PROFESSIONAL SYSTEMIC ENZYME SUPPORT

Advanced Immunomodulation with Professional Strength Systemic Enzyme Support

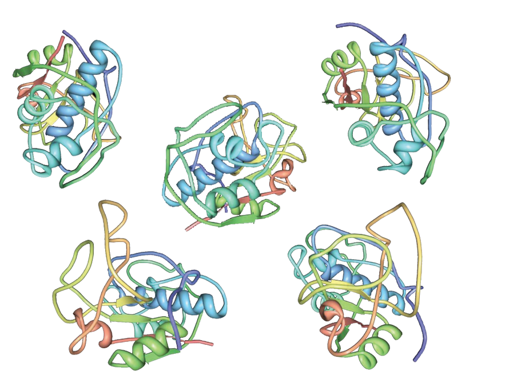
Systemic Enzyme Formulation Functions

Various functions have been documented on the German polyenzyme formulation of trypsin, bromelain and rutin. When administered orally in enteric coated tablets the systemic enzymes support and sustain optimal function of endogenous enzymes that affect immune function, cell signalling, oxidative stress and blood flow. Systemic enzymes have a far-reaching affect in various organ systems due to complex interactions that take place when the specific systemic enzyme formulation is used. The actions of systemic enzymes are briefly summarized in the following list:

1. **Immunomodulatory.** The immunomodulatory benefits of the formulation have been used in dentistry, oncology, otolaryngology, nephrology, endocrinology, hepatology, cardiology, lymphology and neurology.[1-16]
2. **Anti-inflammatory.** The anti-inflammatory (antiphlogistic) properties of the formulation noted in various clinical and research settings are mediated by the clearance of excessive pro-inflammatory cytokines.[7,12,15,17-33]
3. **Anti-edema.** The formulation is associated with reduction of edema and improvement of microcirculation normalize lymphatic circulation in the affected area.[5,7,12-15,18,19,22,25,26,34-36]
4. **Analgesic.** These analgesic effects of the formulation in various clinical settings[7,15,18,22,27,29,33,34,37,38] are due to inhibition of inflammation, as well as direct influences on nociceptors.[19] Analgesic effect is evoked by proteases both directly - by peptidolytic cleavage of pain mediators and indirectly - by lowering of oncotic pressure and restriction of inflammatory reaction.[5]
5. **Fibrinolytic.** Both an increase in blood fibrinolytic activity[39] and an increased proteolysis of extravascularly deposited fibrin[23] are observable when using the formulation in a wide range of clinical conditions.[7,12-14,37,40]
6. **Thrombolysis.** Decreased thrombocyte aggregation and thrombolytic effects as well as improvements in rheological (flow) parameters are evidenced in animal and both open and placebo-controlled human studies.[5,7,15,35,41]
7. **Anti-tumor.** Systemic enzyme support may reduce the metastatic potential or tumor cells[15] and can destroy the net which connects tumor cells with each other and with the endothelium and cause a proteolysis of tumor cell membranes.[12]
8. **Antioxidant.** The antioxidant properties of the formulation may decrease the oxidative stress observed in autoimmune diseases, kidney disease and other conditions.[42-44]

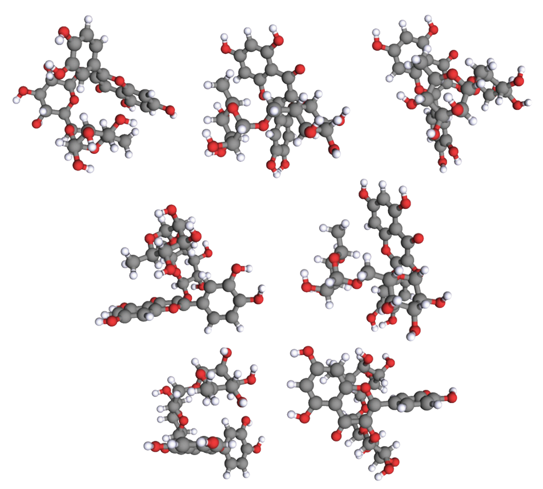
Formula Composition

The formulation that has been shown to be clinically effective is composed of 270mg of bromelain, 300mg of rutoside trihydrate (rutin) and 144mg of trypsin per three pH resistant enteric coated tablets.



