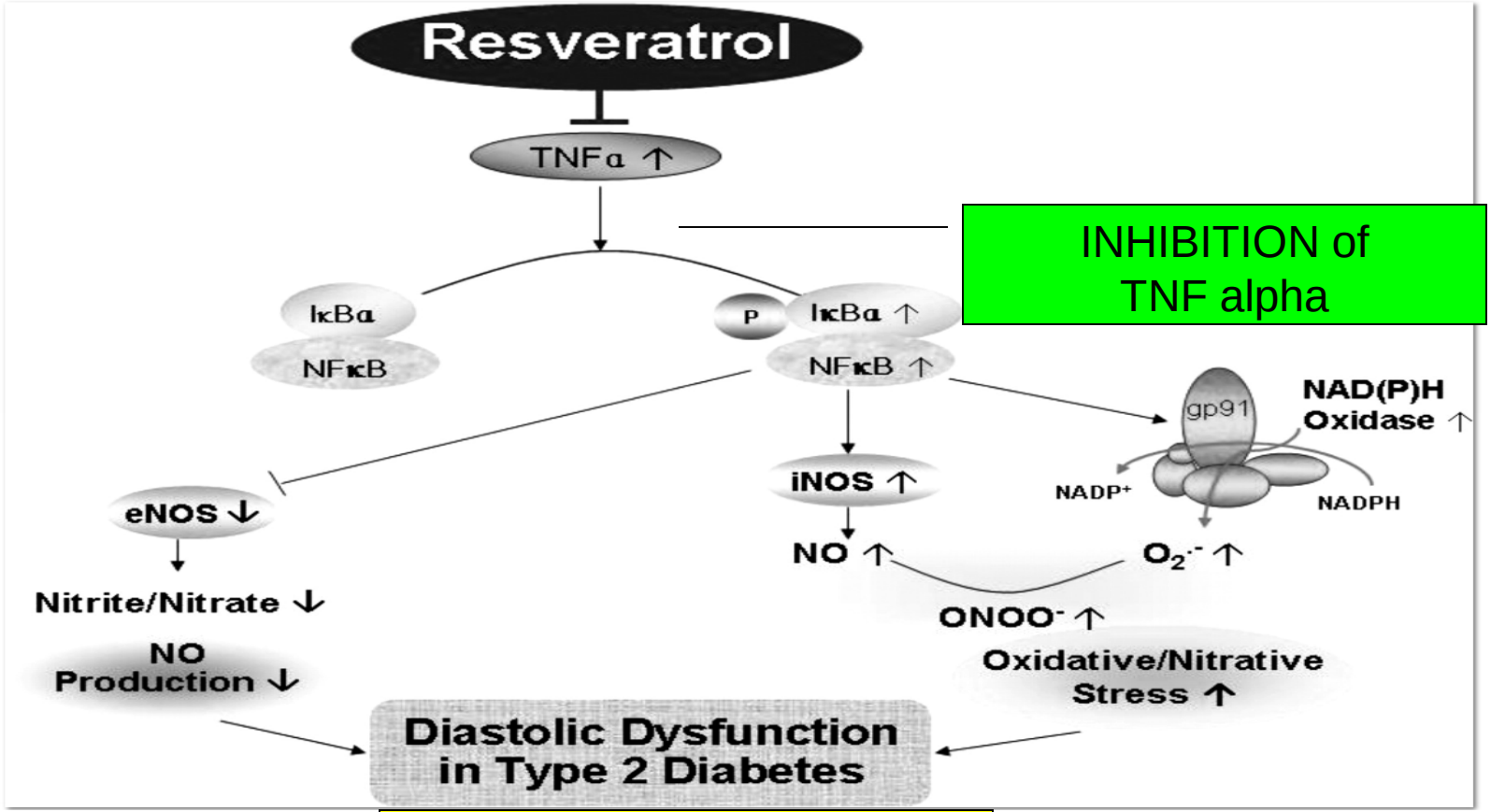
Figure 1: Molecular structures of resveratrol, quercetin and curcumin demonstrating the relative similarities of placement of hydroxyl groups along unsaturated carbon chains and the presence of several phenolic groups.

