

Proteolin™

Patent pending

Product Information

Proteolin™ is a proprietary formulation of anti-inflammatory and immunomodulatory peptides (Hyperimmune Milk Protein Concentrate), Curcuminoids (Turmeric), Proteolytic Enzymes (Bromelain), and Piperin.

All the ingredients are classified as Generally Recognized As Safe (GRAS) by the United States Food and Drug Administration (FDA).

INDICATIONS:

Proteolin™ is intended for use in nutritional management of certain inflammatory processes and related pain symptoms. Processes specifically targeted by this product are trauma-related inflammations of soft tissues and/or joints, and inflammatory processes related to chronic conditions such as arthritic joint condition.

Proteolin™ was developed to address some distinctive nutritional needs arising from these conditions.

Inflammation is a natural response of the body to injury. However, excessive inflammation retards the healing process. Keeping the inflammation process under control is a key factor in expediting the healing process. The two main agents that the human body produces to manage inflammatory processes are Glucocorticoids and Proteolytic enzymes. When production of these agents by the human body is impaired, the inflammatory process becomes deregulated and goes beyond the level necessary to maintain optimal self-healing conditions. Proteolin™ is formulated to deliver the appropriate amount of nutrients with properties that regulate secretion of Glucocorticoids and Proteolytic enzymes and supplement their deficiencies to help the body maintain the optimal healing process. Unlike with other products that target neurotransmitters to inhibit pain symptoms, Proteolin™ reduces pain by keeping its source, the inflammatory process, under control.

Although all ingredients included in the Proteolin™ formulation are derived from regular food products (cow milk, pineapples, black pepper and Turmeric), they are

processed to increase their efficacy, thus making Proteolin™ a medical food that has to be taken under the supervision of a physician.

Proteolin™ is a triple action formula composed of clinically tested ingredients, which provide patients with an all-natural approach to pain management by supplying concentrated nutrients with certain properties.

Proteolin™ has three clinically proven mechanisms of action to provide a multi-targeted approach to the management of the inflammatory processes and pain. While comparable with prescription NSAIDS drugs in its efficacy, Proteolin™ is free of adverse side effects of NSAIDS.

The primary ingredient, derived from milk protein concentrate, carries unique properties associated with human inflammatory response system.

Mechanisms of Action

Hyperimmunized Milk Protein

In 1955, Petersen and Campbell³ presented evidence that cow's milk immunized with a polyvalent vaccine made from human pathogenic bacteria contained high levels of antigen-specific antibodies. Since 1958, research has been conducted on the health benefits of hyperimmune milk from cows exposed to a specific proprietary immune stimulant.³⁻⁷ The hyperimmune milk is derived from a process that involves the delivery of an immune stimulant to pregnant cows, beginning 4 weeks before parturition and continuing every 2 weeks throughout lactation. Exposing cows to a proprietary immune stimulant results in an increase in the synthesis and excretion, in the milk, of anti-inflammatory components that are normally present in cow's milk.²⁰

The concentrated formulation of the hyperimmune milk powder derived from this process, MPC, was used in the study to test anti-inflammatory activity in adults. This study showed that MPC resulted in the increased expression of naturally occurring, biologically active factors in the milk. In addition to high-molecular-weight (HMW) immunoglobulins (Ig) (antigen-specific IgG antibodies), the milk also was discovered to have low-molecular-weight (LMW) components with anti-inflammatory activity.⁴⁻⁷ Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids, including decreased release of vasoactive and chemoattractive factors, and decreased emigration of neutrophils to areas of injury and inflammation.²³ Miller et al²⁴ have shown activity similar to that of glucocorticoids involving neutrophil activity and emigration with hyperimmune milk-derived anti-inflammatory compounds.

Supplementing the diet with naturally occurring, biologically active factors found in the hyperimmunized milk protein concentrate, has shown to inhibit inflammation by decreasing the emigration of neutrophils and may do so by restricting extravasation of neutrophils through vascular tight junctions. The results with nutritional supplementation with hyperimmune milk protein concentrate revealed a significant improvement in joint pain, stiffness, and

swelling in the treatment group compared with the control group ($P < 0.015$).

