Clinical Studies Used In The Research and Development of Heal-n-Soothe®

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1)Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application. An update. J Ethnopharmacol. 1988 Feb-Mar;22(2):191-203.

Source: Department of Food Science and Human Nutrition, School of Tropical Agriculture, University of Hawaii, Honolulu.

Abstract
After a short description of the uses of pineapple as folk medicine by the natives of the tropics, the more important new pharmaceutical applications of bromelain, reported between 1975 and 1978, are presented. Although the exact chemical structure of all active components of bromelain is not fully determined, this substance has shown distinct pharmacological promise. Its properties include: (1) interference with growth of malignant cells; (2) inhibition of platelet aggregation; (3) fibrinolytic activity; (4) anti-inflammatory action; (5) skin debridement properties. These biological functions of bromelain, a non-toxic compound, have therapeutic values in modulating: (a) tumor growth; (b) blood coagulation; (c) inflammatory changes; (d) debridement of third degree burns; (e) enhancement of absorption of drugs. The mechanism of action of bromelain affecting these varied biological effects relates in part to its modulation of the arachidonate cascade.

2) **Source:** Emeruwa AC. Antibacterial substance from Carica papaya fruit extract. J Nat Prod. 1982 Mar-Apr;45(2):123-7.

Abstract
Ripe and unripe Carica papaya fruits (epicarp, endocarp, seeds and leaves) were extracted separately and purified. All the extracts except that of leaves produced very significant antibacterial activity on Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa and Shigella flexneri. The MIC of the substance was small (0.2-0.3 mg/ml) for gram-positive bacteria and large (1.5-4 mg/ml) for gram-negative bacteria. The substance was bactericidal and showed properties of a protein. Other proteins previously found in C. papaya did not show antibacterial activity.

3) **Source:** Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003 Jan 28;107(3):499-511.

II. Evidence for Inflammation as a Key Pathogenetic Mechanism in Atherosclerosis

A role for inflammation has become well established over the past decade or more in theories describing the atherosclerotic disease process.4,5 From a pathological viewpoint, all stages, ie, initiation, growth, and complication of the atherosclerotic plaque,6,7 might be considered to be an inflammatory response to injury. The major injurious factors that promote atherogenesisâ”cigarette smoking, hypertension, atherogenic lipoproteins, and hyperglycemia”are well established. These

risk factors give rise to a variety of noxious stimuli that elicit secretion of both leukocyte soluble adhesion molecules, which facilitate the attachment of monocytes to endothelial cells, and chemotactic factors, which encourage the monocytes' migration into the subintimal space. The transformation of monocytes into macrophages and the uptake of cholesterol lipoproteins are thought to initiate the fatty streak. Further injurious stimuli may continue the attraction and accumulation of macrophages, mast cells, and activated T cells within the growing atherosclerotic lesion. Oxidized low-density lipoproteins may be one of several factors that contribute to loss of smooth muscle cells through apoptosis in the atherosclerotic plaque cap, and secretion of metalloproteinases and other connective tissue enzymes by activated macrophages may break down collagen, weakening the cap and making it prone to rupture. This disruption of the atherosclerotic plaque then exposes the atheronecrotic core to arterial blood, which induces thrombosis. Thus, virtually every step in atherogenesis is believed to involve cytokines, other bioactive molecules, and cells that are characteristic of inflammation.
http://circ.ahajournals.org/content/107/3/499.full

4) Leonard BE. Inflammation, depression and dementia: are they connected? Neurochem Res. 2007 Oct;32(10):1749-56.

Source: Department of Psychiatry and Neuropsychology, Brain and Behaviour Research Institute, University of Maastricht, Maastricht, The Netherlands. belucg@iol.ie

Abstract
Chronic inflammation is now considered to be central to the pathogenesis not only of such medical disorders as cardiovascular disease, multiple sclerosis, diabetes and cancer but also of major depression. If chronic inflammatory changes are a common feature of depression, this could predispose depressed patients to neurodegenerative changes in later life. Indeed there is now clinical evidence that depression is a common antecedent of Alzheimer's disease and may be an early manifestation of dementia before the cognitive declines becomes apparent. This review summarises the evidence that links chronic low grade inflammation with changes in brain structure that could precipitate neurodegenerative changes associated with Alzheimer's disease and other dementias. For example, neuronal loss is a common feature of major depression and dementia. It is hypothesised that the progress from depression to dementia could result from the activation of macrophages in the blood, and microglia in the brain, that release pro-inflammatory cytokines. Such cytokines stimulate a cascade of inflammatory changes (such as an increase in prostaglandin E2, nitric oxide in addition to more pro-inflammatory cytokines) and a hypersecretion of cortisol. The latter steroid inhibits protein synthesis thereby reducing the synthesis of neurotrophic factors and preventing reairto damages neuronal networks. In addition, neurotoxic end products of the tryptophan-kynurenine pathway, such as quinolinic acid, accumulate in astrocytes and neurons in both depression and dementia. Thus increased neurodegeneration, reduced neuroprotection and neuronal repair are common pathological features of major depression and dementia. Such changes may help to explain why major depression is a frequent prelude to dementia in later life.

5) Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP. The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. Diabetes. 2001 Oct;50(10):2384-9.

Source: Division of Endocrinology, Kaiser Permanente of Georgia, and the Division of Endocrinology, Emory University School of Medicine, Atlanta, Georgia 30084, USA. joshua.barzilay@kp.org

Abstract
Several studies suggest that inflammation plays a role in the pathogenesis of some glucose disorders in adults. We tested this hypothesis in a longitudinal cohort study of older individuals who had normal fasting glucose (FG) values at baseline. We compared the baseline levels of six inflammatory markers in participants who had developed glucose disorders at follow-up with those of participants whose FG remained normal at follow-up. Participants were members of the Cardiovascular Health Study, a prospective study of risk factors for cardiovascular disease in adults > or =65 years. All 5,888 participants had baseline testing, including FG and markers of inflammation: white blood cell and platelet counts and albumin, fibrinogen, C-reactive protein (CRP), and factor VIIIc levels. At 3-4 years of follow-up, 4,481 (84.5%) of those who were alive had FG levels retested. Participants who developed diabetes (n = 45) had higher median levels of CRP at baseline than those who remained normoglycemic. On multivariate analysis, those with elevated CRP levels (75th percentile [2.86 mg/l] vs. 25th percentile [0.82 mg/l]) were 2.03 times (95% confidence intervals, 1.44-2.86) more likely to have diabetes on follow-up. Adjustment for confounders and other inflammatory markers did not appreciably change this finding. There was no relationship between the development of diabetes and other markers of inflammation. Inflammation, as measured by CRP levels, is associated with the development of diabetes in the elderly. Understanding the role of inflammation in the pathogenesis of glucose disorders in this age-group may lead to better classification and treatment of glucose disorders among them.

6) Festa A, D'Agostino R Jr, Howard G, MykkÃ¤nen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation. 2000 Jul 4;102(1):42-7.

Source: Department of Medicine, University of Texas Health Science Center at San Antonio, 78228-3900, USA. festa@magnet.at

Abstract
BACKGROUND:
Inflammation has been suggested as a risk factor for the development of atherosclerosis. Recently, some components of the insulin resistance syndrome (IRS) have been related to inflammatory markers. We hypothesized that insulin insensitivity, as directly measured, may be associated with inflammation in nondiabetic subjects.

METHODS AND RESULTS:
We studied the relation of C-reactive protein (CRP), fibrinogen, and white cell count to components of IRS in the nondiabetic population of the Insulin Resistance Atherosclerosis Study (IRAS) (n=1008; age, 40 to 69 years; 33% with impaired glucose tolerance), a multicenter, population-based study. None of the subjects had clinical coronary artery disease. Insulin sensitivity (S(I)) was measured by a frequently sampled intravenous glucose tolerance test, and CRP was measured by a highly sensitive competitive immunoassay. All 3 inflammatory markers were correlated with several components of the IRS. Strong associations were found between CRP and measures of body fat (body mass index, waist circumference), S(I), and fasting insulin and proinsulin (all correlation coefficients >0.3, P<0.0001). The associations were consistent among the 3 ethnic groups of the IRAS. There was a linear increase in CRP levels with an increase in the number of metabolic disorders. Body mass index, systolic blood pressure, and S(I) were related to CRP levels in a multivariate linear regression model.

CONCLUSIONS:
We suggest that chronic subclinical inflammation is part of IRS. CRP, a predictor of cardiovascular events in previous reports, was independently related to S(I). These findings suggest potential benefits of anti-inflammatory or insulin-sensitizing treatment strategies in healthy individuals with features of IRS.

INFLAMMATION IS ASSOCIATED WITH INSULIN RESISTANCE.

7) Walker JA, Cerny FJ, Cotter JR, Burton HW. Attenuation of contraction-induced skeletal muscle injury by bromelain. Med Sci Sports Exerc. 1992 Jan;24(1):20-5.

Source: Department of Physical Therapy/Exercise Science, State University of New York, Buffalo 14214.

Abstract
The proteolytic enzyme, bromelain, reportedly has therapeutic effects in the treatment of inflammation and soft tissue injuries. We tested the hypothesis that bromelain attenuates skeletal muscle injury induced by lengthening contractions. The left extensor digitorum longus (EDL) muscle of anesthetized hamsters was injured using a motorized foot pedal which repeatedly flexed/extended the foot through a range of 125 degrees. The EDL muscle was electrically stimulated for 400 ms during plantarflexion. Animals were assigned randomly to either a 0-d group (evaluated 3-h post-injury) or to untreated (UT) or bromelain-treated (T) groups, evaluated 3, 7, or 14 d post-injury. Following injury, T received 5 mg.kg-1 b.w. of bromelain, twice daily. Maximum isometric tetanic force (Po) was measured in vitro, then muscles were fixed, sectioned, and examined for evidence of fiber damage. The Po of injured muscles from T were higher than Po of injured muscles from UT at 3 (18.7 +/- 0.4 vs 16.5 +/- N.cm-2 and 14 d (20.5 +/- 0.6 vs 18.2 +/- 0.6 N.cm-2) (P less than 0.05), but not 7 d (19.5 +/-0.7 vs 17.7 +/- 0.8 N.cm-2). The Po of UT injured muscles were significantly lower than Po of contralateral control muscles at all time periods. Po of injured muscles from T were lower than Po from control muscles at 3 and 7 d (P less than 0.05), but not 14 d. The number of intact fibers of 3-d UT injured muscles was lower than the number of intact fibers in control muscles ($P < 0.05$). No difference in fiber number between controls and the 3-d treated group was observed. Thus, daily oral bromelain treatments of 10 mg +/- kg-1 attenuated the development of contraction-induced injury in hamster EDL muscles.

8) Walker AF, Bundy R, Hicks SM, Middleton RW. Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults. Phytomedicine. 2002 Dec;9(8):681-6.

Source: Hugh Sinclair Unit of Human Nutrition, The University of Reading, UK. a.f.walker@reading.ac.uk

Abstract
There is preliminary clinical evidence to support the contention that the anti-inflammatory and analgesic properties of bromelain help to reduce symptoms of osteo- and rheumatoid arthritis. However, there have been no controlled studies of its effects on joint health in healthy subjects who lack such diagnosis. The current study investigated the effects of bromelain on mild acute knee pain of less than 3 months duration in otherwise healthy adults. The study was an open, dose-ranging postal study in volunteers who had been recruited through newspaper and magazine articles. Two validated questionnaires (WOMAC knee health Index and the Psychological Well-Being Index) were completed at baseline and after one month's intervention with bromelain,

randomly allocated to volunteers as either 200 mg or 400 mg per day. Seventy seven subjects completed the study. In both treatment groups, all WOMAC symptom dimension scores were significantly reduced compared with baseline, with reductions in the final battery (total symptom score) of 41 and 59% (P = 0.0001 and <0.0001) in the low and high dose groups respectively. In addition, improvements in total symptom score (P = 0.036) and the stiffness (P = 0.026) and physical function (P = 0.021) dimensions were significantly greater in the high-dose (400 mg per day) compared with the low-dose group. Compared to baseline, overall psychological well-being was significantly improved in both groups after treatment (P = 0.015 and P = 0.0003 in the low and high dose groups respectively), and again, a significant dose-response relationship was observed. We conclude that bromelain may be effective in ameliorating physical symptoms and improving general well-being in otherwise healthy adults suffering from mild knee pain in a dose-dependant manner. Double blind, placebo-controlled studies are now warranted to confirm these results.