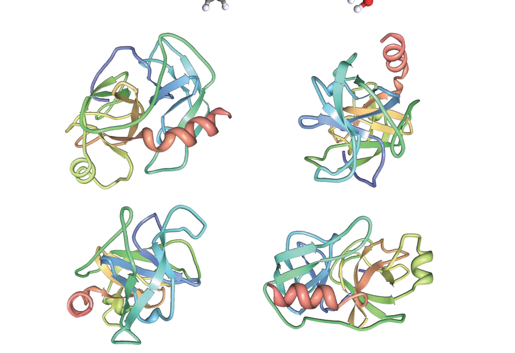
Bromelain

Enzyme Commission number: 3.4.22.32[45]
Protein Data Bank Code: 1W0Q[46]
Chemical Abstracts Service number: 9001-00-7
Description: Stem bromelain is the most abundant cysteine endopeptidase (breaks peptide bonds inside protein molecules) from the stem of the pineapple plant *(Ananas comosus)*. It is distinct from the bromelain found in the pineapple fruit (EC 3.4.22.33). The geometry and the reactivity of the catalytic site are different from those of other cysteine proteinases. Broad specificity for cleavage of proteins, but strong preference for Z-Arg-Arg-|-NHMec among small molecule substrates.[45]
Bromelain is a protease that splits peptide bonds formed by the amino acids lysine, alanine, tyrosine and glycine.[47]



Rutoside Trihydrate (Rutin)

Chemical Abstracts Service number: 250249-75-3
Formula: C27H30O16 3H2O
MOL WT.: 664.59
Synonyms: Rutoside; Sophorin; Vitamin P; Quercetin-3-rutinoside; Violaquercitrin; Rutosidum;
Chemical Name: 3-[[6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl] oxy]-2-(3,4-dihydroxyphenyl)- 5,7-dihydroxy-4H-1-Benzopyran-4-one
Description: Rutin is the rutinose glycoside form of quercetin. It is a bioflavonol having aromatic trimeric heterocyclic structure. It is a naturally occurring pigment. It is a yellow to greenish crystalline powder melting at 190°C.
Rutin increases the strength of the walls of the blood capillaries and regulates their permeability so as to normalize pathologically increased vessel permeability. It is not a dietary essential but is known to have beneficial effects on capillary disorders. It also has antioxidant activity, as well as anti-inflammatory, antihistaminic and antiviral properties.[48,49]



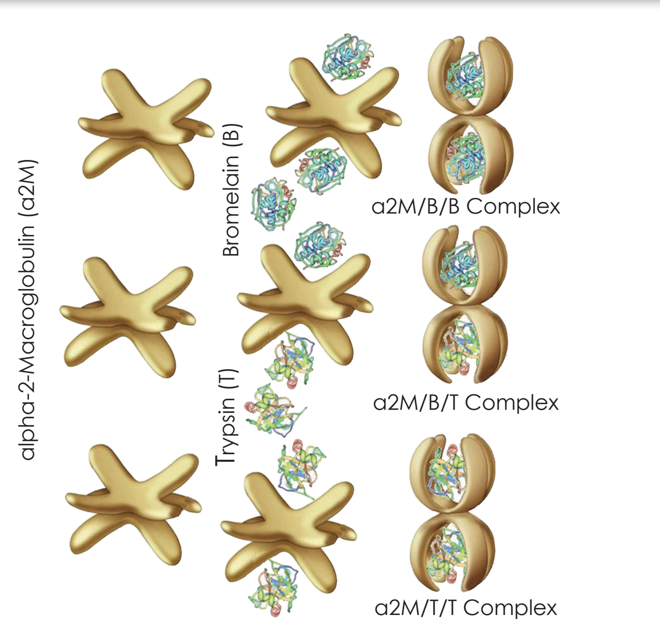
Trypsin

Enzyme Commission number: 3.4.21.4[45]
Protein Data Bank Code: 1S81[46]
Chemical Abstracts Service number: 9002-07-7
Description: Trypsin is an animal serine endoproteinase which breaks peptide bonds inside protein molecules. It is obtained from the pancreas of pigs by repeated refining and subsequent activation of the proenzyme trypsinogen.
Trypsin is a protease that predominantly cleaves peptide chains at the carboxyl side of the amino acids lysine or arginine, except when either is followed by proline.[47]

The high potency standardized bromelain, rutin and trypsin formulation is protected from stomach acid by a special enteric coating. This allows high levels of these activated proteolytic enzymes to be absorbed by the mucosal membrane of the intestine.