A significant improvement in WOMAC Index scores was seen in subjects taking hyperimmunized milk protein concentrate in the clinical study¹. Evidence for this conclusion is based on the fact that the inflammation seen with osteoarthritis is localized to the joint and is multifactorial, but in part neutrophil mediated. Research by Ormrod et al. using the low molecular weight anti-inflammatory component from hyperimmune milk demonstrated suppression of inflammation and an increase in circulating neutrophil count in animal models. They speculated that this component might inhibit inflammation by interfering with the ability of neutrophils to emigrate from the vascular space, and they conducted in vivo studies, which demonstrated that this compound suppressed neutrophil emigration by up to 75%. In a follow-up in vitro study, Ormrod and associates demonstrated the formation and maintenance of vascular tight junctions upon exposure to the hyperimmune milk anti-inflammatory component, theorizing that the anti-inflammatory properties of this compound may be mediated by restriction of the extravasation of neutrophils through vascular tight junctions. The clinical study demonstrated a significant increase in the circulating absolute neutrophil count in the study group.

The parallels can be drawn between the activities of other anti-inflammatory agents such as Glucocorticoids (e.g. cortisol) that share similar anti-inflammatory properties linked to the inhibition of neutrophil functions. These very unique anti-inflammatory mechanisms of action explain the significant improvements in joint pain, stiffness and immobility observed in the clinical study and also account for the favorable side effect profile in the study group.

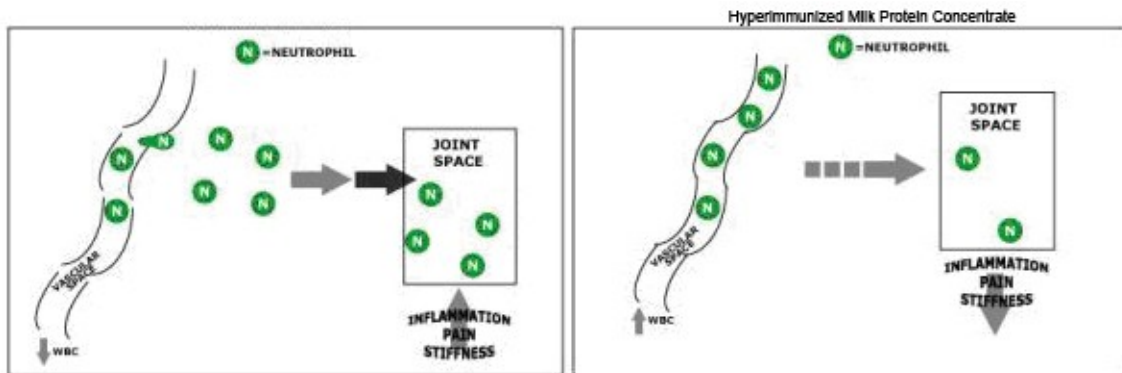


Figure 1. Decreased emigration of neutrophils to areas of injury and inflammation

Turmeric

Turmeric root extract, processed to achieve 95% curcuminoids content. Curcuminoids are nutrients that have shown to possess unique antioxidant and anti-inflammatory properties. The anti-inflammatory strength of curcuminoids is comparable to steroidal drugs such as indomethacin. Turmeric has been reported to be anti-rheumatic, anti-inflammatory and antioxidant^{20,21,22}.

Turmeric provides such essential nutrients as Calcium, Iron, Manganese, Phosphorus, Potassium, Zinc, Vitamins B1, B2, B3, and C.

Turmeric reportedly inhibits enzymes, which participate in the synthesis of inflammatory substances (leukotrienes and prostaglandins) derived from arachidonic acid, and it is claimed they are comparable in activity to the NSAID26. In a double-blind study of individuals with rheumatoid arthritis, curcuminoid products produced significant improvement in all subjects²⁸. Turmeric is also claimed to inhibit platelet aggregation²⁹.