9) Ley CM, Tsiami A, Ni Q, Robinson N. A review of the use of bromelain in cardiovascular diseases. Zhong Xi Yi Jie He Xue Bao. 2011 Jul;9(7):702-10.

Source: Social Care and Human Sciences, School of Psychology, University of West London, Middlesex, TW8 9GA, UK.

Abstract
BACKGROUND:
In 2004 an estimated 17.1 million people died from cardiovascular diseases (CVDs) worldwide, representing 29% of all global deaths. According to the American Heart Association, heart disease and stroke are the main cause of death and disability among people with type 2 diabetes. Additional safe and effective approaches are needed for the prevention and management of CVDs which may include nutritional supplements.

OBJECTIVE: To identify the potential of bromelain (a food supplement) on the risk factors associated with CVDs.

SEARCH STRATEGY:
An electronic and manual search was conducted during November 2009 to March 2010. The databases searched included: Ovid MEDLINE; All EBM Reviews-Cochrane Database of Systematic Reviews (Cochrane DSR), American College of Physicians (ACP) Journal Club, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Methodology Register (CMR), Health Technology Assessment (HTA) and National Health Service Economic Evaluation Database (NHSEED); Allied and Complementary Medicine (AMED); British Nursing Index and Archive; EMBASE; Health Management Information Consortium (HMIC); ScienceDirect and Electronic Thesis Online Services (ETHOS). Only papers in the English language were included.

INCLUSION CRITERIA:
Randomised controlled trials (RCTs), human studies, animal studies and experimental studies related to bromelain for CVDs. Data extraction and analysis: The quality assessment of all the selected studies was conducted by the authors. Data from 3 animal trials and 3 human trials were included in the review. Data collected included: type of trial, drug dosage, duration, outcome measures, characteristics of bromelain used, significance of results and conclusion.

RESULTS:
Out of 223 papers retrieved, 6 papers met the inclusion criteria and could be included in the review. These comprised of 3 animal and 3 human trials, each of which investigated the use of bromelain for CVDs. Results suggested that bromelain could be used for treating acute thrombophlebitis, as it decreases aggregation of blood platelets, has a cardio-protective effect, ameliorates rejection-induced arterial wall remodelling, prevents thrombin-induced human platelet aggregation as well as reduces thrombus formation.

CONCLUSION:
No substantive study of bromelain and clinical CVDs has been carried out in human populations. Only a few studies on bromelain and CVDs were published from 1948 to 2010. This may be an area worthy to be explored in future CVDs research.

10) Loskutoff DJ, Quigley JP. PAI-1, fibrosis, and the elusive provisional fibrin matrix. J Clin Invest. 2000 Dec;106(12):1441-3.

Whether induced surgically or by hypertension, infections, extreme heat, or caustic chemicals, tissue injury invariably leads to vasodilatation, with subsequent leakage of plasma proteins into the connective tissues, rapid activation of the coagulation cascade, and deposition of fibrin. A central paradigm in the field is that the fibrin is organized into a "provisional fibrin matrix," which acts as a road map to direct the migration of invading cells. Leukocytes and possibly fibroblasts migrate into the area and elaborate cytokines which, in turn, stimulate resident cells to synthesize and deposit collagens and other insoluble fibrillar components into the evolving extracellular matrix (ECM). Fibrotic disease occurs when normal control of this process is compromised and excess fibrous material accumulates in the tissues. It is generally assumed that the persistence of fibrin in the matrix promotes fibrosis, and that the extent of fibrosis is limited by that remove the fibrin (i.e., the fibrinolytic system). In a recent issue of the JCI, Hattori et al. (1) affirm previous suggestions that plasminogen activator inhibitor-1 (PAI-1) promotes pathological fibrosis but challenges the concept that fibrin is required.

11) Felton GE. Fibrinolytic and antithrombotic action of bromelain may eliminate thrombosis in heart patients. Med Hypotheses. 1980 Nov;6(11):1123-33.

Abstract
It has been established that a bromelain plasminogen activator will produce plasmin in rat experiments. In addition the plasmin cleaves Hageman factor in a way that leads to a strong release of kallikrein but a weak release of thrombin. A possible mechanism is suggested to explain how the body can maintain thrombin at a level too low to cause platelet aggregation but adequate to stimulate release of prostaglandins and enzymes for more than 24 hours from a single dose of the pineapple enzymes. Since bromelain therapy leads to formation of platelets with increased resistance to aggregation, it is obvious that the dominant endogenous prostaglandins being produced must be from the group that increases platelet cyclicAMP levels (prostacyclin, PGE1, etc.). The combination of fibrinolytic and antithrombic properties appear to be effective and two large scale tests on heart patients have shown a practically complete elimination of thrombosis.

12) Bracale G, Selvetella L. [Clinical study of the efficacy of and tolerance to seaprose S in inflammatory venous disease. Controlled study versus serratio-peptidase]. Minerva Cardioangiol. 1996 Oct;44(10):515-24. [Article in Italian]

Source: Divisione di Chirurgia Vascolare, UniversitÃ degli Studi di Napoli, Federico II.

Abstract
This study was designed to compare the efficacy and safety of seaprose S and serratio-peptidase in the treatment of venous inflammatory disease. Forty patients entered the study (11 males, 29 females), mean age 54.3 years (range 30-77), mean weight 74.8 kg (range 51-96), with superficial thrombophlebitis. The trial was conducted following a controlled, between patients, randomized experimental design. Seaprose S was administered as 30 mg tablets at a daily dosage of 90 mg (one tab t.i.d.), and serratio-peptidase as 5 mg tablets, at a dose of 30 mg per day (two tabs t.i.d.), both orally, for 14 days. Twenty patients received seaprose S and 20 serratio-peptidase. The findings indicate that seaprose S was more effective and better tolerated than serratio-peptidase. Although the group of patients assigned to seaprose S had considerably more severe initial symptoms, by the end of treatment spontaneous pain was reduced 68.7% from the baseline mean score (from 3.2 to 1.0), as compared with a 63.3% reduction in the serratio-peptidase group (from 3.0 to 1.1). Pain on pressure was reduced 61.1% with seaprose S (from 3.6 to 1.4), compared to 57.6% with the reference treatment (from 3.3 to 1.4). Edema was reduced respectively 75% (from 1.6 to 0.4) and 56.2% (from 1.6 to 0.7); erythema diminished 72.4% (from 2.9 to 0.8) and 58.3% (from 2.4 to 1.0); nighttime cramps were 61.1% less (from 1.8 to 0.7) compared with 52.9% (from 1.7 to 0.8); hemorrhagic suffusion was 53.3% less (from 1.5 to 0.7) compared with 41.7% (from 1.2 to 0.7); cutaneous dystrophy was reduced by 11.1% (from 1.8 to 1.6) and 7.7% (from 1.3 to 1.2). At the end of the treatment with seaprose S efficacy was assessed as good or excellent in 85% of the cases, compared with 65% for serratio-peptidase. Seaprose S caused no adverse reactions. During serratio-peptidase treatment one patient reported diarrhea, requiring temporary dosage reduction and specific treatment. It can thus be confirmed that seaprose S was effective and well tolerated in patients with inflammatory venous diseases.

13) Braga PC, Moretti M, Piacenza A, Montoli CC, Guffanti EE. Effects of seaprose on the rheology of bronchial mucus in patients with chronic bronchitis. A double-blind study vs placebo. Int J Clin Pharmacol Res. 1993;13(3):179-85.

Source: Centre for Respiratory Pharmacology, School of Medicine, University of Milan, Italy.

Abstract
There are changes in the rheological characteristics of mucus (viscoelasticity) in several pulmonary pathologies, and especially in chronic bronchitis. Seaprose, a proteolytic enzyme, is one of the pharmacological possibilities for affecting the rheology of bronchial mucus to correct mucostasis and improve its clearance. The action of this drug on the viscoelasticity of bronchial mucus was assessed in a double-blind vs placebo study with 20 randomly balanced chronic bronchitis patients using a new kind of portable rheometer with special features designed for routine bronchial mucus analysis in clinical practice at the patient's bedside. It was found that in the group of patients who were given the placebo, there were no particular changes in the rheological behaviour of mucus, while in those patients who were given seaprose there were significant changes in both viscosity and elasticity at the end of treatment. Eight days after the end of treatment with seaprose, there was still a significant beneficial effect on the viscoelasticity of mucus and a sort of "post-mucolytic effect" can be postulated. Seaprose also had antiinflammatory

action, and since in chronic bronchitis there are variable degrees of inflammations, its beneficial long-lasting effect could also be ascribed to this concomitant action.

14) Moretti M, Bertoli E, Bulgarelli S, Testoni C, Guffanti EE, Marchioni CF, Braga PC. Effects of seaprose on sputum biochemical components in chronic bronchitic patients: a double-blind study vs placebo. Int J Clin Pharmacol Res. 1993;13(5):275-80.

Source: Istituto di Tisiologia e Malattie dell' Apparato Respiratorio, UniversitÃ di Modena, Italy.

Abstract
Seaprose is a semialkaline proteinase endowed with proteolytic effect and antiinflammatory activity tested in different clinical trials. There is clinical evidence that seaprose reduces sputum viscoelastic properties in chronic hypersecretory bronchitis. The present study evaluated (in a double-blind design vs. placebo) the activity of seaprose on bronchial inflammation, mucus glycoprotein secretion and bronchial humoral defence mechanism in chronic bronchitic patients clinically stable (10 per group). Markers of bronchial inflammation (albumin, albumin/total protein ratio) and bronchial infection (DNA), of mucus glycoproteins (fucose and N-acetylneuraminic acid) and of humoral defence mechanism (secretory-IgA) were tested in sputum. We found that ten-day treatment with seaprose (90 mg/day) reduced sputum albumin during the observation period, the difference being statistically significant at the 18th day. The sputum albumin/total protein ratio also decreased by 50% at the end of the study. In the same group, sputum DNA, secretory-IgA, fucose and N-acetylneuraminic acid remained unchanged after treatment. The placebo group did not show any significant changes in the sputum marker substances. This study provides experimental evidence for the antiinflammatory activity of seaprose on bronchial mucosa in chronic bronchitic patients studied in a stable phase of their disease. Furthermore the drug does not seem to affect mucus glycoprotein secretion or secretory-IgA production.

15) Fitzhugh DJ, Shan S, Dewhirst MW, Hale LP.Bromelain treatment decreases neutrophil migration to sites of inflammation. Clin Immunol. 2008 Jul;128(1):66-74.

Source: Department of Pathology, DUMC 3712, Duke University Medical Center, Durham, NC 27710, USA.

Abstract
Bromelain, a mixture of proteases derived from pineapple stem, has been reported to have therapeutic benefits in a variety of inflammatory diseases, including murine inflammatory bowel disease. The purpose of this work was to understand potential mechanisms for this anti-inflammatory activity. Exposure to bromelain in vitro has been shown to remove a number of cell surface molecules that are vital to leukocyte trafficking, including CD128a/CXCR1 and CD128b/CXCR2 that serve as receptors for the neutrophil chemoattractant IL-8 and its murine homologues. We hypothesized that specific proteolytic removal of CD128 molecules by bromelain would inhibit neutrophil migration to IL-8 and thus decrease acute responses to inflammatory stimuli. Using an in vitro chemotaxis assay, we demonstrated a 40% reduction in migration of bromelain- vs. sham-treated human neutrophils in response to rhIL-8. Migration to the bacterial peptide analog fMLP was unaffected, indicating that bromelain does not induce a global defect in leukocyte migration. In vivo bromelain treatment generated a 50-85% reduction in neutrophil migration in 3 different murine models of leukocyte migration into the inflamed peritoneal cavity. Intravital microscopy demonstrated that although in vivo bromelain treatment transiently decreased

leukocyte rolling, its primary long-term effect was abrogation of firm adhesion of leukocytes to blood vessels at the site of inflammation. These changes in adhesion were correlated with rapid re-expression of the bromelain-sensitive CD62L/L-selectin molecules that mediate rolling following in vivo bromelain treatment and minimal re-expression of CD128 over the time period studied. Taken together, these studies demonstrate that bromelain can effectively decrease neutrophil migration to sites of acute inflammation and support the specific removal of the CD128 chemokine receptor as a potential mechanism of action.

