Role of Systemic Enzymes in Infections

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Abstract

Enzymes are complex macromolecules of amino-acids which bio-catalyse various body processes. Adequate concentrations of enzymes are essential for optimal functioning of the immune system. During infections, body’s enzymatic system is attacked and hence the immune system is also likely to derange. This may be detrimental for the host’s well-being and existence. Along with appropriate antimicrobial therapy, administration of enzymes externally could plausibly help to stabilise this disturbed immune system and thus assist the body to overcome the infections. This would especially be useful in multi-drug resistant and severe nosocomial infections. Enzymes have been studied and found to play a supplementary role in control of these infections. They also seem to help in control of difficult to manage viral infections. Besides, their use has been found to be beneficial in prevention of various common infections such as flu and cold. In spite of their potential, they have remained largely underestimated and underexploited. This review on oral enzymes attempts to highlight the role and safety of enzymes as adjunctive therapy in infections.

Introduction

Infections of varying severity continue to scourge Mankind. Their incidence is on the rise. New infections are emerging and old, conquered ones are making a comeback[1, 2]. Also these infections are increasingly seen to be resistant to commonly used antibiotics and though research into newer antibiotics is ongoing, it has failed to keep pace with the rising antimicrobial resistance. Alternative ways to manage these ‘biological killers’ need to be delved into. Oral systemic enzyme therapy seems to hold promise in control and elimination of certain of these infections.

The outcome in an infection is dependent on a multitude of factors such as genes, nutrional status of host, virulence of infecting organism, time duration of infection etc[3]. A favourable outcome ensues when host’s immune response is sufficient enough to arrest the march of the infecting organism into it, whereas an inadequate immune response could prove detrimental. Not only an hypo- but an hyper immune response has also been shown to be harmful. Such suboptimal responses characterize severe, advanced or resistant infections[4]. The ‘battle’ between the host’s immunity and organism leads to a lot of ‘molecular’ morbidity and mortality. Anti-infective agents do help but at times benefit is marginal. These agents may sometimes worsen the situation through release of immune complexes and dead bacilli into the blood stream. They also fail to reverse the hemodynamic instability and immune paralysis characteristic of these infections[4]. Supplementation with drugs targeted against this ‘chaotic’ or ‘dysfunctional’ immune response could be beneficial. Systemic enzymes seem to aid tremendously in ‘taming’ this ‘wilderness’ and optimising the immune response[5].

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS) IN INFECTIONS

SIRS is seen in an infective process [6]. It is in the form of a cascade with counterregulation. It is initiated by lipopolysaccharide (LPS), Lipid A, or endotoxin of gram-negative bacteria, or lipoteichoic acid, peptidoglycan, or exotoxin of gram-positive bacteria (eg.), or similar components of virus, fungi or parasites. LPS binds to a specific plasma protein (LPS binding protein) and this complex then binds to a membrane receptor (CD14) on effector cells such as macrophages and endothelial cells. This initiates intracellular signal transduction via a specific receptor mechanism (Toll-like receptor, TLR) [3]. Complement system is also stimulated which assists in trigger and amplification of various components of the immune system[7, 8].

Lymphocytes, monocytes and other immune cells are attracted to site of infection and pro-inflammatory substances called cytokines are released. More than 120 different cytokines have been identified and described. Monocytes produce nuclear factor-κB which also produces proinflammatory cytokines, tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6). TNF-α and IL-1 in turn generate toxic downstream mediators, such as prostaglandins (by cycloxygenase pathway), leukotrienes, platelet-activating factor, and phospholipase A² [9, 10]. These mediators damage endothelial lining and increase capillary leakage by acting on a group of glycoproteins called selectins on the endothelial cells (E-selectin and P-selectin) and leukocytes (L-selectin). Leukocytes marginate and form strong bonds with the neighbouring cells. These bonds are due to expression of adhesion molecules on the cells. These adhesion molecules include intercellular adhesion molecules 1 and 2 (ICAM-1 and
2) on the endothelial cells, vascular adhesion molecules (VCAM-1), and platelet-endothelial cell adhesion molecule 1 (PECAM-1). The receptors on leukocytes include members of the β2-integrin family of adhesion molecules such as CD11b and CD18 [11]. Neutrophils are also chemactuated to the site. Their interaction with endothelial cells by means of adhesion molecules causes further damage. Stimulated neutrophils release proteases and nitric oxide which further aggravate the inflammation [12-15].