Curcuminoids reportedly have a similar action to that of aspirin, aspirin-like anti-inflammatory agents and Cox-2 inhibitors³⁰. However, an advantage of curcuminoid products over aspirin is claimed, since curcuminoids, unlike aspirin, are reported to selectively inhibit synthesis of inflammatory prostaglandins but do not affect the synthesis of prostacyclin³¹. Curcuminoids may be preferable for individuals who are prone to vascular thrombosis and require anti-inflammatory and/or anti-arthritis therapy.

Many studies have confirmed the effectiveness of anti-inflammatory properties possessed by curcuminoids.

Study by Youn HS, Saitoh SI, Miyake K, Hwang DH³² proved that Curcumin has been shown to decrease the activation of NF-kappaB induced by multiple inflammatory stimuli by preventing IKKbeta kinase activity in MyD88-dependent pathway. Additionally, curcumin prevented LPS-induced IRF3 activation. This study reported that curcumin inhibits ligand-induced and ligand-independent dimerization of TLR4. This all shows that phytochemicals such as curcumin can modulate immune and inflammatory responses.

Results of the study published in Critical Care Medicine³³ show that curcumin is effective in managing even septic conditions.

The antioxidant activity of turmeric is mainly associated with its phenolic fraction, curcuminoids. The mechanisms by which they reportedly exert their antioxidative effects are: intervening in oxidative attacks to restrict or prevent them from occurring; scavenging or neutralizing free radicals; and breaking the oxidative chain reaction caused by free radicals^{25,26,27}.

Bromelain

Bromelain contains proteolytic enzymes - nutrients that have displayed anti-inflammatory and analgesic properties in human and laboratory studies^{41,42,43}. The action of Bromelain is attributed to the inhibition of thromboxane synthesis or bradykinin production⁴⁴. It has been shown to increase fibrinolytic activity and indirectly inhibit pro-inflammatory prostaglandins. Bromelain has been found to inhibit the biosynthesis of pro-inflammatory prostaglandins by lowering kininogen and bradykinin in serum and tissues, and may alter prostaglandin synthesis. It has also been found to activate plasmin production from plasminogen and reduce kinin by inhibiting the conversion of kininogen to kinin. In animal study, bromelain dose-dependently reduced plasma exudate at the site of inflammation by decreasing bradykinin levels and pre-kallikrein levels.

Piperine

Inclusion of Piperine (Black Pepper Extract) into the formulation of Proteolin™ was prompted by its unique ability to increase absorption of curcuminoids in humans, drastically increasing their bioavailability.

