NUT030 Rev. 4/99
CLINICAL NUTRITION INSIGHTS

Understanding The Natural Management of Pain and Inflammation

BY DR. MARK PERCIVAL

ABSTRACT: *The primary reason why people seek the advice of health professionals is that they have some sort of pain. In the most general terms, pain is symptomatic of some form of dysfunction and resultant inflammatory processes in the body. In more specific terms, pain is the result of an injury to tissue either from physical trauma or from toxicity, i.e., the presence of a pathogenic microorganism (infection) or chemical toxin which interferes with normal bodily functions. Certain nutrient insufficiencies or imbalances may also exacerbate pain and inflammation. Many drugs are available that help to reduce inflammation and relieve pain. They work by interfering with the body's natural inflammatory response mechanisms; however, they are not without side effects, particularly when chronically used. A growing body of research suggests a role for more natural and safe alternatives for the management of pain and inflammation. Some areas of research include supplemental essential fatty acids, herbs such as ginger, turmeric, and boswellia, proteolytic enzymes, and bioflavonoids.*

While there is a tendency to consider the inflammatory response as a reaction that is harmful to the body, a more balanced view is that it is actually a protective and restorative response in which the body attempts to either rid itself of chemical toxins or foreign invaders, or to repair itself following an injury. It is when inflammation becomes excessive or uncontrolled that we may begin to see delayed healing or chronic inflammatory conditions.

The healing process is very complex and involves more than just an inflammatory response. Tissue that has been injured must be repaired. It is well established that nutrients can be rate-limiting factors for tissue repair and wound healing. For example, vitamin C deficiencies have been directly linked to slow wound healing. While this paper focuses on nutritional support related to pain and inflammation, nutritional support for connective tissue repair and wound healing is discussed in greater detail in a previous Clinical Nutrition Insight entitled, "Nutritional Support for Connective Tissue and Wound Healing" (NUT026).

THE INFLAMMATORY RESPONSE

The classic signs of inflammation are local redness, swelling, heat, pain, and loss of function. The events of inflammation that underlie these manifestations are induced and regulated by a large number of chemical mediators, including eicosanoids, kinins, complement proteins, histamine, and monokines. Various forms of anti-inflammatory therapy involve regulating the production of some of these chemical mediators. For instance, the regulation of eicosanoid synthesis is a classic mechanism for controlling inflammation.[1,2]

• EICOSANOIDS

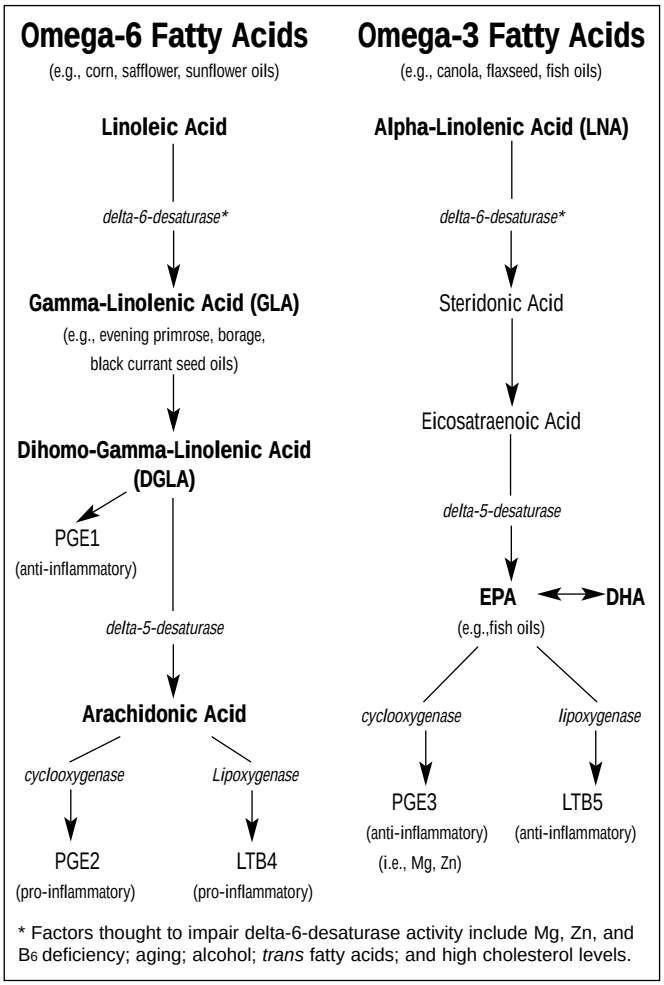
Eicosanoids are short-lived, hormone-like substances present in tissues throughout the body. They function as mediators of a variety of physiological responses such as inflammation, blood clotting, vascular dilation, and immunity. Eicosanoids can be divided into four classes: prostaglandins, leukotrienes, thromboxanes, and prostacyclins. A large part of the inflammatory process is regulated specifically by the prostaglandins and leukotrienes. Some prostaglandins and leukotrienes have pro-inflammatory effects, while others are considered anti-inflammatory.