TNF-α and IL-1 also cause expression of tissue factor on endothelial cells and monocytes. This initiates the coagulation cascade; thrombin is produced which itself is a proinflammatory substance. Fibrin clots form in the microvasculature. TNF-α and IL-1 also activate plasminogen activator inhibitor-1 which inhibits fibrinolysis [16]. They also hamper activation of protein C and antithrombin; which are antithrombotic and also anti-inflammatory [17-19]. Cytokine production continues. Thus an hyperinflammatory atmosphere is produced. This is counterproductive and enhances mortality [20]. Blocking of these cytokines by specific antagonists has been shown to improve survival [21].

In some patients or later in the course of infection, released stress hormones induce lymphocytes to release anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 [22]. These act to deactivate monocytes and decrease TNF-α, IL-1 and IL-6 production. Alpha2 macroglobulin, the cytokine catcher is also converted into its ‘fast’ form. It mops up the excess cytokines and tries to keep inflammation under check [23-25]. But this inflammatory suppression leads to cellular dysfunction and decrease in lymphocyte proliferation. Apoptosis (programmed cell death) of gut lymphocytes and endothelial cells takes place and anergy sets in [26-28].

However, neutrophilic stimulation and consequent tissue damage continues unabated [29]. The released nitric oxide, oxidases and proteases are main culprits in this damage [30, 31].

Thus the infective process is a complex process of inflammation. No single mediator /system/pathway/pathogen drives the pathophysiology of sepsis, but it is a composite output. Complex endothelial-leukocyte interactions are essential for sustaining an inflammatory response. Carefully timed sequence of molecular expression regulate these interactions. Simultaneous release of pro- and anti-inflammatory elements is seen. The equilibrium between these two contrasting signals is vital for recovery from infection [32]. This process is meant to be reparative, but there is always a risk for it to turn counterproductive. Systemic enzyme therapy has been shown to overcome the ‘cytokine storm’ or ‘immunosuppression’ seen in infections and to salvage the host’s immune system.

**ENZYME HISTORY**

During the Mayan civilization, wrapping papaya leaves around wounds was supposed to aid healing. The juice of these leaves contains certain vital enzymes which speeded healing. Pineapple has been used as a medicinal plant by folks of several tropical native cultures and its enzyme bromelain has been chemically known since 1876 [33]. Since 1950’s, role of proteolytic enzymes such as bromelain, papain, protease, and chymotrypsin in anti-inflammation emerged. Due to their systemic action and oral administration, they were called as oral systemic proteolytic enzymes. Gradually as more studies were carried out, utility of oral enzymes for treatment of various infections came forth. Innumerable double-blind randomized and controlled trials were performed and oral enzymes were found to be useful and safe adjuvant therapy in infections. Benefits of topical enzymes for wound debridement was discovered and their use in wound care gained momentum.

**PROPERTIES OF ENZYMES**

Enzymes are albuminoiid, complex macromolecules made up of amino-acids. There can be digestive, metabolic or food enzymes. Digestive and metabolic enzymes are naturally produced in the body. They tend to decline with age, inadequate and imbalanced nutrition, and physical and mental strain [34]. An estimated 80 to 100 thousand enzymes are present in human body; more than 3000 of these have been identified to date [35]. Food enzymes come from plant and animal sources. They are heat-labile and hence raw, fermented and lightly cooked foods are enzyme-rich [36].

When first discovered, enzyme names ended with ‘in’ like pepsin or trypsin. But later, they were suffixed by ‘ase’ such as protease. An elaborate nomenclature by Enzyme Commission (EC) of the International Union of Biocemistry (IUB) classifies the proteolytic enzymes into the hydrolase class (class 3) which includes peptid-hydrolase group (3.4.3) which comprises aminopeptidases (3.4.1), carboxypeptidases (3.4.2), dipeptidases (3.4.3) and proteinases (3.4.4) [37].

Enzymes for pharmaceutical uses are harnessed from plants, fungi, bacteria and animals. They act after internal absorption and function best at specific temperature and pH [35]. Hence processing, handling and storage of the enzymes should be proper. The various enzymes known to be useful in infections are as follows: Bromelain from pineapple stems (Ananas comosus), catalase, chymotrypsin from ox bile, krillase from Antarctic krill (E. superba), lysozyme, pancreatin,
papain from unripe papayas (Carica papaya), pepsin, protease, bioflavonoid rutin, serratiopeptidase or serrapeptase derived from nonpathogenic enterobacteria, Serratia E15, and trypsin. V-8 protease (from Staphylococcus aureus), pronase (from Staphylococcus griseus), Subtilisin, ficin from Ficus tree latex have also been investigated in various infections.