α2M Activation

alpha-2-macroglobulin (α2M) is a high molecular weight plasma glycoprotein that comprise as much as 8-10% of total serum protein. α2M functions as a binding, carrier, and targeting protein. It binds host or foreign peptides and particles, thereby serving as humoral defense barriers against pathogens in both the plasma and the tissue.[50]
The proteolytic enzymes trypsin and bromelain, once absorbed, will preferentially complex to the ***bait region*** of alpha-2-macroglobulin (α2M), a high molecular weight plasma glycoprotein, to create α-2-macroglobulin-protease complexes.[51,52]
This trapping of 2 protease molecules to the α2m changes the configuration of α-2-macroglobulin so that the newly **activated α-2-macroglobulin-protease complex** now has increased binding capacity for certain cytokines[53], as well as other proteins and glycoproteins. Protease activation of α-2-macroglobulin also facilitates its binding to, and elimination of, proteins damaged by oxidative stress or heat[54] and facilitates the degradation and clearance of the amyloid beta peptide (A beta), a major component of senile plaques in Alzheimer's patients.[55-60]

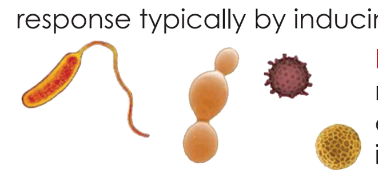


Inflammation Mediators

Inflammatory mediators are molecules and substances that induce inflammation locally at the site of tissue damage and infection and are also able to affect distant sites due to their soluble and diffusible nature. Inflammatory mediators may be endogenous or exogenous. The systemic inflammation that results due to these inflammatory mediators may also trigger other inflammatory mediators; such as exogenous mediators promoting the secretion of endogenous mediators.[61] The accumulative and secondary response can result in autoimmune diseases or decreased immunocompetence.

Exogenous mediators of inflammation

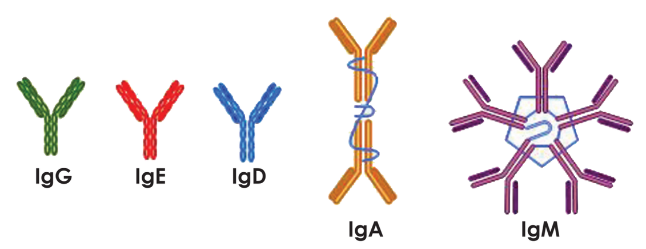
Substances referred to as exogenous mediators of inflammation are best described as foreign substances that initiate an inflammatory immune response typically by inducing endogenous mediators of inflammation.



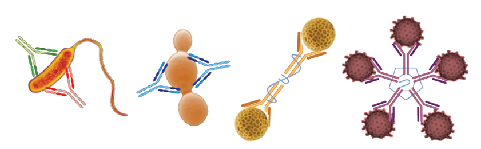
Bacterial, viral, parasitic, fungal and mycobacterial pathogens and the **toxins** they produce can act as exogenous mediators of inflammation. These substances are antigenic and promote the generation of antibodies, which are endogenous mediators of inflammation. Other antigenic substances, such as pollen, may also initiate an inflammatory immune response and act as mediators of inflammation.

Endogenous mediators of inflammation

The endogenous mediators of inflammation are predominantly proteins and glycoproteins produced from within the immune system itself or other body systems as a response to infection or trauma.



Antibodies (also known as immunoglobulins) are produced by specific white blood cells as a response to antigen exposure. Antibodies promote the activation of complement proteins (which promote pathogen death) and induce cytokine release. Antibodies are also called immunoglobulins and present in five different isotypes known as IgG, IgE, IgD, IgA & IgM. Autoantibodies are immunoglobulins which inappropriately target and damage tissues and organs of the body. Decreasing autoantibodies arrests autoimmune disease.