Eicosanoids are produced from omega-6 and omega-3 polyunsaturated fatty acids present in cell membrane phospholipids. They are released from cell membranes by the action of phospholipases. Linoleic acid, which occurs abundantly in vegetable oils, is the predominant omega-6 fatty acid. It is classified as an essential fatty acid (EFA) because the human body must have it but cannot synthesize it. Dietary linoleic acid is primarily converted to arachidonic acid, the

direct precursor of pro-inflammatory mediators, i.e., prostaglandins of the 2-series (PGE2) and leukotrienes of the 4-series (LTB4). Arachidonic acid is also obtained directly from the diet, e.g., from meat, eggs, and a few plant products including, most notably, peanut oil. Arachidonic acid is the major fatty acid released in response to tissue injury and contributes greatly to the inflammatory process.

As illustrated in Figure 1, through a series of enzymatic steps linoleic acid is converted first to gamma-linolenic acid (GLA), then to dihomo-gamma-linolenic acid (DGLA) and, finally, to arachidonic acid. In addition to being an intermediate in the conversion of linoleic acid to arachidonic acid, DGLA is the direct precursor of prostaglandins of the 1-series (PGE1) which have been shown to have anti-inflammatory effects. Compared to arachidonic acid, the amount of DGLA present in the body is small; however, it is possible to increase levels of DGLA by consuming oils rich in GLA such as evening primrose oil, borage, and black currant seed.[3]

Figure 1: Metabolic Pathways of Essential Fatty Acids



* Factors thought to impair delta-6-desaturase activity include Mg, Zn, and B_6 deficiency; aging; alcohol; *trans* fatty acids; and high cholesterol levels.

The omega-3 fatty acids are represented by alpha-linolenic acid (LNA) – also an essential fatty acid – and its derivatives, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Dietary LNA is a bit harder to come by; the more common dietary sources are green leafy vegetables, soybeans, spirulina, and canola and flaxseed oil. EPA and DHA occur naturally in fish and are especially abundant in the fatty, cold water varieties. Eicosanoids produced from omega-3 fatty acids – prostaglandins of the 3-series and leukotrienes of the 5-series – are weak inflammatory mediators and thus contribute less to the inflammatory process than do those produced from arachidonic acid.[1,2]

The final conversion of fatty acids to their respective eicosanoids occurs with the help of the cyclooxygenase and lipoxygenase enzymatic pathways (Figure 1). Indeed, much of the analgesic and anti-inflammatory therapy available is based on the pharmacological manipulation of these two enzyme systems. Anti-inflammatory drugs such as aspirin and ibuprofen work, for example, by inhibiting cyclooxygenase and, therefore, prostaglandin production.

A QUESTION OF BALANCE

The actions of both omega-6 and omega-3-derived eicosanoids are necessary to maintain balance and homeostasis during an inflammatory response.[4,5] It is thought that problems may arise when one type of EFA predominates over the other, leading to an imbalance in eicosanoid production. Many factors, including the urge by some health authorities to substitute dietary polyunsaturated fatty acids for the generally less healthful saturated fats, has led to an enormous increase in the amount of omega-6 fatty acids Westerners consume. Corn, safflower, and sunflower oils, which are rich in linoleic acid, make up a large portion of the fats in many diets. Additionally, the consumption of meat contributes a significant amount of arachidonic acid. The dietary ratio of omega-6 to omega-3 fatty acids in the United States has been estimated to range between 20-25:1. A more healthful ratio may be closer to 5-10:1.[4,6]

Why the more balanced ratio? The type of prostaglandins or leukotrienes produced during an inflammatory response is determined by the composition of cellular membrane lipids, which is directly influenced by the type of fats included in the diet.