Quercetin



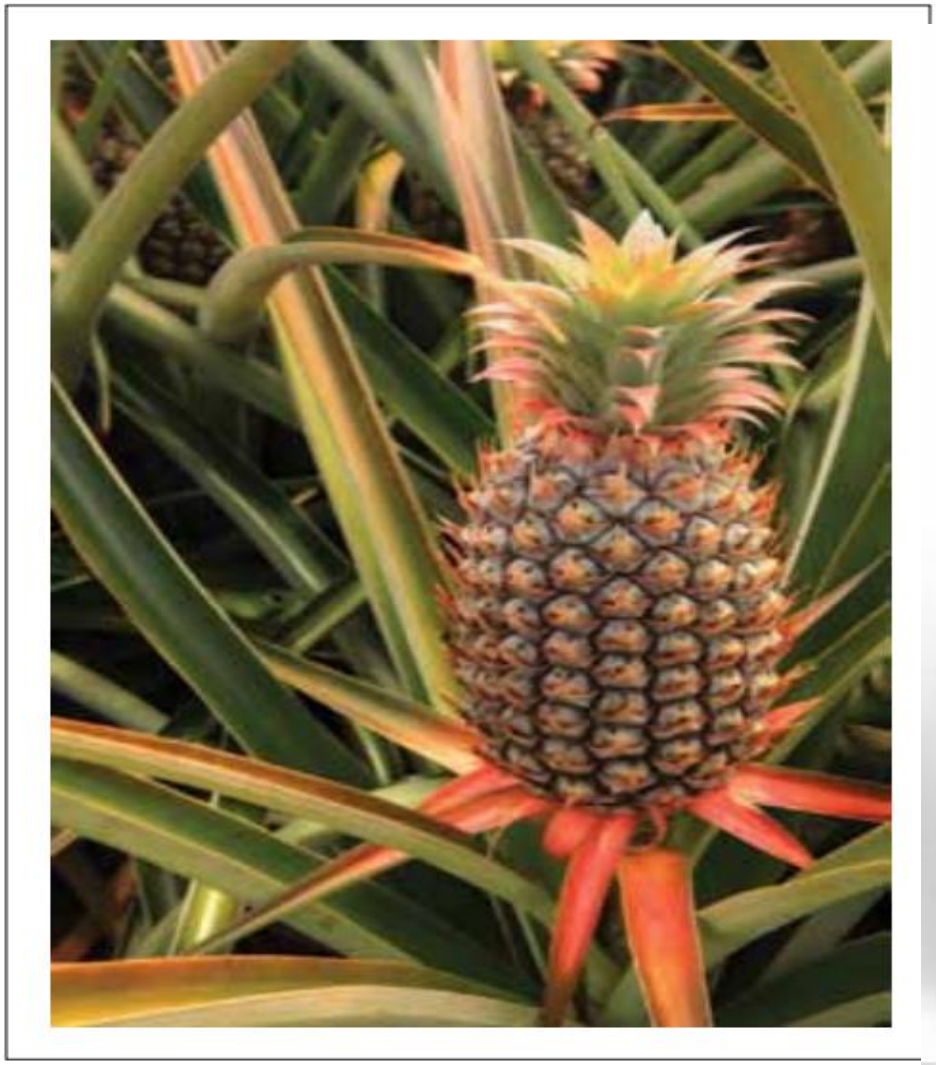
Quercetin stops leaky gut

Resveratrol in Enfla-mend



Resveratrol has its own effects on oxidative stress by blocking TNF alpha

Bromelain
Proteolytic Enzyme From Pineapple



Supplement Facts

Serving Size: 3 capsules | Servings per Container: 25

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

Minimum Constituent BioMarker Per Dose

Boswellic Acid	312 mg
Curcuminoids	60 mg
Piperine	6 mg

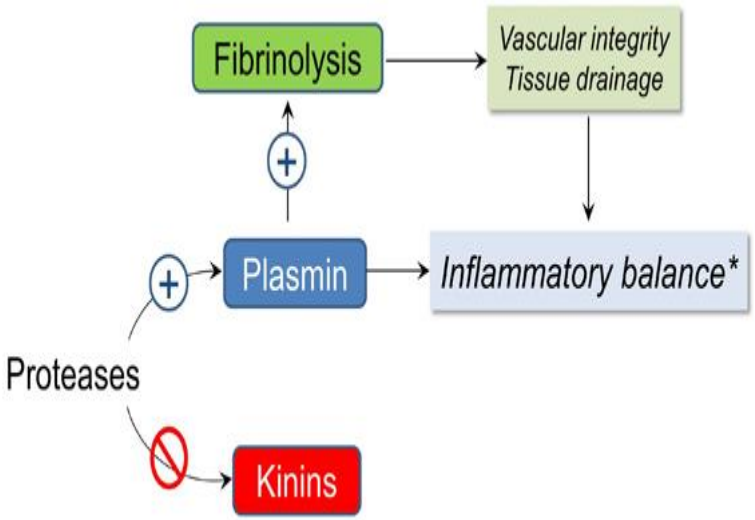
All Organic Herbs are Certified Organic

† 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

Phytother Res. 2013 Feb;27(2):199-204. doi: 10.1002/ptr.4678. Epub 2012 Apr 20.