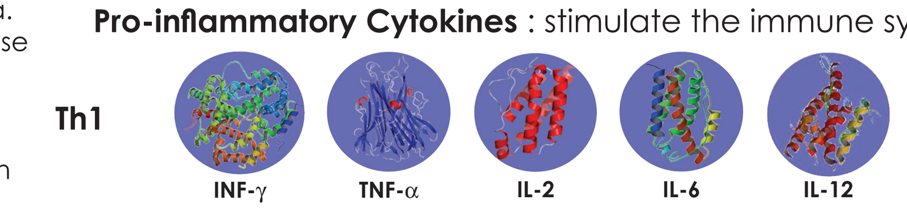
Circulating Immune Complexes (CICs) are formed when antibodies bind to antigens. They are elevated in a number of autoimmune conditions, infectious diseases, and cancers, as well as most immunologically mediated illnesses. They are noted in a number of conditions that adversely affect joint health, circulatory health, skin health, liver health, glucose health and heart health.

Cytokines are secreted as a response to infection or inflammation caused by the exogenous mediators of inflammation, or as a response to trauma. These cytokines are produced de novo in various cells as a direct response to stimulation of the immune system.
Cytokines are signaling proteins and glycoproteins involved in cellular communication, and produced by a wide variety of cells. They are typically subdivided into two categories, Th1 & Th2. A balanced between Th1 and Th2 responses is best for optimal health.

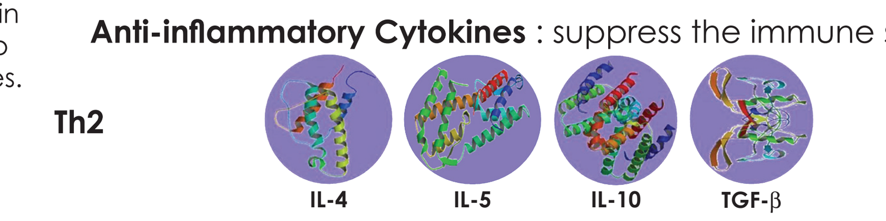
Th1 cytokines tend to produce the pro-inflammatory responses involved in antibacterial and antiviral responses. Excessive Th1 responses can lead to uncontrolled tissue damage and may perpetuate autoimmune responses. A relative excess in Th1 is observed in acute inflammation.

Th2 cytokines tend to produce anti-inflammatory responses and can counteract the Th1 mediated microbicidal actions. Excessive Th2 responses are associated with allergies and atopy (asthma, eczema, allergic rhinitis & allergic conjunctivitis). A relative excess in Th2 is observed in chronic inflammation.

Pro-inflammatory Cytokines : stimulate the immune system

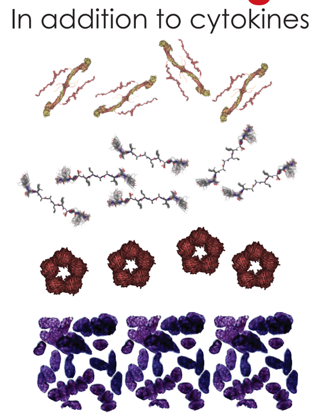


Anti-inflammatory Cytokines : suppress the immune system



Other endogenous mediators of inflammation

In addition to cytokines, other endogenous proteins and glycoproteins mediate inflammation and typically affect cytokine secretion.



Fibrin is a fibrous protein involved in the clotting of blood that acts as an inflammation mediator in response to injury or infection. Fibrin induces the pro-inflammatory cytokines IL-6 and TNF-α. Excessive fibrin increases risks of clots in the brain and heart. Excessive fibrin can accumulate in tissue and inhibit healing, and it can also hide cancer cells from the immune system.

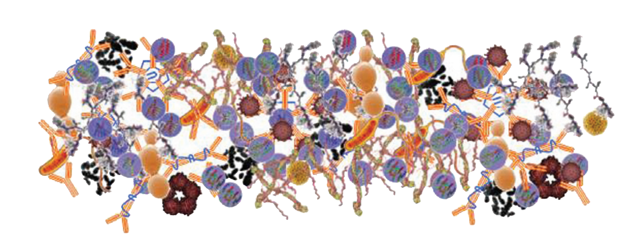
Amyloid is an endogenous fibrous protein that may be induced by TNF-α. It also upregulates the pro-inflammatory cytokines TNF-α and IL-1β. It can accumulate in tissues and may play a role in a number of neurodegenerative diseases.