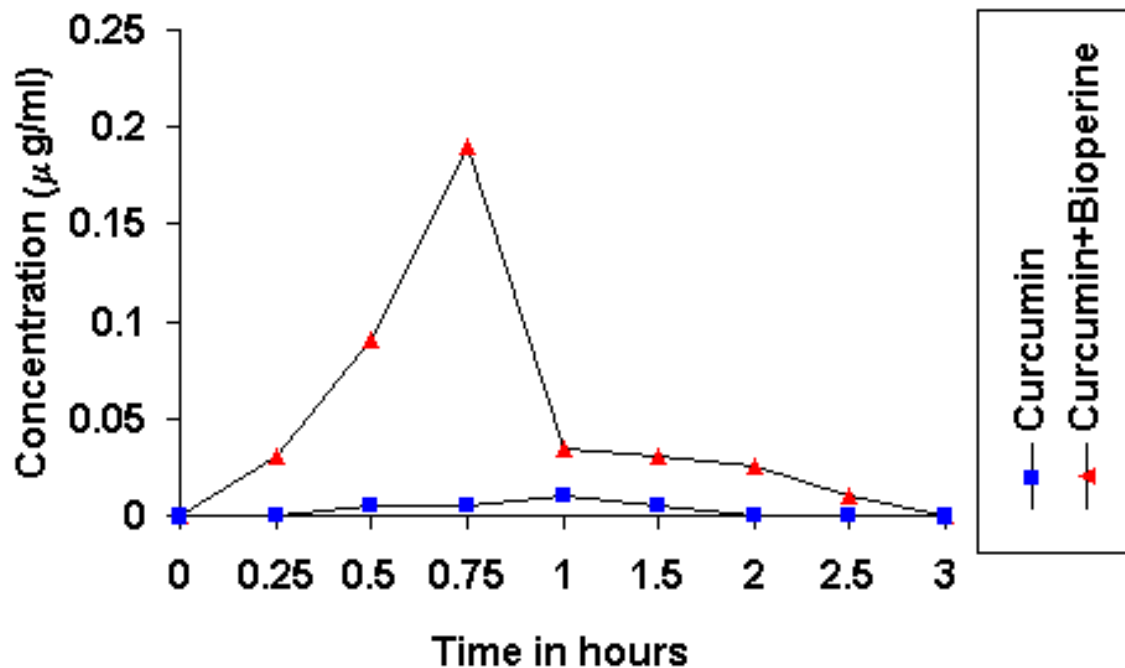


Figure 3: Effect of Bioperin® on serum concentrations of curcumin in human volunteers.

Graph in Figure 3 shows that Bioperin® enhances the serum concentration and bioavailability of curcumin in humans.

While the nutrients, included into the Proteolin™ formulation, are available in raw materials such as cow milk, turmeric root, and pineapple fruit, their concentration in their naturally occurring forms is not sufficient to produce the desired anti-

inflammatory effect. By utilizing highly concentrated and patented ingredients, Proteolin™ provides patients with a sufficient dose of these nutrients in convenient easy to swallow capsules.

Adverse Effects

In the United States turmeric is generally recognized as safe (GRAS) by the FDA³⁴. Serious adverse effects have not been reported in humans taking high doses of curcumin. A dose escalation trial in 24 adults found that single oral dosages up to 12 g were safe, and adverse effects were not dose-related³⁵. In a phase I trial in Taiwan, curcumin supplementation up to 8 g/day for three months was reported to be well-tolerated in patients with precancerous conditions or noninvasive cancer³⁶.

Proteolin™ is 90% lactose free. Only 2% to 5% of the population have an allergy to cow's milk protein. Those individuals should avoid taking Proteolin™.

Drug Interactions

Curcumin has been found to inhibit platelet aggregation in vitro^{85,86}, suggesting a potential for curcumin supplementation to increase the risk of bleeding in people taking anticoagulant or antiplatelet medications, such as aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), and warfarin (Coumadin). In cultured breast cancer cells, curcumin inhibited apoptosis induced by the chemotherapeutic agents, camptothecin, mechlorethamine, and doxorubicin at concentrations of 1-10 micromoles/liter³⁷. In an animal model of breast cancer, dietary curcumin inhibited cyclophosphamide-induced tumor regression. Although it is not known whether oral curcumin administration will result in breast tissue concentrations that are high enough to inhibit cancer chemotherapeutic agents in humans, it may be advisable for women undergoing chemotherapy for breast cancer to avoid curcumin supplements³⁷.

Piperine, which is included for the purpose of increasing the bioavailability of curcumin, may also increase the bioavailability and slow the elimination of a number of drugs, including Phenytoin (Dilantin), Propranolol (Inderal), and Theophylline^{38,39}.

Bromelain is generally safe and free of side effects when taken in moderate amounts. However, because bromelain acts as a blood thinner and not enough studies have been done to explain how bromelain interacts with blood-thinning drugs, combining such drugs with Proteolin™ should be avoided in order to

reduce the theoretical risk of excessive bleeding. Allergic reactions were also reported.

Milk proteins in Proteolin™ may interfere with the activity of tetracycline-type antibiotics.

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