These enzymes are highly substrate specific. Hence combination of them has a better and synergistic effect[38]. Various enzyme combinations for infection and inflammation exist in the market such as Vitalzym, Phloenzym, Medizym, Wobenzym, Wobe-mugos, Chymotrypsin and trypsin combinations, serratiopeptidase, and papain-urea skin creams with or without chlorophyllin.

**ABSORPTION OF ENZYMES**

The initial myth that enzymes are not absorbed by gut has been refuted by numerous animal and human studies[39-46]. Absorption of intact enzymes into rest of body is possible by pinocytosis or by uptake by ‘roaming’ lymphocytes in the small intestinal lumen which are again released into the gut wall. This is similar to the uptake of antibodies (gammaglobulins) into the child’s lymphatic system and blood stream from the mother’s milk. Substantial proportion of bromelain is also absorbed[47]; highest concentration being present in blood 1 hour after administration[46]. Enzymes are likely to be destroyed by acidic gastric milieu and enteric-coating protects them from annihilation and improves their bioavailability[48]. In the small intestine, the released enzymes are absorbed by above mechanisms into portal vein and lymph. Studies have shown that brush border membrane bound enzymes do not degrade the therapeutically administered enzymes. Galenic preparations of these enzymes with bioadhesive polymers such as hydroxyethylcellulose or slightly modified chitosan-EDTA further increases stability of them against proteolytic degradation[49]. Metabolic transformation by liver cells (first pass metabolism) does decrease the enzyme concentration in blood but administration of larger doses per orally achieves optimal concentration of the enzyme in blood and brings about the required actions [50]. Special blood factors such as the antiproteinase, α2-macroglobulin act as carrier for the enzymes and prevents them from digesting the blood proteins. Also these enzymes are protected from being acted upon by the blood proteases. They circulate in the body acting on their appropriate substrates[51].

**MECHANISM OF ACTION**

Enzymes are essential for each and every bodily function. They act as ‘biocatalysts’ and produce big effects with little efforts. They act at multiple sites of the immune system to enhance it and diminish on inflammation. They normalize ‘a derailed immune system’ and hence aid in control and elimination of infection. They are supposed to act in the following ways:

1. The enzymes cleave the antigenic surface protein of organisms and digest their outer coat. Thus they defunct the pathogens. The released enzyme-surface protein complex is ingested by macrophages and dendritic cells and it induces higher antibody production [52-54].

2. They reduce number and activity of receptors for pathogen on host cells. Thus pathogen attachment is hampered and infectivity decreases. For example, Bromelain can disrupt Enterotoxigenic Escherichia Coli (ETEC) receptors in vivo and protect against ETEC induced diarrhea[55, 56].

3. They detoxify blood and remove viruses from circulation. They act as a "biological vacuum cleaners" eliminating impurities, foreign proteins, immune complexes and harmful micro-organisms from the blood stream and tissues. This greatly diminishes the inflammatory response and allows the normal immune functions to operate at a much healthier level.

4. Enzymes cause enhancement of immune cells to kill bacteria, viruses, molds and fungi[57]. Bromelain increases proliferation of peripheral blood mononuclear cells. Production of IL-6, granulocyte-monocyte-colony stimulating factor (GM-CSF), TNF-α and type 1 cytokine IFN-γ production, but not of type 2 cytokines IL-4 and IL-5 are increased[58]. This induction is dose-dependent[59]. Macrophage activity is enhanced up to 700 percent with a combination of enzymes pancreatin, papain, bromelain, trypsin and chymotrypsin[60]. Phagocytosis is also accelerated[61].

5. Enzymes break down immune complexes which block the immune cells[35]. They dissolve immune complex by removing Fc part of immunoglobulin and eliminate immune complexes from circulation[62, 63]. In the early phase, there may be worsening of the situation due to release of immune complexes fixed to tissues into the blood (Jarisch-Herxheimer effect).

6. They accelerate the volume and fluidity of blood flow[64]. This facilitates elimination of inflammatory products. Vascular endothelium is also stabilised[65].