C-Reactive Protein (CRP) is a protein that becomes elevated with inflammation. It is induced by the pro-inflammatory cytokines TNF-α and IL-6. Elevated levels are associated with increased risk of diabetes and heart disease.

Damaged proteins and cellular debris including proteins destroyed by glycosylation, oxidation and cellular debris from apoptosis make up a class of proteins and glycoproteins that can contribute to inflammation by up-regulating cytokine production.

Total Burden of Inflammatory Mediators

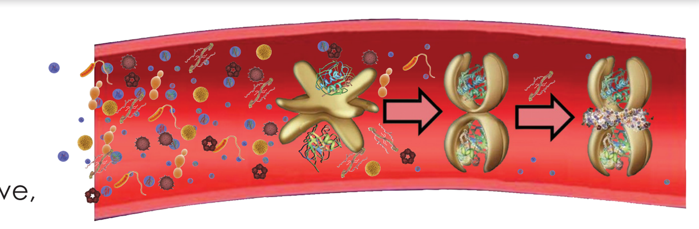
Collectively, the various mediators of inflammation drive a number of processes, such that they can easily exceed the needs of the body to protect itself from pathogens, and contribute to the destruction of healthy tissue if their levels and actions are not modulated. Immunomodulation – the modifying, controlling and tempering of the immune system – is very dependent upon the binding to, and removal of the excessive cytokines, immunoglobulins, fibrin, amyloid and CRP and other inflammatory mediators that are created as a response to inflammation.



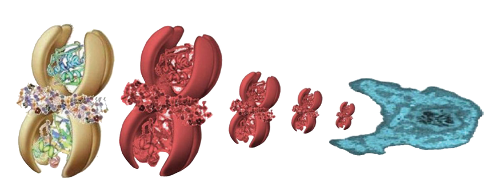
Binding and Clearance of Inflammation Mediators

Binding of Inflammatory Mediators

Activated α-2-macroglobulin-protease complexes bind excessive interstitial and intravascular cytokines[53], immunoglobulins[62,63], fibrin[64], CRP[65], amyloid beta proteins[55-60], and cell debris and proteins damaged by oxidative stress and glycosylation.[54] These inflammatory mediators are bound near the central core of the activated α2M to regions that were not exposed in the native, non-activated form of α2M.



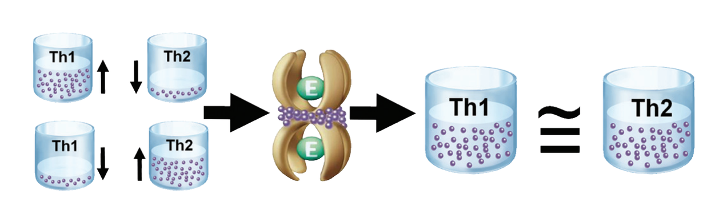
Clearance of Activated α2M complexes & Inflammatory Mediators



The alpha-2-macroglobulin-proteinase complexes are activated for receptor mediated endocytosis and are readily removed by hepatic α-2M-receptors (α-2M-R)[53], as well as other cells expressing α-2M-R, such as macrophages. The alpha 2-macroglobulin-proteinase complexes promote macrophage locomotion and chemotaxis[66], such that the **activated alpha 2-macroglobulin-proteinase complexes and the inflammatory mediators bound to the complex are cleared from the circulation very quickly by macrophages.**[67]