16) Berg A, Peters M, Deibert P, KÃ¶nig D, Birnesser H. Bromelain - Overview and diskussion of therapeutic application and its importance in sports medicine and sports traumatology. Deutsche Zeitschrift FÃ¼r Sportmedizin. Jahrgang 56, Nr. 1 (2005) [German]

Bromelain, a plant-derived proteolytic enzyme, is commercially available and has been approved as a pharmaceutical preparation. Bromelain is mainly prescribed for the treatment and prevention of inflammatory, posttraumatic or postoperative swelling. The mode of action has been investigated in cell-culture and animal experiments. In controlled clinical studies in humans, orally-administered Bromelain has proven its
pharmaceutical efficacy by significantly reducing soft-tissue edema in the above-mentioned conditions. Therefore, Bromelain is also of interest for sports medicine and sports traumatology. Oral treatment with Bromelain has few and only transient and mild side-effects and may therefore be an effective alternative for non-steroidal anti-inflammatory drugs in the treatment of posttraumatic edema and swelling. This review summarizes present knowledge regarding the mode of action of Bromelain and gives an overview about its practical applications from a sports-medical point of view.

17) Hong J, Bose M, Ju J, Ryu JH, Chen X, Sang S, Lee MJ, Yang CS. Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: effects on cytosolic phospholipase A(2), cyclooxygenases and 5-lipoxygenase. Carcinogenesis. 2004 Sep;25(9):1671-9

Source: Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA.

Abstract
Aberrant arachidonic acid metabolism is involved in the inflammatory and carcinogenic processes. In this study, we investigated the effects of curcumin, a naturally occurring chemopreventive agent, and related beta-diketone derivatives on the release of arachidonic acid and its metabolites in the murine macrophage RAW264.7 cells and in HT-29 human colon cancer cells. We also examined their effects on the catalytic activities and protein levels of related enzymes: cytosolic phospholipase A(2) (cPLA(2)), cyclooxygenases (COX) as well as 5-lipoxygenase (5-LOX). At 10 micro M, dibenzoylmethane (DBM), trimethoxydibenzoylmethane (TDM), tetrahydrocurcumin (THC) and curcumin effectively inhibited the release of arachidonic acid and its metabolites in lipopolysaccharide (LPS)-stimulated RAW cells and A23187-stimulated HT-29 cells. Inhibition of phosphorylation of cPLA(2), the activation process of this enzyme, rather than direct inhibition of cPLA(2) activity appears to be involved in the effect of curcumin. All the curcuminoids (10 micro M) potently inhibited the formation of prostaglandin E(2) (PGE(2)) in LPS-stimulated RAW cells. Curcumin (20 micro M) significantly inhibited LPS-induced COX-2 expression; this effect, rather

than the catalytic inhibition of COX, may contribute to the decreased PGE(2) formation. Without LPS-stimulation, however, curcumin increased the COX-2 level in the macrophage cells. Studies with isolated ovine COX-1 and COX-2 enzymes showed that the curcuminoids had significantly higher inhibitory effects on the peroxidase activity of COX-1 than that of COX-2. Curcumin and THC potently inhibited the activity of human recombinant 5-LOX, showing estimated IC(50) values of 0.7 and 3 micro M, respectively. The results suggest that curcumin affects arachidonic acid metabolism by blocking the phosphorylation of cPLA(2), decreasing the expression of COX-2 and inhibiting the catalytic activities of 5-LOX. These activities may contribute to the anti-inflammatory and anticarcinogenic actions of curcumin and its analogs.

18) Sreejayan, Rao MN. Nitric oxide scavenging by curcuminoids. J Pharm Pharmacol. 1997 Jan;49(1):105-7.

Source: Department of Pharmaceutical Chemistry, College of Pharmaceutical Sciences, Manipal, India.

Abstract
Because curcumin, a compound with anti-inflammatory and anticancer activity, inhibits induction of nitric oxide synthase in activated macrophages and has been shown to be a potent scavenger of free radicals we have investigated whether it can scavenge nitric oxide directly. Curcumin reduced the amount of nitrite formed by the reaction between oxygen and nitric oxide generated from sodium nitroprusside. Other related compounds, e.g. demethoxycurcumin, bisdemethoxycurcumin and diacetylcurcumin were as active as curcumin, indicating that the methoxy and the phenolic groups are not essential for the scavenging activity. The results indicate curcumin to be a scavenger of nitric oxide. Because this compound is implicated in inflammation and cancer, the therapeutic properties of curcumin against these conditions might be at least partly explained by its free-radical scavenging properties, including those toward nitric oxide.

19) Otsuki N, Dang NH, Kumagai E, Kondo A, Iwata S, Morimoto C. Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects. J Ethnopharmacol. 2010 Feb 17;127(3):760-7.

Source: Division of Clinical Immunology, Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan.

Abstract
AIM OF THE STUDY:
Various parts of Carica papaya Linn. (CP) have been traditionally used as ethnomedicine for a number of disorders, including cancer. There have been anecdotes of patients with advanced cancers achieving remission following consumption of tea extract made from CP leaves. However, the precise cellular mechanism of action of CP tea extracts remains unclear. The aim of the present study is to examine the effect of aqueous-extracted CP leaf fraction on the growth of various tumor cell lines and on the anti-tumor effect of human lymphocytes. In addition, we attempted to identify the functional molecular weight fraction in the CP leaf extract.

MATERIALS AND METHODS:
The effect of CP extract on the proliferative responses of tumor cell lines and human peripheral blood mononuclear cells (PBMC), and cytotoxic activities of PBMC were assessed by [(3)H]-

thymidine incorporation. Flow cytometric analysis and measurement of caspase-3/7 activities were performed to confirm the induction of apoptosis on tumor cells. Cytokine productions by PBMC were measured by ELISA. Gene profiling of the effect of CP extract treatment was performed by microarray analysis and real-time RT-PCR.

RESULTS:
We observed significant growth inhibitory activity of the CP extract on tumor cell lines. In PBMC, the production of IL-2 and IL-4 was reduced following the addition of CP extract, whereas that of IL-12p40, IL-12p70, IFN-gamma and TNF-alpha was enhanced without growth inhibition. In addition, cytotoxicity of activated PBMC against K562 was enhanced by the addition of CP extract. Moreover, microarray analyses showed that the expression of 23 immunomodulatory genes, classified by gene ontology analysis, was enhanced by the addition of CP extract. In this regard, CCL2, CCL7, CCL8 and SERPINB2 were representative of these upregulated genes, and thus may serve as index markers of the immunomodulatory effects of CP extract. Finally, we identified the active components of CP extract, which inhibits tumor cell growth and stimulates anti-tumor effects, to be the fraction with M.W. less than 1000.

CONCLUSION:
Since Carica papaya leaf extract can mediate a Th1 type shift in human immune system, our results suggest that the CP leaf extract may potentially provide the means for the treatment and prevention of selected human diseases such as cancer, various allergic disorders, and may also serve as immunoadjuvant for vaccine therapy.

20) Gayathri B, Manjula N, Vinaykumar KS, Lakshmi BS, Balakrishnan A. Pure compound from Boswellia serrata extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition of TNFalpha, IL-1beta, NO and MAP kinases. Int Immunopharmacol. 2007 Apr;7(4):473-82.

Source: Centre for Biotechnology, Anna University, Chennai, India.

Abstract
The aim of the present study is to probe the anti-inflammatory potential of the plant Boswellia serrata by studying the effect of the crude extract and the pure compound isolated from it on key inflammatory mediators like TNFalpha, IL-1beta, and NO thus enabling the understanding of the key signaling events involved. The crude methanolic extract and the pure compound were analysed for their inhibitory effect on TNFalpha, IL-1beta and IL-6. The results demonstrated that all three cytokines are down regulated when PBMCs are cultured in the presence of crude extract or the pure compound at various time points. Observations on Th1/Th2 cytokines revealed marked down regulation of Th1 cytokines IFNgamma and IL-12 while the Th2 cytokines IL-4 and IL-10 were up regulated upon treatment with crude extract and pure compound. The extract and the pure compound isolated also showed considerable inhibition of NO production in activated RAW 264.7 cells, possibly via suppression of inducible NO synthase mRNA expression. Further to elucidate the underlying mechanism of action the effect of 12-ursene 2-diketone on LPS-induced activation of MAPK has also been examined. Our results demonstrated that 12-ursene 2-diketone inhibits the expression of pro-inflammatory cytokines and mediators via inhibition of phosphorylation of the MAP kinases JNK and p38 while no inhibition was seen in ERK phosphorylation in LPS-stimulated PBMCs. The above study therefore indicates that the crude methanolic extract and the isolated pure compound are capable of carrying out a natural anti-inflammatory activity at sites where

chronic inflammation is present by switching off the pro-inflammatory cytokines and mediators, which initiate the process.

21) Kokkiripati PK, Bhakshu LM, Marri S, Padmasree K, Row AT, Raghavendra AS, Tetali SD. Gum resin of Boswellia serrata inhibited human monocytic (THP-1) cell activation and platelet aggregation. J Ethnopharmacol. 2011 Sep 1;137(1):893-901.

Source: Department of Plant Sciences, University of Hyderabad, Hyderabad 500046, India.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

Stem bark gum resin extract of Boswellia serrata is traditionally used in India for its hemostatic, antiinflammatory and cardiovascular health effects and it is named as ÅšallakÄ« in Ayurvedic medicine.

AIM OF THE STUDY:

This study was conducted to evaluate the antioxidative and antithrombotic properties of stem bark gum resin extracts of Boswellia serrata (BS).

MATERIALS AND METHODS:

The inhibitory activity of the BSWE and BSAE on FeCl(3) induced lipid peroxidation (in vitro) in rat liver and heart homogenates was measured spectrophotometrically. Their effect on H(2)O(2) induced reactive oxygen species (ROS) generation in human monocytic (THP-1) cells was investigated by tracking intensity of a cell permeable fluorescent dye, H(2)DCFDA and subjecting the cell samples to confocal microscopy. Further, the effect of BSAE and BSWE on ADP-induced platelet aggregation was assessed using a multimode detection plate reader, plasma coagulation times using an automated blood coagulation analyzer and on human blood clotting factors Xa and XIa using chromogenic substrate. Phytomarker analysis of the water (BSWE) and hydroalcoholic (BSAE) extracts of BS-gum resin was done through HPLC using a standard compound AKÎ²BA.

RESULTS:

BSAE and BSWE inhibited, to varied extents, the lipid peroxidation in liver (80%) and heart (50%) tissue homogenates of male Wistar rats. Further, BSAE (30 Î¼g dwt/mL) and BSWE (300 Î¼g dwt/mL) attenuated â‰¥ 60% of H(2)O(2) mediated ROS generation in THP-1 cells. In case of standard compounds, ascorbate (20 Î¼g dwt/mL) and butylated hydroxytoluene (BHT) (10 Î¼g dwt/mL) completely scavenged ROS in the cells. BSAE and BSWE at 3 mg dwt/mL completely inhibited ADP induced platelet aggregation and activities were comparable to 20 Î¼g/mL of heparin. The extracts also showed very high activity in prolonging coagulation time periods. Both types of extracts extended prothrombin time (PT) from â^¼13 to >60s and activated partial thromboplastin time (APTT) from â^¼32s to >90s. BSAE inhibited clotting factors Xa and XIa remarkably at 6 Î¼g of dwt where as BSWE did not show much effect on FXa and showed 30% inhibition on FXIa at 120 Î¼g. 10 Î¼g of heparin was required to inhibit about 30% activity of the above factors. HPLC analyses suggested that BSAE and BSWE had AKÎ²BA of 9% (w/w) and 7.8% (w/w) respectively.

CONCLUSION:

Present study demonstrated antioxidant and antithrombotic anticoagulant activities of water and hydroalcoholic extracts of Boswellia serrata's gum resin. We suggest that BS-gum resin as a good

source for lead/therapeutic compounds possessing antioxidant, antiplatelet and anticoagulant activities.

22) Piacente S, Montoro P, Oleszek W, Pizza C. Yucca schidigera bark: phenolic constituents and antioxidant activity. J Nat Prod. 2004 May;67(5):882-5.

Source: Dipartimento di Scienze Farmaceutiche, UniversitÃ degli Studi di Salerno, Via Ponte Don Melillo, 84084 Fisciano, Salerno, Italy.