Balancing a typically linoleic acid- and arachidonic acid-rich diet with GLA and omega-3 fatty acids may help to: (1) displace arachidonic acid from membrane phospholipids and (2) compete with arachidonic acid for cyclooxygenase and lipoxygenase, thereby changing the balance of eicosanoid synthesis toward anti-inflammatory mediators and away from pro-inflammatory mediators.[1-4]

As stated earlier, arachidonic acid is the major fatty acid released in response to injury. By increasing the availability of DGLA and EPA with food choices or fatty acid supplements, it is possible they will competitively inhibit the release of arachidonic acid and pro-inflammatory eicosanoids. Fish oil supplementation for the potential management of inflammation and inflammatory disease, e.g., arthritis, is a classic example of this kind of fatty acid manipulation.[4,7-11] Kremer et al. reported significant improvement in joint tenderness and joint swelling in patients with rheumatoid arthritis after receiving fish oil supplements for a period of 24 weeks.[12] Indeed, many additional experimental studies support the use of fish oil supplements for inflammatory diseases including, among others, heart disease and hypertension, cancer, atopic dermatitis, and diabetes.[4,13]

Supplemental GLA, as from evening primrose oil or borage oil, may be of potential benefit for certain inflammatory conditions as well. Areas of research that show the most promise regarding the use of GLA-rich oils are that of inflammatory and auto-immune disorders (e.g., rheumatoid arthritis) and skin disorders (atopic eczema).[3,14-19] Leventhal et al. reported a reduction in the signs and symptoms of disease activity in patients with rheumatoid arthritis when treated with supplemental black currant seed oil.[15] On another occasion, they reported similar results with supplemental borage oil.[16] Fiocchi et al. reported a gradual improvement in children treated with evening primrose oil for atopic dermatitis.[19] The amount of itching and use of antihistamines were significantly reduced.

In addition, it is important to note that supplementation with polyunsaturated fatty acids may require additional vitamin E intake to prevent increased peroxidation of membrane lipids.[20]

HERBAL SUPPORT

The number of chemical compounds, called phytochemicals, found within the plant kingdom is truly vast and their range of activity is equally as great. Some of the phytochemicals found in certain herbs and plants are reported to demonstrate pain and inflammation-reducing properties. Like aspirin, many are presumed to work by blocking the cyclooxygenase and lipoxygenase pathways and possibly by other mechanisms as well. Bioflavonoids are a broad class of phytochemicals found largely in citrus fruits, tea, and wine. Research suggests that bioflavonoids, such as quercetin, may confer pain and inflammation reducing activity by inhibiting cyclooxygenase, lipoxygenase, and phospholipase.[21]

• Ginger and Turmeric

Ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*), two very popular herbs used within the East Indian system of medicine known as Ayurveda, have long been used in folk medicine for a variety of both acute and chronic inflammatory conditions such as sprains and arthritis. Numerous animal and *in vitro* studies have demonstrated significant anti-inflammatory and antioxidant activities for both ginger and turmeric.[5,23-32] These studies suggest that both herbs may block cyclooxygenase and lipoxygenase activity, thereby inhibiting prostaglandin and leukotriene release. In addition, turmeric may inhibit the release of histamine.[26]

In a recent investigation which evaluated the effects of ginger on patients with osteoarthritis, rheumatoid arthritis, and muscular discomfort, more than 75% of the arthritic patients reported improvements in pain and swelling, while all patients who experienced muscle discomfort reported relief.[23] There were no reported side effects during the time of ginger supplementation, which ranged from 3 months to 2 1/2 years.

The anti-inflammatory properties of curcumin, the principal compound found in turmeric, were studied in a double-blind clinical trial of 49 patients with rheumatoid arthritis.[32] One group of patients received 1,200 mg/day curcumin for 5 to 6 weeks while the other group received phenylbutazone (300 mg/day), an anti-inflammatory drug. Significant improvement was seen in both groups, with relief of morning stiffness and joint swelling comparable in the two groups.

• Cayenne Pepper

Another compound structurally related to those found in ginger and turmeric is capsaicin, the main constituent of cayenne pepper (*Capsicum annuum*). Capsaicin may play a role in inhibiting prostaglandin synthesis by blocking cyclooxygenase activity.[33] In addition, cayenne pepper has been shown to possess powerful antioxidant compounds, reduce platelet aggregation, and improve blood circulation, and thus may play a role in reducing inflammation.[34]

• Boswellia

Boswellia gum resin, derived from the *Boswellia serrata* tree, is a traditional Ayurvedic remedy that is used for a variety of inflammatory diseases, such as rheumatoid arthritis, osteoarthritis, and cervical spondylitis.[35] The main constituents of the gum resin are boswellic acids, which have been found to inhibit leukotriene synthesis by specifically inhibiting 5-lipoxygenase, the key enzyme of leukotriene biosynthesis.[30,36,37] Boswellic acids have also been shown *in vitro* to inhibit the complement system, a set of enzymes that work with antibodies to attack foreign cells and bacteria.[38,39] Pathologically prolonged and sustained activation of the complement system is implicated in a variety of inflammatory disorders.