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[1], März R, Schmolz M, Drewelow B, Eschmann K, Meiser P.

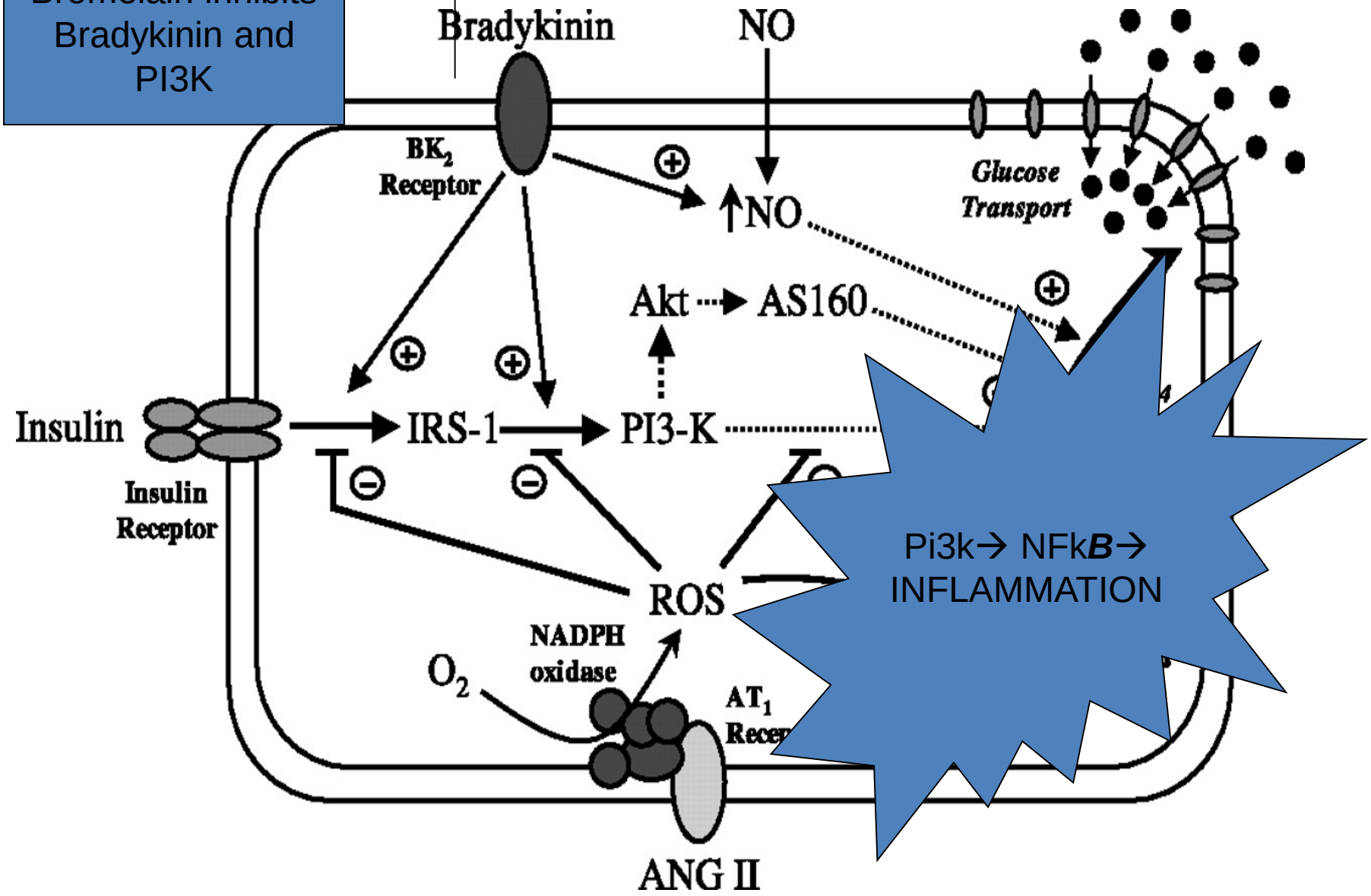
⊕ **Author information**

Abstract

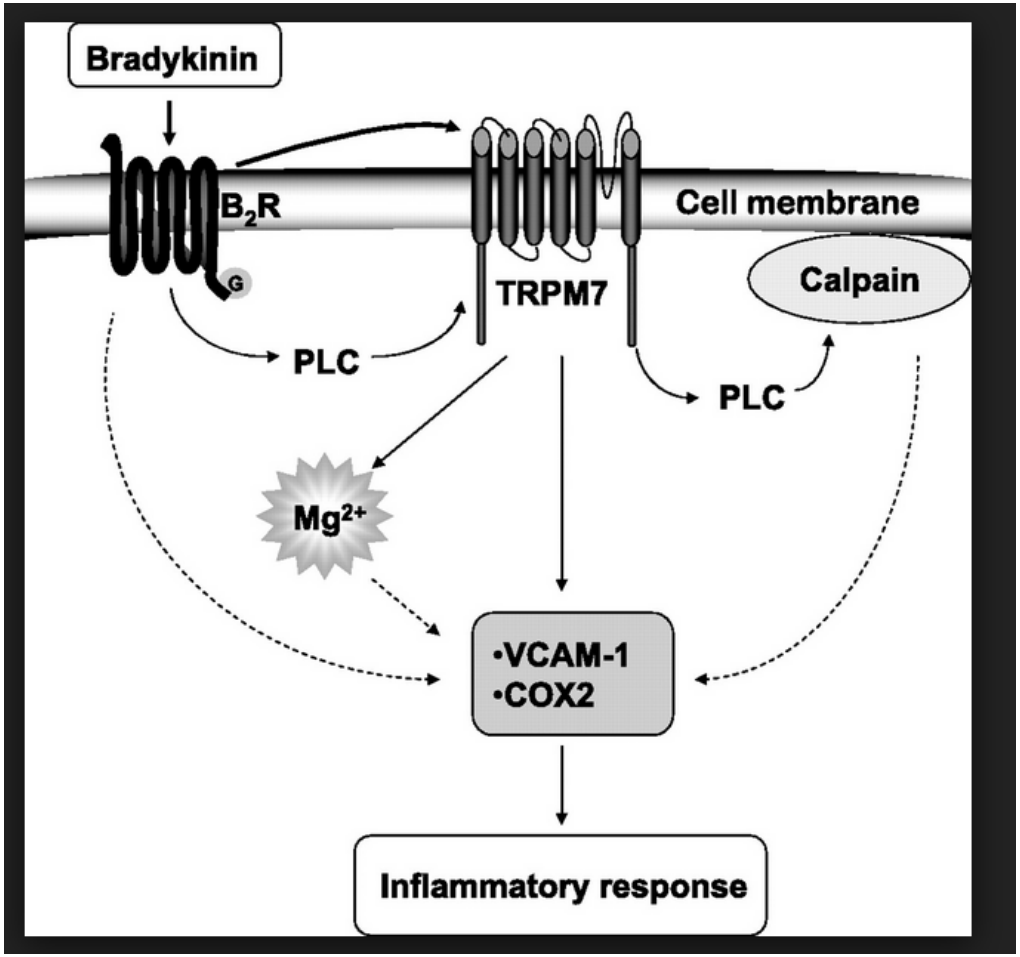
Bromelain has been used for treatment of inflammatory diseases for decades. However, the exact mechanism of action remains poorly understood. While in vitro investigations have shown conflicting effects on the release of various cytokines, no in vivo data were available. In this study, the effects on inflammation-related cytokines of two doses of bromelain were tested in a single dose placebo-controlled 3 × 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.