Abstract
Two new phenolic constituents with unusual spirostructures, named yuccaols D (1) and E (2), were isolated from the MeOH extract of Yucca schidigera bark. Their structures were established by spectroscopic (ESIMS and NMR) analysis. The new yuccaols D and E, along with resveratrol (3), trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene (4), yuccaols A-C (5-7), yuccaone A (8), larixinol (9), the MeOH extract of Yucca schidigera bark, and the phenolic portion of this extract, were assayed for antioxidant activity by measuring the free radical scavenging effects using two different assays, namely, the Trolox Equivalent Antioxidant Capacity (TEAC) assay and the coupled oxidation of beta-carotene and linoleic acid (autoxidation assay). The significant activities exhibited by the phenolic fraction and its constituents in both tests show the potential use of Y. schidigera as a source of antioxidant principles.

23) Cheeke PR, Piacente S, Oleszek W. Anti-inflammatory and anti-arthritic effects of Yucca schidigera: a review. J Inflamm (Lond). 2006 Mar 29;3:6.

Source: Department of Animal Sciences, Oregon State University, Corvallis, OR 97333, USA. peter.r.cheeke@oregonstate.edu

Abstract
Yucca schidigera is a medicinal plant native to Mexico. According to folk medicine, yucca extracts have anti-arthritic and anti-inflammatory effects. The plant contains several physiologically active phytochemicals. It is a rich source of steroidal saponins, and is used commercially as a saponin source. Saponins have diverse biological effects, including anti-protozoal activity. It has been postulated that saponins may have anti-arthritic properties by suppressing intestinal protozoa which may have a role in joint inflammation. Yucca is also a rich source of polyphenolics, including resveratrol and a number of other stilbenes (yuccaols A, B, C, D and E). These phenolics have anti-inflammatory activity. They are inhibitors of the nuclear transcription factor NFkappaB. NFkB stimulates synthesis of inducible nitric oxide synthase (iNOS), which causes formation of the inflammatory agent nitric oxide. Yucca phenolics are also anti-oxidants and free-radical scavengers, which may aid in suppressing reactive oxygen species that stimulate inflammatory responses. Based on these findings, further studies on the anti-arthritic effects of Yucca schidigera are warranted.
THE PHENOLS FOUND IN YUCCA SCHIDIGERA HAVE ANTI-INFLAMMATORY ACTIVITIES AND INHIBIT NITRIC OXIDE, WHICH IS AN INFLAMMATORY AGENT. THEY ALSO HAVE ANTIOXIDANT ACTIVITIES WHICH MAY MODULATE INFLAMMATORY RESPONSE. FULL STUDY AVAILABLE HERE:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1440857/ Anti-inflammatory and anti-arthritic effects of yucca schidigera: A review (FULL STUDY)

24) Grzanna R, Lindmark L, Frondoza CG. Ginger--an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005 Summer;8(2):125-32.

Source: RMG Biosciences, Inc.

Abstract
The anti-inflammatory properties of ginger have been known and valued for centuries. During the past 25 years, many laboratories have provided scientific support for the long-held belief that ginger contains constituents with antiinflammatory properties. The original discovery of ginger's inhibitory effects on prostaglandin biosynthesis in the early 1970s has been repeatedly confirmed. This discovery identified ginger as an herbal medicinal product that shares pharmacological properties with non-steroidal anti-inflammatory drugs. Ginger suppresses prostaglandin synthesis through inhibition of cyclooxygenase-1 and cyclooxygenase-2. An important extension of this early work was the observation that ginger also suppresses leukotriene biosynthesis by inhibiting 5-lipoxygenase. This pharmacological property distinguishes ginger from nonsteroidal anti-inflammatory drugs. This discovery preceded the observation that dual inhibitors of cyclooxygenase and 5-lipoxygenase may have a better therapeutic profile and have fewer side effects than non-steroidal anti-inflammatory drugs. The characterization of the pharmacological properties of ginger entered a new phase with the discovery that a ginger extract (EV.EXT.77) derived from Zingiber officinale (family Zingiberaceae) and Alpina galanga (family Zingiberaceae) inhibits the induction of several genes involved in the inflammatory response. These include genes encoding cytokines, chemokines, and the inducible enzyme cyclooxygenase-2. This discovery provided the first evidence that ginger modulates biochemical pathways activated in chronic inflammation. Identification of the molecular targets of individual ginger constituents provides an opportunity to optimize and standardize ginger products with respect to their effects on specific biomarkers of inflammation. Such preparations will be useful for studies in experimental animals and humans.

25) Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. Br J Anaesth. 2000 Mar;84(3):367-71.

Source: Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, UK.

Abstract
Ginger (Zingiber officinale) is often advocated as beneficial for nausea and vomiting. Whether the herb is truly efficacious for this condition is, however, still a matter of debate. We have performed a systematic review of the evidence from randomized controlled trials for or against the efficacy of ginger for nausea and vomiting. Six studies met all inclusion criteria and were reviewed. Three on postoperative nausea and vomiting were identified and two of these suggested that ginger was superior to placebo and equally effective as metoclopramide. The pooled absolute risk reduction for the incidence of postoperative nausea, however, indicated a non-significant difference between the ginger and placebo groups for ginger 1 g taken before operation (absolute risk reduction 0.052 (95% confidence interval -0.082 to 0.186)). One study was found for each of the following conditions: seasickness, morning sickness and chemotherapy-induced nausea. These studies collectively favoured ginger over placebo.

26) Huang TH, Tran VH, Duke RK, Tan S, Chrubasik S, Roufogalis BD, Duke CC. Harpagoside suppresses lipopolysaccharide-induced iNOS and COX-2 expression through inhibition of NF-kappa B activation. J Ethnopharmacol. 2006 Mar 8;104(1-2):149-55.

Source: Pharmaceutical Chemistry and Herbal Medicines Research and Education Centre, Faculty of Pharmacy A15, University of Sydney, NSW 2006, Australia.

Abstract
Preparations of Harpagophytum procumbens, known as devil's claw, are used as an adjunctive therapy for the treatment of pain and osteoarthritis. Pharmacological evaluations have proven the effectiveness of this herbal drug as an anti-inflammatory and analgesic agent. The present study has investigated the mechanism of action of harpagoside, one of the major components of Harpagophytum procumbens, using human HepG2 hepatocarcinoma and RAW 264.7 macrophage cell lines. Harpagoside inhibited lipopolysaccharide-induced mRNA levels and protein expression of cyclooxygenase-2 and inducible nitric oxide in HepG2 cells. These inhibitions appeared to correlate with the suppression of NF-kappaB activation by harpagoside, as pre-treating cells with harpagoside blocked the translocation of NF-kappaB into the nuclear compartments and degradation of the inhibitory subunit IkappaB-alpha. Furthermore, harpagoside dose-dependently inhibited LPS-stimulated NF-kappaB promoter activity in a gene reporter assay in RAW 264.7 cells, indicating that harpagoside interfered with the activation of gene transcription. These results suggest that the inhibition of the expression of cyclooxygenase-2 and inducible nitric oxide by harpagoside involves suppression of NF-kappaB activation, thereby inhibiting downstream inflammation and subsequent pain event.

27) Kidd P. Glutathione: Systemic Protectant Against Oxidative and Free Radical Damage. Alt Med Rev. 1997; Vol.2 (3):155-76.

ABSTRACT
The tripeptide thiol glutathione (GSH) has facile electron-donating capacity, linked to its sulfhydryl (â€•SH) group. Glutathione is an important water-phase antioxidant and essential cofactor for antioxidant enzymes; it provides protection also for the mitochondria against endogenous oxygen radicals. Its high electron-donating capacity combined with its high intracellular concentration endows GSH with great reducing power, which is used to regulate a complex thiol-exchange system (â€•SH â†” â€•S-Sâ€•). This functions at all levels of cell activity, from the relatively simple (circulating cysteine/â€•SH thiols, ascorbate, other small molecules) to the most complex (cellular â€•SH proteins).
Glutathione is homeostatically controlled, both inside the cell and outside. Enzyme systems synthesize it, utilize it, and regenerate it as per the gamma-glutamyl cycle. Glutathione is most concentrated in the liver (10 mM), where the "P450 Phase II" enzymes require it to convert fat-soluble substances into water-soluble GSH conjugates, in order to facilitate their excretion. While providing GSH for their specific needs, the liver parenchymal cells export GSH to the outside, where it serves as systemic source of â€•SH/reducing power.
GSH depletion leads to cell death, and has been documented in many degenerative conditions. Mitochondrial GSH depletion may be the ultimate factor determining vulnerability to oxidant attack. Oral ascorbate helps conserve GSH; cysteine is not a safe oral supplement, and of all the oral GSH precursors probably the least flawed and most cost-effective NAC (N-acetylcysteine). FULL STUDY AVAILABLE HERE: http://www.dockidd.com/pdf/KiddGSHAMR.pdf

28) Dieber-Rotheneder M, Puhl H, Waeg G, Striegl G, Esterbauer H. Effect of oral supplementation with D-alpha-tocopherol on the vitamin E content of human low density lipoproteins and resistance to oxidation. J Lipid Res. 1991 Aug;32(8):1325-32.

Source: Institute of Biochemistry, University of Graz, Austria.

Abstract
Twelve clinically healthy subjects participated in a vitamin E supplementation study. Eight were given daily dosages of 150, 225, 800, or 1200 IU RRR-alpha-tocopherol for 21 days (two persons per dose) and four received placebo. Prior, during, and after the supplementation period, alpha-tocopherol, gamma-tocopherol, and carotenoids were determined in plasma and low density lipoprotein (LDL). The maximum levels of alpha-tocopherol were 1.7- to 2.5-times the baseline values in plasma and 1.7- to 3.1-times in LDL. A high correlation existed between alpha-tocopherol in plasma and LDL. gamma-Tocopherol significantly decreased in plasma and LDL during vitamin E supplementation. No significant influence on the lipoprotein and lipid status and carotenoid levels of the participants occurred throughout the supplementation. The resistance of LDL against copper-mediated oxidation was also measured. The oxidation resistance of LDL was significantly higher during vitamin E supplementation. However, the efficacy of vitamin E in protecting LDL varied from person to person. The statistical evaluation of all data gave a correlation of r2 = 0.51 between alpha-tocopherol in LDL and the oxidation resistance as measured by the length of the lag-phase preceding the oxidation of LDL. No association was seen between levels of carotenoids and vitamin E in plasma and LDL. The present study clearly shows that in humans the oxidation resistance of LDL can be increased by vitamin E supplementation. FULL STUDY AVAILABLE HERE: http://www.jlr.org/content/32/8/1325.full.pdf
SUPPLEMENTING WITH VITAMIN E REDUCES LDL OXIDATION.
NOTE: 1 IU of tocopherol is defined as â…” milligrams of RRR-alpha-tocopherol (formerly named d-alpha-tocopherol)

29) Reaven PD, Khouw A, Beltz WF, Parthasarathy S, Witztum JL. Effect of dietary antioxidant combinations in humans. Protection of LDL by vitamin E but not by beta-carotene. Arterioscler Thromb. 1993 Apr;13(4):590-600.

Source: Department of Medicine, University of California, San Diego, La Jolla 92093-0682.

Abstract
Experimental and epidemiological evidence supports the hypothesis that oxidation of low density lipoprotein (LDL) appears to be important in mediating the atherogenicity of LDL. To test this hypothesis in humans, it will be necessary to perform intervention studies in large populations. We performed two studies to assess the effectiveness of supplementation with beta-carotene and vitamin E, used alone and in combination with each other, and with vitamin C, to protect LDL from oxidation. In phase 1, after a placebo period, eight subjects were given beta-carotene (60 mg/day) for 3 months, then beta-carotene plus vitamin E (1,600 mg/day) for another 3 months, and then beta-carotene plus vitamin E plus vitamin C (2 g/day) for 3 months. During phase 2, beta-carotene and vitamin C were discontinued, and subjects took only vitamin E for 5 months. During each period, LDL samples were isolated, and measurements of susceptibility to oxidation were performed. beta-Carotene levels in LDL increased nearly 20-fold, but LDL susceptibility to oxidation did not change. Addition of vitamin E increased LDL vitamin E levels nearly 2.5-fold, and this decreased LDL oxidation 30-40%. During the vitamin C supplementation period, plasma levels of beta-carotene and vitamin E rose, but only beta-carotene increased in LDL. However, the

susceptibility of LDL to oxidation in this period was not decreased further. During phase 2, when subjects took only vitamin E, LDL susceptibility to oxidation was decreased by 50% as measured by thiobarbituric acid-reactive substances, conjugated dienes, and lipid peroxide formation as well as by macrophage degradation. Thus, long-term supplementation with large doses of vitamin E alone, but not beta-carotene, conferred increased protection to LDL in in vitro assays of oxidation. These data should be useful in planning therapeutic strategies to test the antioxidant hypothesis in humans.