7. Enzymes such as bromelain modulate arachidonate pathway in such a way that thromboxane production is decreased with no effect on cyclooxygenase. This leads to a decrease in edema and inflammation and reestablishment of balance between the 2 types of prostaglandins[33, 47].
8. Enzymes such as Serrapeptase enhance the bactericidal effect of antibiotics in cultures and prevents the formation of biofilms. This is valuable in treating problematic prosthetic infections[66, 67]. Papain has also been found to enhance chemotherapeutic efficacy of antibiotics on an average by 50% in mice with septicemia[68]. Bromelain also has been shown to increase blood and tissue levels of antibiotics[69-71]. This potentiation of antibiotics may be due to enhanced absorption, as well as increased permeability of the diseased tissue which increases access of antibiotics to site of infection. Bromelain might also provide a similar access to specific and non-specific components of immune system, therefore, enhancing the body’s utilization of its own healing resources.

9. Enzymes such as rutin are powerful anti-oxidants and effectively combat the harmful free radicals such as nitric oxide, released during the inflammatory process[72, 73].

10. Enzymes block pro-inflammatory metabolites that propagate the inflammation. Evidence also suggests an immunomodulatory and hormone like activity acting via intracellular signalling pathways for bromelain. It can inhibit induced T cell production of IL - 4 and to a lesser degree of the IL-2 and induced IFN-γ via modulation of the extracellular regulated kinase-2 (ERK-2) intracellular signaling pathway[74]. Bromelain significantly reduces CD4 T-lymphocytes of peyer’s patches[75]. Hence it ameliorates exaggerated inflammation. Trypsin-chymotrypsin has also been shown to modulate cytokine levels in burns[76].

11. Cell surface receptors such as hyaluronan receptor CD44 is reduced by bromelain. Hence leukocyte migration and induction of proinflammatory mediators declines[57, 77]. Enzymes down-regulate and degrade over-expressed inflammatory adhesion molecules. In vitro chemotaxis assay has shown that bromelain decreases chemokine receptor CD128 and hence there is reduction in neutrophil migration in response to IL-8[78].

12. Enzymes activate alpha-2 macroglobulin, the cytokine catcher which usually exists in blood in an inactive form (slow form). This in turn promotes faster clearance of cytokine, TNF-α. Thus stimulus for expression of the adhesion molecules is reduced. This assists in minimizing the heightened inflammatory process[79].

13. Enzymes inhibit platelet aggregation and their adhesion to endothelial cells. Clot formation is reduced[64, 80-82]. Enzymes also break down fibrin deposits and also remove necrotic debris and excess fibrin from the bloodstream[83].

14. Enzymes possess anti-secretory and mucolytic qualities. They act indirectly to decrease volume and viscosity of infected secretions so that they can be easily coughed out[84-86]. Bromelain’s liquefying potential is greater than that of other enzymes. It acts by decreasing contents of acid glycoprotein and sialic acid in sputum.

15. Enzymes decrease acute phase reactants[87]. Systemic enzymes thus supplement antibiotics to overcome infections. Enzymes reduce inflammation and beneficially modulate the immune system. They have no direct action on the organism per se but can tame the host’s upset immune system in order to harness its benefits.

Preclinical and Clinical Studies

Innumerable studies, controlled or otherwise, randomized or not, have been conducted to prove efficacy and safety of systemic enzymes in infections. Enzymes have been found useful in following conditions-

1. **Airway infections and inflammations** - Serrapeptase has been found to be effective in alleviating thick infected respiratory secretions. Ninety-seven percent of those taking serrapeptase reported good or excellent results compared to 22% in the control subjects. In a multi-center, double-blind, randomized study involving 193 participants, serratapeptidase acted rapidly to reduce local inflammation and ease symptoms in people suffering from ear, nose and throat disorders[88]. Serrapeptase also is beneficial in patients with bronchitis and other chronic lower airway diseases[89, 90]. Combination of trypsin and chymotrypsin with antibiotics is effective for management of acute or chronic non-tubercular bronchopneumonias[91]. Bromelain is effective and safe in acute sinusitis. It decreases sinus pain and throat pain. It changes the consistency of nasal mucus favourably[47, 71, 92-98].