Boswellic acids have been shown to possess anti-inflammatory and anti-arthritic activity in a variety of animal experimental models as well as human studies.[40,41] The effectiveness of boswellia extract was evaluated on 260 rheumatoid arthritis patients using a range of different clinical approaches.[42] Compared to placebo, boswellia produced a significant reduction in joint pain and swelling and morning stiffness, and the patients' general health and well-being improved. Overall, boswellia was found to be effective in reducing the symptoms of rheumatoid arthritis in 50% to 60% of the patients. Unlike traditional NSAIDs, boswellia extract appears to exhibit no significant side effects or toxicity.[43]

PROTEOLYTIC ENZYMES

A great deal of the research that describes an anti-inflammatory effect of proteolytic enzymes centers around acute (e.g., sports) injuries, although post-surgery and degenerative joint conditions have been studied as well.[5,44-48] In most cases, the patients that received the enzymes demonstrated significant reductions in pain and inflammation and faster recovery rates compared to the placebo groups (the duration of healing was reduced by half in some instances).

The anti-inflammatory activity of proteolytic enzymes is believed to be, in part, the result of eicosanoid modulation. Animal studies suggest that oral proteases may inhibit the synthesis of pro-inflammatory prostaglandins. Additional mechanisms of actions may include fibrinolytic activity, the activation of endogenous proteases (plasmin), and removal of necrotic tissue (debridement).

Supplemental proteolytic enzymes are derived from plant and animal sources. Common proteases include bromelain from pineapple; papain and chymopapain from papaya; the fungal protease from the *Aspergillus oryzae* fungi; and trypsin, chymotrypsin, and pancreatin usually from porcine (pig) or bovine (cow) origin. However, porcine sources yield higher specific activity than do bovine sources.

HOMEOPATHIC REMEDIES

Homeopathic remedies for pain and inflammation have been around for over 100 years. Believed to provide an "energetic" stimulus to the natural healing qualities of the body, homeopathic remedies are reported to be highly effective and at the same time quite innocuous. Traditionally, they have been used for both acute and chronic injuries. The growing interest in alternative medicine and the numerous anecdotal reports of homeopathy's effectiveness have led to an increase in the number of clinical trials performed. While these trials may not provide scientific explanations as to how homeopathy works, many do support their use.

INFLAMMATION INCREASES FREE RADICAL DAMAGE

A direct result of inflammation is an increase in free radical production.[49] Free radicals react with the polyunsaturated fatty acids of cell membranes leading to the eventual destruction of the cell. One single free radical can destroy an entire membrane through a self-propagating chain reaction. The body defends itself against free radical damage with an integrated antioxidant defense system that utilizes antioxidants produced naturally within the body and from antioxidants found within foods. During inflammation, the need for a variety of antioxidant nutrients may be increased.

Vitamin E, which is an important membrane antioxidant, provides chain-breaking free radical protection. As stated earlier, it may be especially important to include vitamin E with routine essential fatty acid supplementation since fatty acids are readily oxidized. It has been suggested that long-term fish oil supplementation, for example, may increase lipid peroxidation and compromise vitamin E status.[20] Additionally, some animal studies indicate that a deficiency in vitamin E may lead to a significant increase in arachidonic acid metabolites.[50]

CONCLUSION

In general, essential fatty acid (EFA) manipulation with supplemental omega-3 and specific omega-6 fatty acids may play important roles in managing chronic pain and inflammation. Theoretically, increasing levels of EFAs, specifically EPA, DHA, or GLA, may help to displace arachidonic acid from membrane phospholipids and compete with arachidonic acid for cyclooxygenase and lipoxygenase pathways. Basically, the idea is to shift the balance of eicosanoid synthesis toward anti-inflammatory mediators and away from pro-inflammatory mediators. Furthermore, it has been suggested that a healthful balance of omega-3 and omega-6 fatty acids leads to better overall health and may help reduce the risk of several common diseases such as hypertension, heart disease, and cancer.