30) Boshtam M, Rafiei M, Sadeghi K, Sarraf-Zadegan N. Vitamin E can reduce blood pressure in mild hypertensives. Int J Vitam Nutr Res. 2002 Oct;72(5):309-14.

Source: Isfahan Cardiovascular Research Center, PO Box 81465-1148, Isfahan, Iran.

Abstract
This triple-blind placebo-controlled clinical trial was performed to determine the effects of the anti-oxidant vitamin E on blood pressure and heart rate in patients with mild hypertension. A total of 70 new mild hypertensive subjects (systolic blood pressure, SBP: 140-160 mmHg; diastolic blood pressure, DBP: 90-100 mmHg) without secondary hypertension were selected from among people referred to the Hypertension Unit of Isfahan Cardiovascular Research Center and divided randomly into two groups of drug (DG) and placebo (PG). All subjects were aged from 20 to 60 years old, without any other cardiovascular risk factors. The drug group received vitamin E tablets (200 IU/day) and the placebo group received placebo only for 27 weeks. At the beginning and the end of the study, the blood vitamin E level was measured fluorimetrically in all subjects according to the Hansen and Warwick method [14, 15]. Blood pressure and heart rate were measured at the beginning, during, and at the end of the study. Blood pressure was measured by a physician using one random zero mercury sphygmomanometer. Personal information and dietary habits of subjects were collected by separate questionnaire. At the end of the study, it was found that the vitamin E supplement had caused a remarkable decrease in SBP (-24% in DG versus -1.6% in PG) and a less remarkable decrease in DBP (-12.5% in DG versus -6.2% in PG) ($p < 0.05$). The change in heart rate was -4.3% in DG, and -14.0% in PG ($p < 0.05$). It is concluded that a vitamin E supplement of 200 IU/day can be effective in mild hypertensive patients in the long term, probably due to nitric oxide, and improve their blood pressure status. Therefore, vitamin E supplement could be recommended to such patients.

31) Office of Dietary Supplements - National Institutes of Health
http://ods.od.nih.gov/factsheets/vitamine/#en6 last accessed 03/12/2012

Vitamin E is a fat-soluble antioxidant that stops the production of ROS formed when fat undergoes oxidation. Scientists are investigating whether, by limiting free-radical production and possibly through other mechanisms, vitamin E might help prevent or delay the chronic diseases associated with free radicals.
In addition to its activities as an antioxidant, vitamin E is involved in immune function and, as shown primarily by in vitro studies of cells, cell signaling, regulation of gene expression, and other metabolic processes [1]. Alpha-tocopherol inhibits the activity of protein kinase C, an enzyme involved in cell proliferation and differentiation in smooth muscle cells, platelets, and monocytes [6]. Vitamin-Eâ€“replete endothelial cells lining the interior surface of blood vessels are better able to resist blood-cell components adhering to this surface. Vitamin E also increases the expression of two enzymes that suppress arachidonic acid metabolism, thereby increasing the release of

prostacyclin from the endothelium, which, in turn, dilates blood vessels and inhibits platelet aggregation [6].

32) Martha Clare Morris, ScD; Denis A. Evans, MD; Julia L. Bienias, ScD; Christine C. Tangney, PhD; Robert S. Wilson, PhD. Vitamin E and Cognitive Decline in Older Persons. Arch Neurol.Â 2002;59:1125-1132.

Background:
Previous studies raise the possibility that antioxidants protect against neurodegenerative diseases.

Objective: To examine whether intake of antioxidant nutrients, including vitamin E, vitamin C, and carotene, is associated with reduced cognitive decline with age.

Design: Longitudinal population-based study conducted from September 17, 1993, to November 20, 2000, with an average follow-up of 3.2 years.

Patients: The patients were 2889 community residents, aged 65 to 102 years, who completed a food frequency questionnaire, on average 18 months after baseline.

Main Outcome:
Measure: Cognitive change as measured by 4 tests (the East Boston Memory Test, which tests immediate and delayed recall; the Mini-Mental State Examination; and the Symbol Digit Modalities Test) at baseline and 3 years for all participants, and at 6 months for 288 randomly selected participants.

Results: We used random-effects models to estimate nutrient effects on individual change in the average score of the 4 cognitive tests. The cognitive score declined on average by 5.0 x 10-2 standardized units per year. There was a 36% reduction in the rate of decline among persons in the highest quintile of total vitamin E intake (-4.3 x 10-2 standardized units per year) compared with those in the lowest quintile (-6.7 x 10-2 standardized units per year) (P = .05), in a model adjusted for age, race, sex, educational level, current smoking, alcohol consumption, total calorie (energy) intake, and total intakes of vitamin C, carotene, and vitamin A. We also observed a reduced decline with higher vitamin E intake from foods (P = .03 for trend). There was little evidence of association with vitamin C or carotene intake.

Conclusion: Vitamin E intake, from foods or supplements, is associated with less cognitive decline with age.

33) Teixeira S. Bioflavonoids: proanthocyanidins and quercetin and their potential roles in treating musculoskeletal conditions. J Orthop Sports Phys Ther. 2002 Jul;32(7):357-63.

Source: Huber Associates, Auburn, ME 04210, USA. shan.tex@verizon.net

Abstract
As a clinician treating musculoskeletal conditions, one is continually in search of safe and more effective treatment methods that will hasten tissue healing. Chronic inflammation has been shown to cause connective tissue degradation. Typically, nonsteroidal anti-inflammatory drugs (NSAIDs)

and/or corticosteroids are used to control the inflammatory process, however, long-term use has been associated with potentially serious side effects. The purpose of this article is to introduce and describe literature on 2 natural compounds, namely, proanthocyanidin (PCO) and quercetin, which are 2 specific types of bioflavonoids, and to discuss their potential benefits in treating musculoskeletal conditions. There is evidence to suggest that flavonoids may be beneficial to connective tissue for several reasons, which include the limiting of inflammation and associated tissue degradation, the improvement of local circulation, as well as the promoting of a strong collagen matrix. An overview of bioflavonoids as well as relevant research, safety issues, absorption, and specific sources of PCO and quercetin in foods and through supplementation is included.

Inflammation and Tissue Degradation
Inflammation is a normal biological process and the primary means by which tissue healing is initiated and infection is limited in the human body. However, chronic inflammation has been shown to cause connective tissue degradation. This occurs through 2 primary mechanisms: (1) proteolytic enzymes and (2) oxygen-free radicals such as superoxide ion (O2), singlet, and hydroxyl radicals.
Proteolytic enzymes including elastase, collagenase, and hyaluronidase are involved in the inflammatory process and are associated with the presence of polymorphonuclear leukocytes (PMNs) and macrophages. They have been shown to be more prevalent in
tissue with chronic conditions and to cause degradation of collagen, elastin, and hyaluronic acid.
FULL STUDY AVAILABLE HERE: http://www.osptla.com/JOSPT%20Flavonoid%20Article.pdf

34) Ishita Chattopadhyay, Kaushik Biswas, Uday Bandyopadhyay and Ranajit K. Banerjee.
Turmeric and curcumin: Biological actions and medicinal applications.
Current Science, 2004, Jul 10, vol. 87, no. 1

Turmeric (Curcuma longa) is extensively used as a spice, food preservative and colouring material in India, China and South East Asia. It has been used in traditional medicine as a household remedy for various diseases, including biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis. For the last few decades, extensive work has been done to establish the biological activities and pharmacological actions of turmeric and its extracts. Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has been shown to have a wide spectrum of biological actions. These include its antiinflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antifertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, antivenom, antiulcer, hypotensive and hypocholesteremic activities. Its anticancer effect is mainly mediated through induction of apoptosis. Its antiinflammatory, anticancer and antioxidant roles may be clinically exploited to control rheumatism, carcinogenesis and oxidative stress-related pathogenesis. Clinically, curcumin has already been used to reduce post-operative inflammation. Safety evaluation studies indicate that both turmeric and curcumin are well tolerated at a very high dose without any toxic effects. Thus, both turmeric and curcumin have the potential for the development of modern medicine for the treatment of various diseases.
FULL STUDY AVAILABLE HERE: http://repository.ias.ac.in/5196/1/306.pdf

OTHER RELATED RESEARCH
Hale LP, Greer PK, Sempowski GD. Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. Clin Immunol. 2002

Aug;104(2):183-90.

Source: Department of Pathology, Duke University, Durham, NC 27710, USA.

Abstract
Bromelain is a natural proteinase preparation derived from pineapple stem that is marketed for oral use as a digestive aid and as an antiinflammatory agent. Bromelain treatment in vitro has been previously shown to selectively remove certain cell surface molecules that may affect lymphocyte migration and activation. This study reports the effects of bromelain on a broad range of cell surface molecules and on lymphocytes, monocytes, and granulocytes under physiologically relevant conditions. In vitro bromelain treatment of leukocytes in whole blood proteolytically altered 14 of 59 leukocyte markers studied. Constitutively expressed bromelain-sensitive molecules included CD7, CD8alpha, CD14, CD16, CD21, CD41, CD42a, CD44, CD45RA, CD48, CD57, CD62L, CD128a, and CD128b. The proteolytic effect of bromelain increased as the concentration of plasma decreased, with EC50 ranging from >1000 microg/ml for 100% plasma to approximately 1 microg/ml in the absence of plasma, indicating the presence of an inhibitor of bromelain in plasma. alpha2-macroglobulin purified from plasma mimicked the inhibitory effect of whole plasma on bromelain activity. If proteolysis is required for the antiinflammatory actions of oral bromelain, these data suggest that the required concentrations are more likely to be achieved locally in the gastrointestinal tract or in other tissue sites where the plasma concentration is low, rather than in the bloodstream. The cell surface molecules altered by bromelain are involved in leukocyte homing and cellular adhesion and activation. Thus bromelain could potentially exert an antiinflammatory effect by multiple mechanisms, including alterations in leukocyte migration and activation.

THE ANTIINFLAMMATORY EFFECT OF BROMELAIN MAY BE CAUSED BY AN ALTERATION IN LEUKOCYTE MIGRATION AND ACTIVATION.

Masson M. [Bromelain in blunt injuries of the locomotor system. A study of observed applications in general practice]. Fortschr Med. 1995 Jul 10;113(19):303-6.
[Article in German]

Abstract
METHOD: In an open case observation study involving patients with blunt injuries to the musculoskeletal system, the efficacy and tolerability of high-dose Bromelain POS, a plant-derived enzyme preparation, were investigated. The investigating physician was an orthopedic surgeon who, in addition to the usual therapeutic measures, treated 59 of his patients with the bromelaine preparation. The duration of the application was determined by the nature and severity of the lesion, and varied between one and three weeks. The test criteria were swelling, pain at rest and during movement, and tenderness. These parameters were evaluated on the day of the injury and on five subsequent dates. RESULTS: Treatment with bromelaine resulted in a clear reduction in all four parameters tested. Both swelling and the symptoms of pain had improved appreciably at all evaluation time points as compared with baseline. The tolerability of the preparation was very good, and patient compliance was correspondingly high.

What was dosage? Where is full study? What is bromelain pos?
Brien S, Lewith G, Walker A, Hicks SM, Middleton D. Bromelain as a Treatment for Osteoarthritis: a Review of Clinical Studies. Evid Based Complement Alternat Med. 2004 Dec;1(3):251-257.

Abstract
Bromelain, an extract from the pineapple plant, has been demonstrated to show anti-inflammatory and analgesic properties and may provide a safer alternative or adjunctive treatment for osteoarthritis. All previous trials, which have been uncontrolled or comparative studies, indicate its potential use for the treatment of osteoarthritis. This paper reviews the mechanism of its putative therapeutic actions, those clinical trials that have assessed its use in osteoarthritis to date, as well as considering the safety implications of this supplement for osteoarthritis and reviewing the evidence to date regarding the dosage for treating this condition. The data available at present indicate the need for trials to establish the efficacy and optimum dosage for bromelain and the need for adequate prospective adverse event monitoring in such chronic conditions as osteoarthritis. Find full study. Not enough here to draw conclusions.

Fossati A. Antiinflammatory effects of seaprose-S on various inflammation models. Drugs Exp Clin Res. 1999;25(6):263-70.