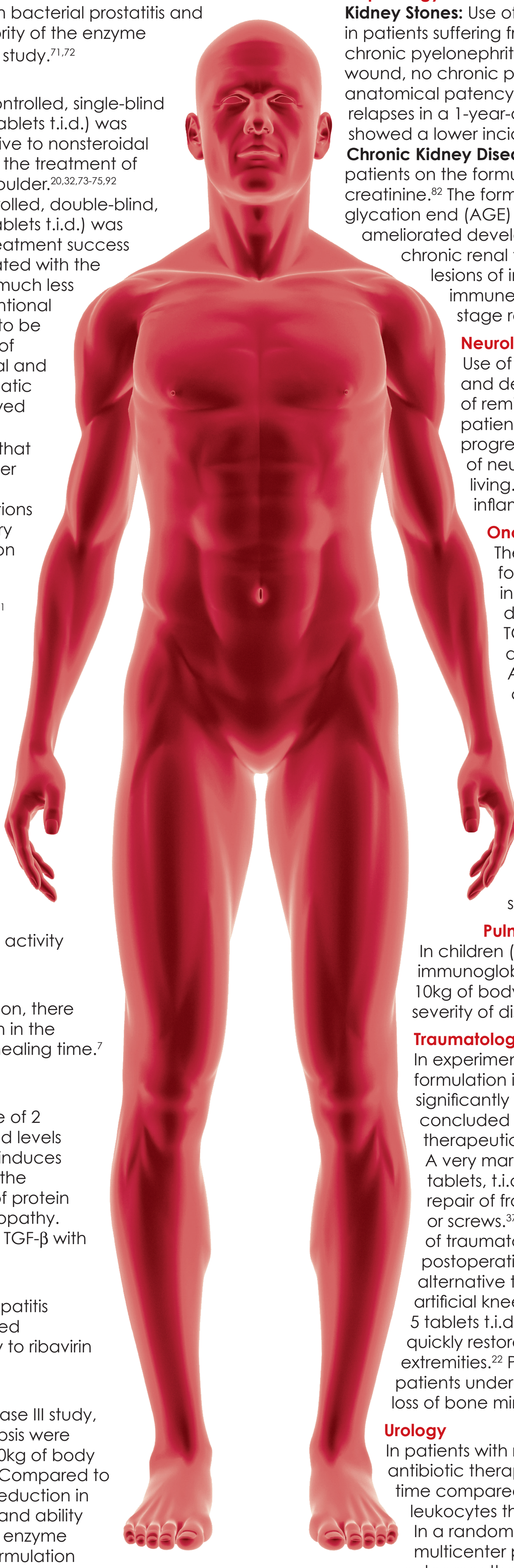
Benefits of Immunomodulation

The binding and removal of cytokines and other mediators of inflammation allows cytokine levels to be in their optimal physiologically balanced state.[53,68,69] This immunomodulation decreases the consequences of chronic inflammation such as degenerative conditions and proliferative disorders, which are associated with increased morbidity and mortality.[53,70]
Immunomodulation prevents the destructive consequences of excessive Th1 cytokines during acute inflammation as well as the onset and progression of autoimmune diseases that typically occur with excessive Th1 cytokines.[68]
Immunomodulation may also decrease development and progression of allergies and atopy (asthma, eczema, allergic rhinitis & allergic conjunctivitis) that typically manifest with a chronic excess of Th2 cytokines.[70]



Clinical Applications

The formulation is clinically effective in a broad range of conditions due to its immunomodulatory, anti-inflammatory, anti-edema, analgesic, fibrinolytic, thrombolysis, anti-tumor and antioxidant properties. Dozens of randomized, blinded and placebo studies have evidenced the specific formulation can be used in various clinical specialties, including the following:



Andrology, Men's Health
At a dosage of 2 tablets t.i.d., 17 patients with bacterial prostatitis and 23 with abacterial prostatitis showed "superiority of the enzyme preparation" over placebo in a double blind study.[71,72]