For acute pain and inflammation, a more natural method for inhibiting cyclooxygenase and lipoxygenase pathways (the mechanism behind NSAIDs) is with herbal support such as ginger, turmeric, and boswellia, and with bioflavonoids. In addition, homeopathic remedies and proteolytic enzymes are widely used as part of a comprehensive holistic approach to managing pain and inflammation.

REFERENCES

1. Mahan LK, Arlin M. Krouse's Food, Nutrition and Diet Therapy 8th ed. WB Saunders Co, 1992.
2. Linder MC, ed. Nutritional Biochemistry and Metabolism. 2nd ed. Elsevier, 1991.
3. Horrobin DF. Nutritional and medical importance of gamma-linolenic acid. *Prog Lipid Res* 1992;31(2):163-94.
4. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991;54:438-63.
5. Bucci LR. Nutrition Applied to Injury Rehabilitation and Sports Medicine. Boca Raton: CRC Press, 1995.
6. Erasmus U. Fats That Heal, Fats That Kill. 2nd ed. Burnaby, BC, Canada: Alive Books, 1993.
7. Christophe A, Robberecht E. Effects of feeding a supplement of GLA-containing oils with fish oil on the fatty acid composition of serum phospholipids in healthy volunteers. American Oil Chemists' Society, Annual Meeting Abstracts, May, 1995.
8. Haglund O, et al. The effects of fish oil on triglycerides, cholesterol, fibrinogen and malondialdehyde in humans supplemented with vitamin E. *J Nutr* 1991;121:165-9.
9. Cobiac L, et al. Lipid, lipoprotein, and hemostatic effects of fish vs. fish-oil n-3 fatty acids in mildly hyperlipidemic males. *Am J Clin Nutr* 1991;53:1210-16.
10. Chandra RK. Dietary n-3 polyunsaturated fatty acid modulation of immune cell function before or after trauma. *Nutrition* 1995;11(1):1-11.
11. Leaf A, Weber P. Cardiovascular effects of n-3 fatty acids. *N Engl J Med* 1988;318:549-57.
12. Kremer JM, et al. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. *Arth and Rheum* 1990;33(6):810-20.
13. Bjorneboe A, et al. Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. *Br J Dermatol* 1987;117(4):463-9.
14. Kunkel SL, et al. Suppression of chronic inflammation by evening primrose oil. *Prog Lipid Res* 1982;20:885-8.
15. Leventhal LJ, et al. Treatment of rheumatoid arthritis with black currant seed oil. *Br J Rheum* 1994;33:847-52.
16. Leventhal LJ, et al. Treatment of rheumatoid arthritis with gamma-linolenic acid. *Ann Intern Med* 1993;119:867-73.
17. Morse PF, et al. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. *Br J Derm* 1989;121:75-90.
18. Kerscher MJ, Korting HC. Treatment of atopic eczema with evening primrose oil: rationale and clinical results. *Clin Investig* 1992;70:167-71.
19. Fiocchi A, et al. The efficacy and safety of gamma-linolenic acid in the treatment of infantile atopic dermatitis. *J Int Med Res* 1994;22:24-32.
20. Meydani M, et al. Effect of long-term fish oil supplementation on vitamin E status and lipid peroxidation in women. *J Nutr* 1991;121:484-91.
21. Havsteen B. Flavonoids, a class of natural products of high pharmacological potency. *Biochemical Pharmacology* 1983;32(7):1141-8.
22. Blazso G, Gabor M. Edema-inhibiting effect of procyanidin. *Acta Physiolgica Academiae Scientiarum Hungaricae* 1980;56(2):235-40.
23. Srivastava KC, Mustafa T. Ginger *(Zingiber officinale)* in rheumatism and musculoskeletal disorders. *Medical Hypotheses* 1992;39:342-8.
24. Arora RB, et al. Anti-inflammatory studies on *Curcuma longa* (Turmeric) *Indian J Med* 1971;59:1289-95.
25. Chandra D, Gupta SS. Anti-inflammatory and anti-arthritic activity of volatile oil of *Curcuma longa* (Haldi). *Indian J Med* 1972;60:138-42.
26. Yegnanarayan R, et al. Comparison of anti-inflammatory activity of various extracts of *Curcuma longa* (Linn). *Indian J Med* 1976;64:601-8.