Abstract
The antiinflammatory activity of seaprose-S in different experimental models involving different biochemical mediators of inflammation was investigated. In vivo experiments were performed using male Sprague-Dawley rats and in vitro experiments were performed using articular cartilage explants of pig joints. In acute experimental models of inflammation, 0.5, 1 or 2 mg/kg of seaprose-S was injected intravenously (i.v.) before challenge with inflammatory agents. In adjuvant-induced arthritis, seaprose-S was given as a 2 mg/kg i.v. dose once a day for 4 consecutive days from day 8 after injection of the adjuvant. In cartilage-synovium cocultures, seaprose-S was incubated at a concentration of 0.001 microM and 0.05 microM. Paw volume was measured with a plethysmograph and proteoglycan synthesis was determined in articular cartilage-synovium coculture by incorporation of 35S-sulfate. Seaprose-S inhibited inflammation dose-dependently in carrageenan, concanavalin-A, FeCl2, nystatin-induced paw edema and in carrageenan-induced pleurisy and acetic acid-induced peritonitis. In Freund's adjuvant-induced arthritis, seaprose-S significantly reduced the primary and secondary lesions. In vitro on articular cartilage, seaprose-S increased proteoglycan synthesis in the cartilage alone and reduced the inhibition of proteoglycan synthesis in the cartilage cocultured with minced synovium.
IN THIS ANIMAL STUDY SEAPROSE S WAS SHOWN TO HAVE ANTI-INFLAMMATORY ACTIVITY.

Esch PM, Gerngross H, Fabian A. [Reduction of postoperative swelling. Objective measurement of swelling of the upper ankle joint in treatment with serrapeptase-- a prospective study]. Fortschr Med. 1989 Feb 10;107(4):67-8, 71-2. [Article in German]

Abstract
Using a quantitative standardized procedure, the swelling of the ankle produced by supination trauma was measured. In the 66 patients with fresh rupture of the lateral ligament treated surgically at our Department between December 1986 and April 1987, a prospective study of the effect of serrapeptase (Aniflazym) SILKWORM! on post-operative swelling and pain was carried out in 3 randomized groups of patients. In the group receiving the test substance, the swelling had

decreased by 50% on the third post-operative day, while in the other two control groups (elevation of the leg, bed rest, with and without the application of ice) no reduction in swelling had occurred at that time. The difference is statistically significant (p = 0.013). Decreasing pain correlated for the most part with the reduction in swelling. Thus, the patients receiving the test substance more rapidly became pain-free than did the control groups. On the basis of these results, serrapeptase would appear to be an effective preparation for the post-operative reduction of swelling, in comparison with the classical conservative measures, for example, the application of ice.
SERRAPEPTASE IN ANIFLAYZM IS FROM SILKWORMS, SO THIS STUDY IS NOT APPLICABLE

Selloum L, Bouriche H, Tigrine C, Boudoukha C. Anti-inflammatory effect of rutin on rat paw oedema, and on neutrophils chemotaxis and degranulation. Exp Toxicol Pathol. 2003 Mar;54(4):313-8.

Source: Laboratory of Applied Biochemistry, Department of Biology, Faculty of Sciences, University of Ferhat ABBAS, 19000 Setif, Algeria. laidsel@yahoo.com

Abstract
BACKGROUND:
Rutin, a natural flavone derivative, is known for its pharmacological properties. We have previously reported that this flavonol exerted a potent inhibitory effect on respiratory burst of fMet-Leu-Phe-stimulated neutrophils, as well as on phosphoinositide 3-kinase gamma activity in a cell free system. In the present study, the anti-inflammatory effect of rutin was investigated in vivo and in vitro.

METHODS:
rutin or aspirin (100 mg/kg, body weight) were given orally to rats 1 hour before paw oedema induction, using lambda-carrageenan 1%. The rat paw volume was measured by mean of plethysmometer, initially and during 6 hours. The chemotaxis of neutrophils towards 10(-7) M fMet-Leu-Phe was performed using 48-well chemotaxis chamber. Neutrophils that migrated through 5 microm pore size polycarbonate filter, in presence or in absence of rutin, were counted microscopically. Elastase exocytosis of either phorbol 12-myristate 13-acetate or fMet-Leu-Phe/cytochalasin B-stimulated neutrophils was assessed in absence or in presence of rutin using the synthetic substrate N-Suc-Ala-Ala-Ala-p-nitroanilide. The absorbance of released p-nitroaniline was measured at 405 nm using microplate reader.

RESULTS:
The maximal swelling in placebo group was observed at 5 hours, after lambda-carrageenan injection. Oral administration of rutin reduced rat paw swelling starting 2 hours after lambda-carrageenan injection. Rutin reduced significantly ($p < 0.05$) and in a dose-dependant manner the polymorphonuclear neutrophils chemotaxis to fMet-Leu-Phe. Furthermore, elastase exocytosis, induced by both stimuli, was partially inhibited by rutin up to 25 microM.

CONCLUSION:
The present study revealed that rutin possesses anti-inflammatory properties.
IN THIS ANIMAL STUDY, ORAL ADMINISTRATION OF RUTIN REDUCED SWELLING WITHIN TWO HOURS.

Guardia T, Rotelli AE, Juarez AO, Pelzer LE. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. Farmaco. 2001 Sep;56(9):683-7.

Source: Departamento de Farmacia, Facultad de QuÃmica, BioquÃmica y Farmacia, Universidad Nacional de San Luis, Argentina.

Abstract
The anti-inflammatory activities of three flavonoids were investigated in rats using the Mizushima et al. model of acute and chronic inflammation. Intraperitoneal administration of rutin, quercetin (flavonols) and hesperidin (flavanone), given at daily doses equivalent to 80 mg/kg, inhibited both acute and chronic phases of this experimental model of inflammation. Rutin was the most active in the chronic phase.
IN THIS ANIMAL STUDY RUTIN REDUCED INFLAMMATION IN THE ACUTE STAGE, BUT WAS MOST ACTIVE AT THE CHRONIC PHASE OF INFLAMMATION.

Rotelli AE, Guardia T, JuÃ¡rez AO, de la Rocha NE, Pelzer LE. Comparative study of flavonoids in experimental models of inflammation. Pharmacol Res. 2003 Dec;48(6):601-6.

Source: CÃ¡tedra de FarmacologÃa, Facultad de QuÃmica, BioquÃmica y Farmacia, Universidad Nacional de San Luis, Chacabuco y Pedernera, 5700 San Luis, Argentina. arotelli@unsl.edu.ar

Abstract
The anti-inflammatory activities of flavonols (quercetin, rutin and morin) and flavanones (hesperetin and hesperidin) were investigated in animal models of acute and chronic inflammation. Rutin was only effective in the chronic process, principally in adjuvant arthritis. On neurogenic inflammation induced by xylene, only the flavanones were effective; besides, these compounds were the most effective on subchronic process. The most important compound in reducing paw oedema induced by carrageenan was quercetin.
IN THIS ANIMAL STUDY RUTIN EFFECTIVELY REDUCED INFLAMMATION AT THE CHRONIC PHASE OF INFLAMMATION.

S Sontakke, V Thawani, S Pimpalkhute, P Kabra, S Babhulkar, L Hingorani. Open, randomized, controlled clinical trial of Boswellia serrata extract as compared to valdecoxib in osteoarthritis of knee. Indian Journal of Pharmacology. 2007; 39(1) 27-29

Objective: To compare the efficacy, safety and tolerability of Boswellia serrata extract (BSE) in osteoarthritis (OA) knee with valdecoxib, a selective COX-2 inhibitor. Materials and Methods: In a randomized, prospective, open-label, comparative study the efficacy, safety and tolerability of BSE was compared with valdecoxib in 66 patients of OA of knee for six months. The patients were assessed by WOMAC scale at baseline and thereafter at monthly interval till 1 month after drug discontinuation. Antero-posterior radiographs of affected knee joint were taken at baseline and after 6 months. Results: In BSE group the pain, stiffness, difficulty in performing daily activities showed statistically significant improvement with two months of therapy which even lasted till one month after stopping the intervention. In valdecoxib group the statistically significant improvement in all parameters was reported after one month of therapy but the effect persisted only as long as drug therapy continued. Three patients from BSE group and two from valdecoxib group complained of acidity. One patient from BSE group complained of diarrhea and abdominal cramps. Conclusion: BSE showed a slower onset of action but the effect persisted even after stopping therapy while the action of valdecoxib became evident faster but waned rapidly after stopping the treatment.
SUBJECTS WITH PAINFUL KNEES SHOWED SIGNIFICANT IMPROVEMENT WITH TWO

MONTHS OF THERAPY ON BOSWELLIA. DOSE WAS 333MG 3X DAILY. FULL STUDY AVAILABLE HERE: http://www.bioline.org.br/pdf?ph07006
Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial. Phytomedicine. 2003 Jan;10(1):3-7.

Source: MS Orthopedics, Indira Gandhi Medical College, Nagpur, India.

Abstract
Osteoarthritis is a common, chronic, progressive, skeletal, degenerative disorder, which commonly affects the knee joint. Boswellia serrata tree is commonly found in India. The therapeutic value of its gum (guggulu) has been known. It possesses good anti-inflammatory, anti-arthritic and analgesic activity. A randomized double blind placebo controlled crossover study was conducted to assess the efficacy, safety and tolerability of Boswellia serrata Extract (BSE) in 30 patients of osteoarthritis of knee, 15 each receiving active drug or placebo for eight weeks. After the first intervention, washout was given and then the groups were crossed over to receive the opposite intervention for eight weeks. All patients receiving drug treatment reported decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was decreased. Radiologically there was no change. The observed differences between drug treated and placebo being statistically significant, are clinically relevant. BSE was well tolerated by the subjects except for minor gastrointestinal ADRs. BSE is recommended in the patients of osteoarthritis of the knee with possible therapeutic use in other arthritis.

PATIENTS TREATED WITH BOSWELLIA EXTRACT HAD A DECREASE IN KNEE PAIN AND SWELLING. IT ALSO IMPROVED KNEE FLEXION AND ALLOWED THEM TO INCREASE WALKING DISTANCE.
Note: No dosage was given in the abstract however when referenced in another study it was said to be 999 mg. daily. Other study available here:
http://www.academicjournals.org/AJB/PDF/pdf2012/9Feb/We%20et%20al.pdf
Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, Dey D, Raychaudhuri SP. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. Arthritis Res Ther. 2008;10(4):R85

Source: Cellular and Molecular Biology Division, Laila Impex R&D Center, Jawahar Autonagar, Vijayawada, India.

Abstract
INTRODUCTION:
5-Loxin is a novel Boswellia serrata extract enriched with 30% 3-O-acetyl-11-keto-beta-boswellic acid (AKBA), which exhibits potential anti-inflammatory properties by inhibiting the 5-lipoxygenase enzyme. A 90-day, double-blind, randomized, placebo-controlled study was conducted to evaluate the efficacy and safety of 5-Loxin in the treatment of osteoarthritis (OA) of the knee.

METHODS:
Seventy-five OA patients were included in the study. The patients received either 100 mg (n = 25) or 250 mg (n = 25) of 5-Loxin daily or a placebo (n = 25) for 90 days. Each patient was evaluated for pain and physical functions by using the standard tools (visual analog scale, Lequesne's Functional Index, and Western Ontario and McMaster Universities Osteoarthritis Index) at the baseline (day 0), and at days 7, 30, 60 and 90. Additionally, the cartilage degrading enzyme matrix metalloproteinase-3 was also evaluated in synovial fluid from OA patients. Measurement of a

battery of biochemical parameters in serum and haematological parameters, and urine analysis were performed to evaluate the safety of 5-Loxin in OA patients.

RESULTS:
Seventy patients completed the study. At the end of the study, both doses of 5-Loxin conferred clinically and statistically significant improvements in pain scores and physical function scores in OA patients. Interestingly, significant improvements in pain score and functional ability were recorded in the treatment group supplemented with 250 mg 5-Loxin as early as 7 days after the start of treatment. Corroborating the improvements in pain scores in treatment groups, we also noted significant reduction in synovial fluid matrix metalloproteinase-3. In comparison with placebo, the safety parameters were almost unchanged in the treatment groups.