2. **Sepsis and septic shock** - Enzymes when used in conjunction with appropriate antibiotics can lead to early recovery from sepsis in pediatric patients[72]. Papain has also been found to enhance the chemotherapeutic efficacy of antibiotics on an average by 50% in mice with septicemia[68]. Ishikawa et al has also shown that bromelain has a protective effect when used with antibiotics in experimental infection in mice produced by Streptococcus hemolyticus, Streptococcus pneumoniae and Pseudomonas aeruginosa[99].

3. **Oro-dental infections** - Since 1960s, proteolytic enzymes have been used in stomatology. Varney-Burch used peroral trypsin and chymotrypsin...
in postdental surgery and found that these enzymes reduced the healing time by 50%[100, 101]. Proteolytic enzymes are also found to be useful in dental infections. Used as a mouthwash, the enzymes help in combating gingivitis and reducing plaque formation in children and young adults[102, 103].

4. Skin and soft tissue infections- Adequate debridement of wound and burn areas is essential for prevention and management of infections. Experimental runs of enzymes as wound debridement agents have given positive results. Papain-urea, papain-urea-chlorophyllin, bromelain, ficin and bacterial collagenase has been extensively investigated for use in wound bed preparation[104-112]. A novel streaming technique has been tried in order to improve efficiency of enzyme solutions to cause early wound debridement and healing[113]. Bromelain scores over collagenase in efficacy and safety as a wound debridement agent[114].

5. Genito-urinary infections- Enzymes have been studied in urinary tract infections and found to play a favourable role. They can also help eradicate chlamydial infections of prostate[115].

6. Joint infections- Intraarticular serratiopeptidase enzyme has also been found useful in eradication of infection caused by biofilm-forming bacteria in experimental animal model. The serratiopeptidase group had significantly less persistence of infection as compared to the control group (5.6% s 37.5% respectively)[66].

7. Viral hepatitis- Oral enzymes have been found to be useful in hepatitis B infection. When administered, they tended to lead to faster recovery, with early normalization of spleen and liver size, and restoration of liver function[116-118]. Enzymes are also superior to ribavarin and α-interferon in hepatitis C patients[119, 120].

8. Varicella-zoster infection- Various studies have shown that enzyme therapy is beneficial in herpes infections. Oral enzymes decreased significantly ‘segmental pain’ on day 7 and 14 of the herpes zoster illness, as compared to the virostatic drug, acyclovir. Global judgement of the drug by physicians was in favour of the enzymes with similar tolerability in both groups. Hyperaesthesia and postzosteric neuralgia was also less in enzyme group[121-123]. Billigmann et al in their study found no difference in segmental pain in enzyme or acyclovir group, but adverse events were significantly less in enzyme group[124]. Mikazans used enzymes per os as well as locally in herpes-zoster infection and observed that as compared to oral acyclovir, enzyme therapy reduced clinical symptoms and signs faster and also was free of any side-effects. Postherpetic neuralgia was also less in the enzyme group[125].

9. Recurrent laryngeal papillomatosis- In an uncontrolled study, Mudrak et al found that after the surgical extirpation of the laryngeal papillomatosis, subsequent application of peroral proteases caused a significant improvement in clinical and laboratory results in these patients. Also they were disease-free for 10-18 months[126]. But this result has not been confirmed by means of a randomized controlled study.

10. Human immunodeficiency virus (HIV)- Auto-antibodies and circulating immune complexes characterize HIV. Jaeger used hydrolytic enzymes in HIV infections and found that they improved functional ability and weight of patients and are also well-tolerated[127].

11. Fungal infections- Bromelain has been found to enhance the killing actity of human white cells against candida albicans[61]. But no clinical studies of use of enzymes in fungal infections could be found.

12. Parasitic infections- There are very few studies on role of enzymes in parasitic infections. Enzymes are found to have a limited role in treatment of intestinal helminthiasis[128-130]. More clinical studies are needed to evaluate the role and safety of enzymes as adjuvant therapy in intestinal worms.

**DOSING**

The different enzyme preparations available in market contain different enzyme combinations in different strengths/potencies. The strengths are measured in grams or milligrams or in units of activity or international units. Food Chemical Codex (FCC) published by the National Academy Press is the accepted standard for activity units. Plant based enzymes have more activity, more duration of action and more pH stability compared with animal based enzymes. The recommended dose varies according to the enzyme preparation and the type of disease for which it is used. Usually 2-4 tablets are taken 2-3 times a day. But even higher dosages are free of side-effects. For children, powder forms of enzymes are also available. It is advisable to take enzymes 30 minutes before meals or 2 hours after meals with a sufficient amount of water.