Arthritis, Rheumatology
Osteoarthritis: In a number of randomized, controlled, single-blind and double-blind studies the formulation (2 tablets t.i.d.) was considered as an effective and safe alternative to nonsteroidal antiinflammatory drugs such as diclofenac in the treatment of active osteoarthritis of the knee, hips, and shoulder.[20,32,73-75,92]
Rheumatoid Diseases: In a multicentric, controlled, double-blind, randomised, clinical trial the formulation (2 tablets t.i.d) was found to be as effective as sulfasalazine.[76] Treatment success was higher in rheumatic disease patients treated with the formulation when compared to NSAIDs with much less adverse events when compared with conventional doses of NSAID.[33] The formulation turned out to be more effective than NSAIDs in the treatment of activated, inflammatory - degenerative spinal and joint diseases, fibromyalgias and other rheumatic soft tissue diseases.[77] Animal studies also showed similar results when compared to ibuprofen.[93]
Reactive Arthritis: An autoimmune condition that develops in response to an infection in another part of the body, treated adjuvantly with the formulation showed faster relief of manifestations of joint lesion syndrome, decreased laboratory evidence of disease activity and normalization of interferon profile. In addition, the effect of antibacterial drugs was improved and chlamydia elimination was more effective.[24,91]
Fibromyalgia: Based on controlled, multicentric, retrospective analysis of therapeutical data the formulation turned out to be more effective than NSAIDs in the treatment of fibromyalgias and other rheumatic soft tissue diseases.[33,77]

Cardiology
At doses corresponding to the mean therapeutic dose for men proteolytic enzymes palliated pathological changes in the course of experimental atherosclerosis.[78] Arteriosclerosis and arterial wall remodeling were inhibited in other experimental models.[1] These findings are consistent with clinical observations that demonstrate antiatherogenic and fibrinolytic activity in humans given systemic enzymes.[49,79-81]

Dentistry
When the formulation is given before extraction, there is a shortening in the time of edema and pain in the extraction place and also the shortening of healing time.[7]

Diabetology
A clinical pilot study in patients with diabetic nephropathy demonstrated that at a dosage of 2 tablets t.i.d. the formulation reduced elevated levels of both serum and urine IL-6, a cytokine that induces over expression of TGF-β, the main trigger for the elevated protein synthesis and an inhibition of protein degradation associated with diabetic nephropathy. Animal studies also evidenced a decrease in TGF-β with decreased renal degradation.[8,16,82]

Hepatology
In an open, randomized, clinical pilot trial, hepatitis C patients treated with the formulation showed improvement in liver enzymes, and superiority to ribavirin and α-interferon.[4,83]

Immunology & Infectious Diseases
In a double-blind, randomized, controlled phase III study, children aged one month to 12 years with sepsis were treated with 1 tablet of the formulation per 10kg of body weight as an adjuvant to antibiotic therapy. Compared to antibiotic alone, the group showed a faster reduction in fever, improvement of Glasgow coma scale and ability to resume oral feeding, with no deaths in the enzyme treated group. The study suggests that the formulation has a place as an adjuvant with antibiotics and supportive treatment for early improvement of pediatric patients with sepsis.[84]

Lymphology
The formulation normalizes lymphatic circulation in the affected area restores the transporting capacity of lymphatic system.[5,85] Even in the stage III and IV lymphedema the formulation significantly improves nutrient supply to already induced and sclerotized tissue.[5]

Nephrology
Kidney Stones: Use of the formulation (2 tablets q.i.d. x 4 wks) as an adjuvant in patients suffering from nephrolithiasis (kidney stones), complicated by a chronic pyelonephritis resulted in non-complicated healing of postsurgical wound, no chronic pyelonephritis deterioration, faster functional and anatomical patency of urinary tract and a marked decrease of concretion relapses in a 1-year-observation.[86] Patients treated with the formulation showed a lower incidence of kidney stone recurrence.[87]
Chronic Kidney Disease: In a double-blind placebo controlled pilot study patients on the formulation had showed a decline in albuminuria and serum creatinine.[82] The formulation also decreases the accumulation of advanced glycation end (AGE) products.[82,90] In animal studies, the formulation ameliorated development of tubulointerstitial fibrosis and the progression of chronic renal failure[88] and decreased clinical signs and morphologic lesions of immune complex glomerulonephritis, reduces the immune deposits, and prevents or retards the progression to end stage renal disease.[89]

Neurology
Use of the formulation for 1 to 3 years decreased the incidence and degree of MS complications, increased the duration of remissions, and slowed the progression of the illness in 74 patients with remitting, remitting-progressive, and secondary progressive course of multiple sclerosis.[6] There is a stabilization of neurological impairment and improved activities of daily living. The findings are causatively linked to a decrease in inflammatory activity.[11]