CONCLUSION:
5-Loxin reduces pain and improves physical functioning significantly in OA patients; and it is safe for human consumption. 5-Loxin may exert its beneficial effects by controlling inflammatory responses through reducing proinflammatory modulators, and it may improve joint health by reducing the enzymatic degradation of cartilage in OA patients.
100-250 MG OF 5-LOXIN, A BOSWELLIA EXTRACT, REDUCED INFLAMMATORY RESPONSE AND CARTILAGE DEGRADATION WHILE IMPROVING PAIN AND PHYSICAL FUNCTION SCORES. USE OF THIS STUDY WOULD DEPEND UPON THE TYPE OF EXTRACT YOU ARE USING, AND MAY NOT APPLY.

A. Sharma, S. Bhatia, M. D. Kharya, V. Gajbhiye, N Ganesh, A. G. Namdeo, K. R. Mahadik. Anti-inflammatory and analgesic activity of different fractions of Boswellia serrata. Int Jnl of Phytomedicine. 2010 V 2 No 1

Abstract
The study was designed to investigate the anti-inflammatory and analgesic effect of different fractions of Boswellia serrata. The effect of different fractions of Boswellia serrata were studied using carrageenan induced paw edema, acetic acid induced writhing response, formalin induced pain, hot plate and tail flick method for studying anti-inflammatory and analgesic activity, respectively. The different fractions of B. serrata, essential oil (10 ml/kg), gum (100 mg/kg, resin (100 mg/kg) oleo-resin (100 mg/kg) and oleo-gum-resin (100 mg/kg) significantly reduces carrageenan induced inflammation in rats and shows analgesic activity, as determined by acetic acid induced writhing response, formalin induced pain, hot plate and tail flick method. The different fractions of B. serrata showed prompt anti-inflammatory and analgesic activity due to the inhibition of 5-lipoxygenase enzyme.

IN THIS ANIMAL STUDY BOSWELLIA REDUCED INFLAMMATION IN RATS.
Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V. Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. J Altern Complement Med. 2009 Aug;15(8):891-7.

Source: Department of Rehabilitation Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. sivth@mahidol.ac.th

Abstract
OBJECTIVE:
The objective of this study was to determine the efficacy and safety of Curcuma domestica extracts

in pain reduction and functional improvement in patients with knee osteoarthritis.

STUDY DESIGN AND SETTING:
The design and setting were a randomized controlled study at a university hospital in Bangkok, Thailand.

METHODS:
One-hundred and seven (107) patients with primary knee osteoarthritis (OA) with pain score of > or =5 were randomized to receive ibuprofen 800 mg per day or C. domestica extracts 2 g per day for 6 weeks. The main outcomes were improvement in pain on level walking, pain on stairs, and functions of knee assessed by time spent during 100-m walk and going up and down a flight of stairs. The adverse events were also recorded.

RESULTS:
Fifty-two (52) and 55 patients were randomized to C. domestica extracts and ibuprofen groups, respectively. Baseline characteristics of the patients in both groups were not different. The mean scores of the aforementioned outcomes at weeks 0, 2, 4, and 6 were significantly improved when compared with the baseline values in both groups. There was no difference in those parameters between the patients receiving ibuprofen and C. domestica extracts, except pain on stairs ($p = 0.016$). No significant difference of adverse events between both groups was found (33.3% versus 44.2%, $p = 0.36$ in C. domestica extracts and ibuprofen groups, respectively).

CONCLUSIONS:
C. domestica extracts seem to be similarly efficacious and safe as ibuprofen for the treatment of knee OA. CANNOT USE/DOSAGE

Olas B, Wachowicz B, Nowak P, Stochmal A, Oleszek W, Glowacki R, Bald E. Comparative studies of the antioxidant effects of a naturally occurring resveratrol analogue -- trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene and resveratrol -- against oxidation and nitration of biomolecules in blood platelets. Cell Biol Toxicol. 2008 Aug;24(4):331-40.

Source: Department of General Biochemistry, Institute of Biochemistry, University of Lodz, Lodz, Poland. olasb@biol.uni.lodz.pl

Abstract
The action of two phenolic compounds isolated from the bark of Yucca schidigera: trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene and its analogue -- resveratrol (trans-3,4',5-trihydroxystilbene, present also in grapes and wine) on oxidative/nitrative stress induced by peroxynitrite (ONOO(-), which is strong physiological oxidant and inflammatory mediator) in human blood platelets was compared. The trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene, like resveratrol, significantly inhibited protein carbonylation and nitration (measured by enzyme-linked immunosorbent assay method) in the blood platelets treated with peroxynitrite (0.1 mM) and markedly reduced an oxidation of thiol groups of proteins (estimated with 5,5'-dithio-bis(2-nitro-benzoic acid)] or glutathione (measured by high performance liquid chromatography method) in these cells. The trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene, like resveratrol, also caused a distinct reduction of platelet lipid peroxidation induced by peroxynitrite. The obtained results indicate that in vitro trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene and resveratrol have very similar protective effects against peroxynitrite-induced oxidative/nitrative damage to the human platelet proteins and lipids. Moreover, trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene proved to be even more potent than resveratrol in antioxidative tests. We conclude that the novel tested phenolic compound -- trans-

3,3',5,5'-tetrahydroxy-4'-methoxystilbene isolated from Y. schidigera bark possessing Generally Recognized As Safe label given by the Food and Drug Administration and allows their human dietary use -- seems to be a promising candidate for future evaluations of its antioxidative activity and may be a good candidate for scavenging peroxynitrite.

YUCCA SCHIDIGERA BARK MAY REDUCE INFLAMMATORY OXIDATIVE STRESS INDUCED BY PEROXYNITRITE

Piacente S, Montoro P, Oleszek W, Pizza C. Yucca schidigera bark: phenolic constituents and antioxidant activity. J Nat Prod. 2004 May;67(5):882-5.

Source: Dipartimento di Scienze Farmaceutiche, UniversitÃ degli Studi di Salerno, Via Ponte Don Melillo, 84084 Fisciano, Salerno, Italy.

Abstract
Two new phenolic constituents with unusual spirostructures, named yuccaols D (1) and E (2), were isolated from the MeOH extract of Yucca schidigera bark. Their structures were established by spectroscopic (ESIMS and NMR) analysis. The new yuccaols D and E, along with resveratrol (3), trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene (4), yuccaols A-C (5-7), yuccaone A (8), larixinol (9), the MeOH extract of Yucca schidigera bark, and the phenolic portion of this extract, were assayed for antioxidant activity by measuring the free radical scavenging effects using two different assays, namely, the Trolox Equivalent Antioxidant Capacity (TEAC) assay and the coupled oxidation of beta-carotene and linoleic acid (autoxidation assay). The significant activities exhibited by the phenolic fraction and its constituents in both tests show the potential use of Y. schidigera as a source of antioxidant principles.

YUCCA SCHIDIGERA BARK DEMONSTRATES ANTIOXIDANT ACTIVITY.
Chantre P, Cappelaere A, Leblan D, Guedon D, Vandermander J, Fournie B. Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. Phytomedicine. 2000 Jun;7(3):177-83.

Source: Laboratoires Arkopharma, Carros, France.

Abstract
In a double-blind, randomized, multicentre clinical study, the efficacy and tolerance of a herbal medicine product, Harpadol (6 capsules/day, each containing 435 mg of powdered cryoground powder Harpagophytum procumbens), was compared with diacerhein 100 mg/day in the treatment, for 4 months, of 122 patients suffering from osteoarthritis of the knee and hip. Assessments of pain and functional disability were made on a 10 cm horizontal visual analogue scale; severity of osteoarthritis was evaluated by Lequesne's index. Spontaneous pain showed a significant improvement during the course of the study and there was no difference in the efficacy of the two treatments. Similarly, there was a progressive and significant reduction in the Lequesne functional index and no statistical difference was found between Harpadol and diacerhein. At completion of the study, patients taking Harpadol were using significantly less NSAIDs and antalgic drugs. The frequency of adverse events was significantly lower in the Harpadol group. The most frequent event reported was diarrhea, occurring in 8.1% and 26.7% of Harpadol and diacerhein patients respectively. The global tolerance assessment by patients at the end of treatment favoured Harpadol. The results of this study demonstrate that Harpadol is comparable in efficacy and superior in safety to diacerhein.

CANNOT USE/DOSAGE
Chrubasik S, Junck H, Breitschwerdt H, Conradt C, Zappe H. Effectiveness of Harpagophytum extract WS 1531 in the treatment of exacerbation of low back pain: a randomized, placebo-controlled, double-blind study. Eur J Anaesthesiol. 1999 Feb;16(2):118-29.

Source: Department of Medical Biometry, University of Heidelberg, Germany.

Abstract
Two daily doses of oral Harpagophytum extract WS 1531 (600 and 1200, respectively, containing 50 and 100 mg of the marker harpagoside) were compared with placebo over 4 weeks in a randomized, double-blind study in 197 patients with chronic susceptibility to back pain and current exacerbations that were producing pain worse than 5 on a 0-10 visual analogue scale. The principal outcome measure, based on pilot studies, was the number of patients who were pain free without the permitted rescue medication (tramadol) for 5 days out of the last week. The treatment and placebo groups were well matched in physical characteristics, in the severity of pain, duration, nature and accompaniments of their pain, the Arhus low back pain index and in laboratory indices of organ system function. A total of 183 patients completed the study. The numbers of pain-free patients were three, six and 10 in the placebo group (P), the Harpagophytum 600 group (H600) and the Harpagophytum 1200 group (H1200) respectively (P = 0.027, one-tailed Cochrane-Armitage test). The majority of responders' were patients who had suffered less than 42 days of pain, and subgroup analyses suggested that the effect was confined to patients with more severe and radiating pain accompanied by neurological deficit. However, subsidiary analyses, concentrating on the current pain component of the Arhus index, painted a slightly different picture, with the benefits seeming, if anything, to be greatest in the H600 group and in patients without more severe pain, radiation or neurological deficit. Patients with more pain tended to use more tramadol, but even severe and unbearable pain would not guarantee that tramadol would be used at all, and certainly not to the maximum permitted dose. There was no evidence for Harpagophytum-related side-effects, except possibly for mild and infrequent gastrointestinal symptoms.

HEAL-N-SOOTHE CONTAINS DEVILS CLAW, BUT IT IS UNCLEAR WHAT THE LEVEL OF HARPAGOSIDES ARE. 50-100 MG HARAGOSIDES WERE USED IN THIS STUDY AND WORKED BETTER THAN PLACEBO.
Gagnier JJ, van Tulder M, Berman B, Bombardier C. Herbal medicine for low back pain. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD004504.

Source: Provincal Medical Centre, 5955 Ontario St., Unit 307, Windsor, Ontario, Canada, N8S1W6. j.gagnier@utoronto.ca

Abstract
BACKGROUND:
Low-back pain is a common condition and a substantial economic burden in industrialized societies. A large proportion of patients with chronic low-back pain use complementary and alternative medicine (CAM), visit CAM practitioners, or both. Several herbal medicines have been purported for use in low-back pain.

OBJECTIVES:
To determine the effectiveness of herbal medicine for non-specific low-back pain.

SEARCH STRATEGY:
We searched the following electronic databases: Cochrane Complementary Medicine Field Trials Register (Issue 3, 2005), MEDLINE (1966 to July 2005), EMBASE (1980 to July 2005); checked reference lists in review articles, guidelines and retrieved trials; and personally contacted individuals with expertise in this very specialized area.

SELECTION CRITERIA:
We included randomized controlled trials, examining adults (over 18 years of age) suffering from acute, sub-acute or chronic non-specific low-back pain. The interventions were herbal medicines, defined as plants that are used for medicinal purposes in any form. Primary outcome measures were pain and function.

DATA COLLECTION AND ANALYSIS:
Two authors (JJG & MVT) conducted the database searches. One author contacted content experts and acquired relevant citations. Full references and abstracts of the identified studies were downloaded. A hard copy was retrieved for final inclusion decisions. Methodological quality and clinical relevance were assessed separately by two individuals. Disagreements were resolved by consensus.

MAIN RESULTS:
Ten trials were included in this review. Two high quality trials examining the effects of Harpagophytum Procumbens (Devil's Claw) found strong evidence that daily doses standardized to 50 mg or 100 mg harpagoside were better than placebo for short-term improvements in pain and rescue medication. Another high quality trial demonstrated relative equivalence to 12.5 mg per day of rofecoxib (Vioxx). Two trials examining the effects of Salix Alba (White Willow Bark) found moderate evidence that daily doses standardized to 120 mg or 240 mg salicin were better than placebo for short-term improvements in pain and rescue medication. An additional trial demonstrated relative equivalence to 12.5 mg per day of rofecoxib. Three low quality trials on Capsicum Frutescens (Cayenne), examining various topical preparations, found moderate evidence that Capsicum Frutescens produced more favourable results than placebo and one trial found equivalence to a homeopathic ointment.