27. Mascolo N, Jain R, Jain SC, et al. Ethnopharmacologic investigation of ginger (*Zingiber officinale*). *J Ethnopharmacol* 1989;27:129-40.
28. Kiuchi F, Iwakami S, Shibuya M. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. *Chem Pharm Bull* 1992;40:387-91.
29. Srivastava KC, Bordia A, Verma SK. Curcumin, a major component of food spice turmeric *(Curcuma longa)* inhibits platelet aggregation and alters eicosanoid metabolism in human blood platelets. *Prostaglandins Leukotr Essent Fatty Acids* 1995;52:223-7.
30. Ammon HPT, Safayhi H, Mack T, et al. Mechanism of antiinflammatory actions of curcumine and boswellic acids. *J Ethnopharmacol* 1993;38:113-9.
31. Ruby AJ, Kuttan G, Babu KD, et al. Anti-tumor and antioxidant activity of natural curcuminoids. *Cancer Lett* 1995;94:79-83.
32. Deodhar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin. *Indian J Med Res* 1980;71:632-4.
33. Flynn DL, Rafferty MF. Inhibition of human neutrophil 5-lipoxygenase activity by gingerdione, shogaol, capsaicin and related pungent compounds. *Prostaglandins Leukotr Med* 1986;24:195-8.
34. Govindarajan VS, Sathyanarayana MN. Capsicum production, technology, chemistry, and quality. Part V. Impact on physiology, pharmacology, nutrition, and metabolism; structure, pungency, pain, and desensitization sequences. In: Food Science and Nutrition 1991;29:435-74.
35. Ammon HPT. Salai Guggal-*Boswellia serrata*: from a herbal medicine to a specific inhibitor of leukotriene biosynthesis. *Phytomedicine* 1996;3:67-70.
36. Ammon HPT, Mack T, Singh GB, et al. Inhibition of leukotriene B4 formation in rat peritoneal neutrophils by an ethanolic extract of the gum resin exudate of *Boswellia serrata*. *Planta Med* 1991;57:203-7.
37. Safayhi H, Sailer ER, Ammon HPT. 5-lipoxygenase inhibition by acetyl-11-keto-ß-boswellic acid (AKBA) by a novel mechanism. *Phytomedicine* 1996;3:71-2.
38. Kapil A, Moza N. Anticomplementary activity of boswellic acids — an inhibitor of C3-convertase of the classical complement pathway. *Int J Immunopharmac* 1992;14:1139-43.
39. Knaus U, Wagner H. Effects of boswellic acid of *Boswellia serrata* and other triterpenic acids on the complement system. *Phytomedicine* 1996;3:77-81.
40. Singh GB, Atal CK. Pharmacology of an extract of salai guggal ex-*Boswellia serrata*, a new non-steroidal anti-inflammatory agent. *Agents and Actions* 1986;18:407-12.
41. Singh GB, Singh S, Bani S. Anti-inflammatory actions of boswellic acids. *Phytomedicine* 1996;3:81-5.
42. Etzel R. Special extract of *Boswellia serrata* (H 15) in the treatment of rheumatoid arthritis. *Phytomedicine* 1996;3:91-4.
43. Singh GB, Bani S, Singh S. Toxicity and safety evaluation of boswellic acids. *Phytomedicine* 1996;3:87-90.
44. Izaka K, et al. Gastrointestinal absorption and anti-inflammatory effect of bromelain. *Japan J Pharmacol* 1972;22:519-34.
45. Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple *(Ananas comosus)* and its clinical application. An update. *J Ethnopharmacology* 1988;22:191-203.
46. Christie RB. The medical uses of proteolytic enzymes. In: Wisman A. (ed.) Topics in enzyme and fermentation biotechnology. Chicester, England: Ellis Horwood Ltd, 1980:25-83.
47. Blonstein JL. Oral enzyme tablets in the treatment of boxing injuries. *The Practitioner* 1967;198:547-8.
48. Shaw PC. The use of a trypsin-chymotrypsin formulation in fractures of the hand. *Br J Clin Practice* 1969;23(1):25-6.
49. Kehrer J, Smith CV. Free radicals in biology: sources, reactivities, and roles in the etiology of human diseases. In: Natural antioxidants in health and disease. Frei B. (ed) Ch 2, 25-62. San Diego: Academic Press, 1994.
50. Calder PC, Newsholme EA. Influence of antioxidant vitamins on fatty acid inhibition of lymphocyte proliferation. *Biochem Mol Biol Int* 1983;29:175-83.