Oncology
The formulation triggered the formation of intermediate forms of α2-macroglobulin displaying high affinity to TGF-β in volunteers.[94] High concentrations of TGF-β are reduced due to enhanced clearance of α2-macroglobulin-TGF-β complexes, which can benefit certain cancers accompanied by excessively high TGF-β concentrations.[70] As an adjuvant, 2 tablets, t.i.d. alleviated the consequences of radiation-induced epithelitis in patients with laryngeal cancer.[36] It also decreases post-irradiation reactions in breast cancer patients.[12]

Otolaryngology
The formulation showed the best result in treating both anterior acute uveitis and chronic anterior uveitis mostly associated with juvenile chronic arthritis.[95] The formulation as an adjuvant significantly clinical outcomes in children suffering from chronic secretory otitis and decreased the negative influence on a speech development.[13]

Pulmonology & Respiratory Diseases
In children (3-15 y/o) showing a high sickness rate and abnormal immunoglobulin levels, adjuvant use of the formulation (1 tablet per 10kg of body weight) resulted in reduction of both frequency and severity of diseases.[63]

Traumatology, Surgery
In experimentally induced hematomas, 6 tablets/day of the formulation is as effective as the dose of 12 tablets/day, and significantly better than 2 tablets/day or placebo.[96,97,21] Researchers concluded that the investigated preparation is an effective therapeutic agent for injuries resulting in pain and hematoma.[21]
A very marked anti-oedematous effect of the formulation (3 tablets, t.i.d.) was noted in postoperative period after surgical repair of fractured long bones with metal plates, pins, rods, wires or screws.[37] The formulation significantly improves the outcomes of traumatological surgery, by reducing post-traumatic and postoperative swelling.[34,98] The formulation is an effective and safer alternative to NSAIDs in the postoperative rehabilitation phase after artificial knee implantation.[27] Pre-surgical dosing for 3 to 6 days with 5 tablets t.i.d., and postsurgical dosing at 2 tablets t.i.d. was able to quickly restore the impaired function of affected upper and lower extremities.[22] Postoperative edema was significantly decreased in patients undergoing septoplasty.[99] The formulation may decrease the loss of bone mineral density.[100]

Urology
In patients with relapsing urinary tract infections responding poorly to antibiotic therapy, the formulation significantly decreased healing time compared to a placebo and showed a reduction of ESR and leukocytes that correlated with the decrease of inflammation.[101]
In a randomized, placebo controlled, clinical, double-blind, multicenter phase III study, the formulation plus antibiotics had outcomes that were superior than antibiotics plus placebo in patients with acute hemorrhagic cystitis.[102]

Vascular Medicine
In patients presenting with acute thrombophlebitis and postthrombophlebitic syndrome, the formulation demonstrated a decrease of pain, reduction of edema and throphic ulcers, and improvement of microcirculation.[35]
At a dosage of 2 tablets, t.i.d. clinical effect was pronounced with regression of chronic venous insufficiency in postphlebitic syndrome.[9] The formulation significantly reduces plasma viscosity and erythrocyte aggregation and increases blood fibrinolytic activity.[3,40]

Therapeutic Dosing

Optimal Dosage: The preponderance of clinical studies have shown the formulation to be effective at a dosage of 6 tablets per day, taken as either 3 tablets twice a day, or 2 tablets three times a day. This dosage has been used to treat osteoarthritis[28,30,74,75], rheumatoid arthritis[23,33,76], tendonitis[29], chronic prostatitis[71,72], relapsing urinary tract infections[101], recurrent respiratory tract infection[63], sepsis[84], diabetic nephropathy[82], multiple sclerosis[6], trauma[22,25,26,96], postphlebitic syndrome[39], as well as pre & post surgically.[34]

Surgical Dosage: One group dosed 3 tablets, five times daily for 2 to 6 days before surgery, followed by 3 tablets twice a day after surgery.[22] Another group dosed, 3 tablets t.i.d. for the first 3 days after surgery. Followed by 2 tablets 3 times/day.[34]

Pediatric Dosage: In two separate conditions, children aged 1 month to 15 years were given 1 tablet per 10kg/body up to a maximum of six tablets for a duration of days to six months.[63,84]

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