AUTHORS' CONCLUSIONS:
Harpagophytum Procumbens, Salix Alba and Capsicum Frutescens seem to reduce pain more than placebo. Additional trials testing these herbal medicines against standard treatments are needed. The quality of reporting in these trials was generally poor. Trialists should refer to the CONSORT statement extension for reporting trials of herbal medicine interventions.

HEAL-N-SOOTHE CONTAINS DEVILS CLAW, BUT IT IS UNCLEAR WHAT THE LEVEL OF HARPAGOSIDES ARE. 50-100 MG HARAGOSIDES WERE USED IN THESE STUDIES AND WORKED BETTER THAN PLACEBO.

REFERENCE NOTE ABOUT DEVIL'S CLAW: Devil's claw has been studied for low back pain, muscle pain, and osteoarthritis using daily doses of crude tuber up to 9 g daily, 1 to 3 g of extract, and 50 to 100 mg of harpagoside. Standardized preparations include LI 174 (Rivoltan), Doloteffin (more than 50 mg harpagoside), and WS 1531. A level of more than 1% harpagoside in root is considered acceptable. Commercial sources of devil's claw extract contain 1.4% to 2% harpagoside.

GÃ¶bel H, Heinze A, Ingwersen M, Niederberger U, Gerber D. [Effects of Harpagophytum procumbens LI 174 (devil's claw) on sensory, motor und vascular muscle reagibility in the treatment of unspecific back pain]. Schmerz. 2001 Feb;15(1):10-8.
[Article in German]

Source: Neurologisch-verhaltensmedizinische, Schmerzklinik Kiel in Kooperation mit der UniversitÃ¤t Kiel. h.gobel@neurologie.uni-kiel.de

Abstract
PROBLEM:
This randomised, double-blind, placebo controlled study was intended to investigate the effects of Harpagophytum procumbens (Devil's Claw) on sensory, motor and vascular mechanisms of muscle pain. In addition to clinical efficacy and tolerability, possible action mechanisms were analysed by means of experimental algesimetric methods.

METHODOLOGY:
The study was performed on patients with slight to moderate muscular tension or slight muscular pain of the back, shoulder and neck. On a double-blind randomised basis the verum group received 2x1 film tablets per day, i. e. 2x480 mg/day, of Harpagophytum extract LI 174 (Rivoltan(R)) at 8.00 a.m. and 8.00 p.m. over a certain period. The duration of the therapy was 4 weeks. Data recording at 14-day intervals was made using a visual analogue scale, pressure algometer test, recording of antinociceptive muscular reflexes, muscle stiffness test, EMG surface activity, muscular ischaemia test, clinical global score and subjective patient and physician ratings.

RESULTS:
A total of 31 patients in the verum group and 32 in the placebo group were treated. After four weeks of treatment there was found to be a clear clinical efficacy of the verum on the clinical global score and in the patient and physician ratings. Highly significant effects were found in the visual analogue scale, the pressure algometer test, the muscle stiffness test and the muscular ischaemia test. No difference from placebo was found in the recording of antinociceptive muscular reflexes or in the EMG surface activity. Tolerability was good; no serious adverse effects occurred.

CONCLUSIONS:
A highly significant clinical efficacy was achieved with a monotherapy of Harpagophytum dry extract LI 174 after four weeks' treatment at a dosage of 2x480 mg/day in cases of slight to moderate muscular pain. With regard to the action mechanisms investigated, it may be concluded that treatment with Harpagophytum extract LI 174 may be expected to have a significant influence on sensory and vascular muscular response and bring about a reduction in muscle stiffness. No central nervous effects were discovered.

CANNOT USE/DOSAGE
Leblan D, Chantre P, FourniÃ© B. Harpagophytum procumbens in the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. Joint Bone Spine. 2000;67(5):462-7.

Source: Laboratoires Arkopharma, Carros, France.

Abstract
OBJECTIVE:
To evaluate the efficacy and safety of Harpagophytum in the treatment of hip and knee

osteoarthritis comparatively with the slow-acting drug for osteoarthritis, diacerhein.

PATIENTS AND METHODS:
A multicenter, randomized, double-blind, parallel-group study was conducted in 122 patients with hip and/or knee osteoarthritis. Treatment duration was four months and the primary evaluation criterion was the pain score on a visual analog scale. Harpagophytum 2,610 mg per day was compared with diacerhein 100 mg per day.

RESULTS:
After four months, considerable improvements in osteoarthritis symptoms were seen in both groups, with no significant differences for pain, functional disability, or the Lequesne score. However, use of analgesic (acetaminophen-caffeine) and nonsteroidal anti-inflammatory (diclofenac) medications was significantly reduced in the Harpagophytum group, which also had a significantly lower rate of adverse events.

CONCLUSION:
In this study, Harpagophytum was at least as effective as a reference drug (diacerhein) in the treatment of knee or hip osteoarthritis and reduced the need for analgesic and nonsteroidal anti-inflammatory therapy.
CANNOT USE/DOSAGE

Sasaki T, Kojima S. Ga uptake and heparan sulfate content of Ehrlich solid tumor in mice. Eur J Nucl Med. 1986;12(4):182-6.

Abstract
The relationship between 67Ga uptake and heparan sulfate (HS) content in Ehrlich solid tumor (EST) of mice was investigated, and the effect of cyanomethylamine, papain, streptozotocin, or bleomycin pretreatment on 67Ga uptake in EST was studied. 67Ga uptakes in EST and kidney were much higher than other tissues, and these tissues also contained large amounts of HS. 67Ga uptakes and HS synthesis in the EST were inhibited by pretreatment with cyanomethylamine or papain (inhibitors of fibrosis). Parallel reductions of 67Ga uptake and HS synthesis in EST were observed in EST transplanted into streptozotocin-induced diabetic mice. The weight of EST in the bleomycin-injected group was decreased to less than half of the control, but no effect was observed on 67Ga uptake per gram of EST. These results suggest that 67Ga uptake in the tumor and inflammatory lesions are related to the quantity of HS in these tissues, and the correlation between the uptake of 67Ga and the rate of cellular proliferation is secondary.

PAPAIN IS AN INHIBITOR OF FIBROSIS BUT COULD NOT FIND HUMAN STUDIES TO SUPPORT SAME.
Skyrme-Jones RA, O'Brien RC, Berry KL, Meredith IT. Vitamin E supplementation improves endothelial function in type I diabetes mellitus: a randomized, placebo-controlled study. J Am Coll Cardiol. 2000 Jul;36(1):94-102.

Source: Centre for Heart and Chest Research, Monash Medical Centre and Monash University, Melbourne, Australia.

Abstract
OBJECTIVES:
We sought to determine, in a double-blind, placebo-controlled, randomized study, whether vitamin E supplementation (1,000 IU for three months) would improve impaired conduit and resistance

vessel endothelial vasodilator function (EVF) and systemic arterial compliance (SAC) in type I diabetes mellitus (DM).

BACKGROUND:
Oxidative stress is thought to be important in the pathogenesis of impaired EVF. Consistent with this hypothesis, we have recently shown that impaired EVF is related to low density lipoprotein (LDL) vitamin E content (VEC) in young subjects with type 1 DM.

METHODS:
We assessed EVF in the brachial artery (using noninvasive ultrasound, flow-mediated vasodilation [FMD]; n = 41) and in the forearm resistance vessels (by flow responses to intrabrachial acetylcholine [ACh]; n = 21) and measured SAC (simultaneous aortic blood flow and carotid pressure measurements; n = 41) before and after active or placebo therapy.

RESULTS:
The LDL VEC was increased by 127% after supplementation, resulting in a significant reduction in the oxidative susceptibility of LDL. There was no time-dependent change in FMD or in the response to ACh or SAC in the placebo group. A significant improvement in FMD (2.6 +/- 0.6% to 7.0 +/- 0.7%, $p < 0.005$) and the dose response to ACh ($p < 0.05$) were observed in those randomized to vitamin E therapy. Systemic arterial compliance was not affected by vitamin E (0.41 +/- 0.03 vs. 0.49 +/- 0.06 arbitrary compliance units, p = NS). The change in FMD was related to the change in LDL VEC ($r = 0.42$, $p < 0.05$) and the change in the oxidative susceptibility of LDL ($r = 0.64$, $p < 0.0001$).

CONCLUSIONS:
Short-term daily oral supplementation with vitamin E improves EVF in both the conduit and resistance vessels of young subjects with type I DM.

CANNOT USE/DOSAGE
Li Y, Schellhorn HE. New developments and novel therapeutic perspectives for vitamin C. J Nutr. 2007 Oct;137(10):2171-84.

Source: Department of Biology, McMaster University, Hamilton, Ontario, Canada L8S 4K1.

Abstract
Vitamin C is required for collagen synthesis and biosynthesis of certain hormones and recommended dietary intake levels are largely based these requirements. However, to function effectively as an antioxidant (or a pro-oxidant), relatively high levels of this vitamin must be maintained in the body. The instability of vitamin C combined with its relatively poor intestinal absorption and ready excretion from the body reduce physiological availability of this vitamin. This inability to maintain high serum levels of vitamin C may have serious health implications and is particularly relevant in the onset and progression of degenerative disease, such as cancer and cardiovascular disease (CVD), which have a strong contributing oxidative damage factor. In this review, we examine recent studies on the regulation of transport mechanisms for vitamin C, related clinical ramifications, and potential implications in high-dose vitamin C therapy. We also evaluate recent clinical and scientific evidence on the effects of this vitamin on cancer and CVD, with focus on the key mechanisms of action that may contribute to the therapeutic potential of this vitamin in these diseases. Several animal models that could be utilized to address unresolved questions regarding the feasibility of vitamin C therapy are also discussed.

Singh RK, Rai D, Yadav D, Bhargava A, Balzarini J, De Clercq E. Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid. Eur J Med Chem. 2010 Mar;45(3):1078-86. Epub 2010 Jan 19.

Source: Nucleic Acids Research Laboratory, Department of Chemistry, University of Allahabad, Allahabad 211002, India.

Abstract
Curcumin bioconjugates, viz. di-O-tryptophanylphenylalanine curcumin (2), di-O-decanoyl curcumin (3), di-O-pamitoyl curcumin (4), di-O-bis-(gamma,gamma)folyl curcumin (6), C(4)-ethyl-O-gamma-folyl curcumin (8) and 4-O-ethyl-O-gamma-folyl curcumin (10) have been synthesized and tested for their antibacterial and antiviral activities. The conjugates 2, 3, 4, 6 and 8 have shown very promising antibacterial activity with MIC ranging between 0.09 and 0.67 microM against Gram-positive cocci and Gram-negative bacilli. Further, the conjugates 2, 3, 6, 8 and 10 have been screened for their antiviral activities against HSV, VSV, FIPV, PIV-3, RSV and FHV and the molecules 2 and 3 have shown good results with EC(50) 0.011 microM and 0.029 microM against VSV and FIPV/FHV, respectively. However, the molecules did not show expected results against HIV-1 III(B) and ROD strains in MTT assay.

Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life Sci. 2006 Mar 27;78(18):2081-7. Epub 2006 Jan 18.

Source: Department of Pathology, Uniformed Services University of the Life Sciences, Center for Combat Casualty and Life Sustainment Research, Bethesda, Maryland 20814, USA. maheshwari@usuhs.mil

Abstract
Turmeric (Curcuma longa rhizomes), commonly used as a spice is well documented for its medicinal properties in Indian and Chinese systems of medicine. It has been widely used for the treatment of several diseases. Epidemiological observations, though inconclusive, are suggestive that turmeric consumption may reduce the risk of some form of cancers and render other protective biological effects in humans. These biological effects of turmeric have been attributed to its constituent curcumin that has been widely studied for its anti-inflammatory, anti-angiogenic, anti-oxidant, wound healing and anti-cancer effects. As a result of extensive epidemiological, clinical, and animal studies several molecular mechanisms are emerging that elucidate multiple biological effects of curcumin. This review summarizes the most interesting in vitro and in vivo studies on the biological effects of curcumin.