**SAFETY PROFILE**

Enzymes are safe and well-tolerated in all age groups. A lethal dose (LD50) could never be found. There are no undesirable adverse effects on bone marrow or immunological system even with high or prolonged enzyme administration[35]. Even consumption of 3700 tablets per day produced only mild diarrhea[131]. Harmless alteration in the consistency, colour and odour of stool may occur as a consequence of enzyme action. Nausea, vomiting, mild abdominal pain may be
seen in some cases. Pancreatic enzyme may impair folic acid absorption and hence extra folate should be taken with long-term enzyme supplementation[132]. High doses of serratiopeptidase could cause esophageal ulcers. Its use has also been associated with acute eosinophilic pneumonia[133], subepidermal bullous dermatosis and inability to move. Serious allergic reaction, anaphylaxis or hypersensitivity to enzymes are rare[134, 135]. Papain can cause problems only in those with papaya or latex allergy. Topical papain can cause eruption of painful blisters and rashes in some patients. Bromelain has been found to potentiate the action of sedative drugs and antibiotics. It can cause changes in heart rate and blood pressure, especially in hypertensive patients[136]. Seraapeptase also slows heart rate and can lead to drowsiness. Enzymes can affect the coagulation system and hence it should not be used with blood thinning drugs such as aspirin, warfarin, or coumadin. They are contraindicated in hemophiliacs, pregnant or nursing mother, and in severe liver damage. Animal studies have demonstrated no teratogenic effect of enzyme mixtures. Dosages of 1.5 g/kg/day of bromelain administered to rats showed no carcinogenic or teratogenic effects. There is no development of tolerance on prolonged use of enzymes.

CURRENT STATUS
Thus, enzymes are a useful adjunct to antibiotics in both acute and chronic infections. Studies have shown it to possess a useful role in correcting an ‘upset’ immune system. It may be of use in cases where modern pharmacotherapy has very limited role. It could minimize morbidity and lead to early recovery from infections. It could enhance the actions of antimicrobials and assist in prompt and better control of infections. However, at present, enzymes are used mainly for their digestive functions, for gut health, for general well-being and for decreasing inflammation after surgery or trauma. It is being extensively used for sports injuries and in the orthopedic field. In spite of significant positive research on enzymes in infections, its usefulness in infections remains underexploited. It has not been adequately used as supplementation in advanced infections, septic shock, resistant infections and severe illnesses. This could possibly be due to lack of awareness about its benefits amongst the practicing physicians. Research on enzymes has remained mainly concentrated in Europe and Far East. Also not much literature in English has been published to highlight the efficacy and safety of enzymes in infections. Besides, since enzymes cannot be patented, they are of little interest to drug companies and there is a general unwillingness to use therapies not made by ‘big pharma’. There is also still skepticism in medical fraternity about findings that proteinases are absorbed from the gastrointestinal tract in a functionally intact form, and consequently they deny any efficacy of oral enzymes.

FUTURE ROLE
There exists a remarkable list of clinical studies conforming to Good Clinical Practice(GCP) guidelines and performed with polypolymer drugs, which shows that enzymes are beneficial in infections. The pharmacological efficacy of proteinases is evidence-based. Hence future for enzyme therapy seems bright. They of course cannot replace antimicrobials in infections but can play in pivotal supportive role in overcoming the infections. More randomized and controlled clinical trials on enzymes to further elucidate its clinical potential would be beneficial. More and widespread dissemination of knowledge on its clinical utility is required. As more forms and patents on enzymes are produced, and as more studies are performed, its use in the day to day management of infections would increase. It could play an important role in care of patients with nosocomial infections, especially in geriatric and pediatric age groups, and in viral and resistant infections. Its safety profile, lack of development of resistance and inability to show tolerance would make it a preferred supplementary option in elderly and pediatric population. It could serve as an effective, safe and cheap immunotherapeutic aid in infections.

Conclusion
Systemic enzyme therapy has been shown to be useful for prevention and treatment of a variety of infections. It holds promise for management of patients with infections which are unable to be treated with newer antibiotics and antiviral drugs. It could help where resistance to the antimicrobials is high such as in viral hepatitis and HIV. However, its benefits have not been harnessed enough. More clinical studies and improved awareness amongst the practicing physicians would be one step forward in helping mankind overcome the curse of these terrifying infections.

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