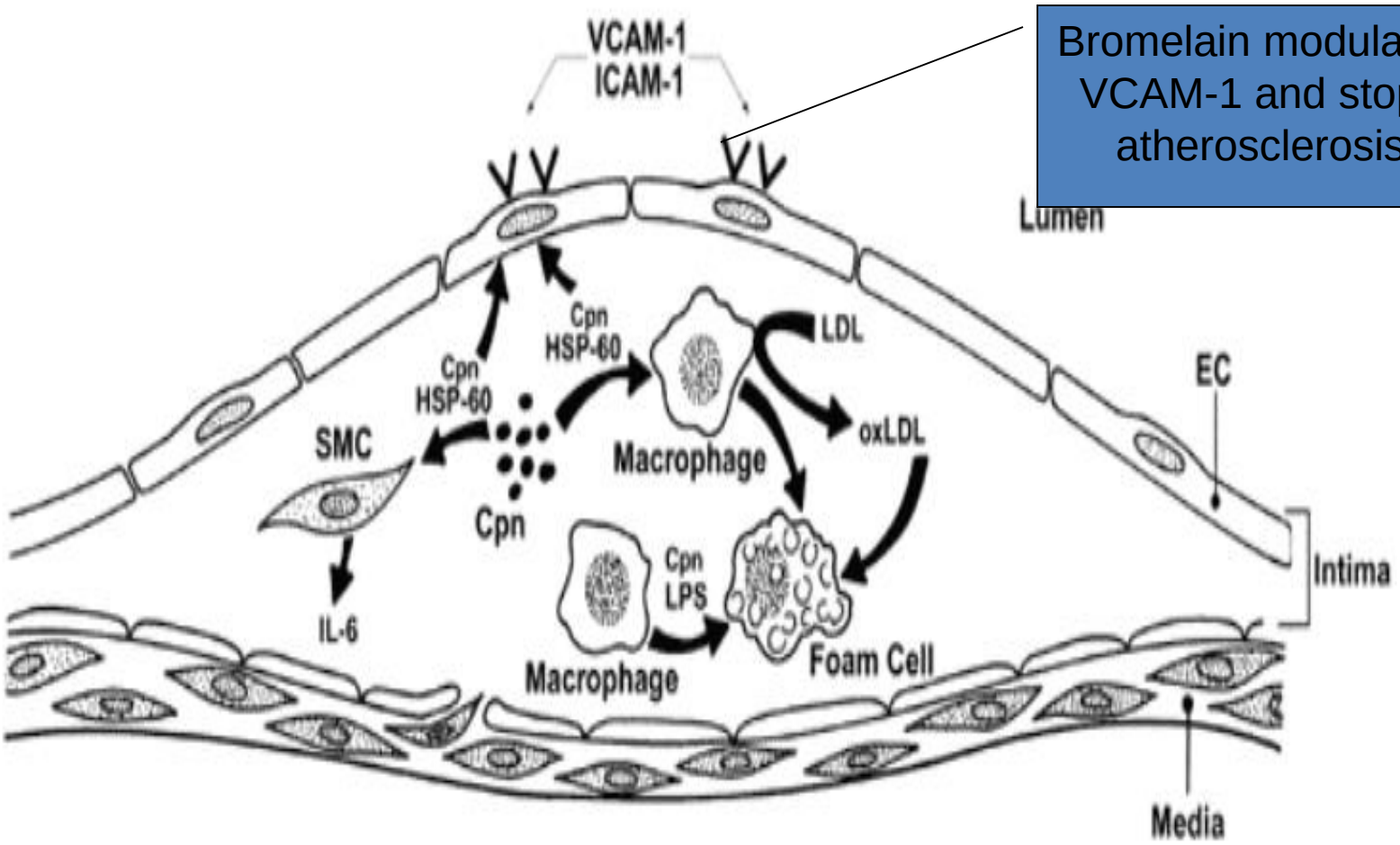
Bradykinin stimulates
PI3k and AKT which causes pain
{

Bromelain inhibits Bradykinin and PI3K



Bromelain blocks bradykinin,VCAM-1 and Cox 2





Bromelain modulated VCAM-1 and stops atherosclerosis

Bromelain versus NSAIDS: an effective and healthier choice

http://www.tbyil.com/BromelainT4.jpg

Table 4 .

Conditions in which Bromelain has Documented Therapeutic Benefits

Angina
Arthritis
Athletic and musculoskeletal injuries
Bacterial infections
Bronchitis
Cellulitis
Cutaneous Staphylococcus infection
Debridement of Burns
Dysmenorrhea
Edema
Inflammation
Maldigestion
Pancreatic insufficiency and Steatorrhea
Platelet aggregation
Pneumonia
Pyelonephritis
Rectal abscesses
Sinusitis
Surgical traumas
Thrombophlebitis

Osteoarthritis and Sports Medicine References for Bromelain

References

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4. Kerkhoffs GM, Struijs PA, de Wit C, Rahlfs VW, Zwipp H, van Dijk CN. A double blind, randomized, parallel group study on the efficacy and safety of treating acute lateral ankle sprain with oral hydrolytic enzymes. Br J Sports Med. 2004 Aug;38(4):431-5.