Enzyme Therapy: Current Perspectives

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Enzymes control all metabolic processes in human system from simple digestion of food to highly complex immune response. Physiological reactions occurring in healthy individuals are disturbed when enzymes are deficient or absent. Enzymes are administered for normalizing biological function in certain pathologies. Initially, crude proteolytic enzymes were used for the treatment of gastrointestinal disorders. Recent advances have enabled enzyme therapy as a promising tool in the treatment of cardiovascular, oncological and hereditary diseases. Now, a spectrum of other diseases are also covered under enzyme therapy. But, the available information on the use of enzymes as therapeutic agents for different diseases is scanty. This review details the enzymes which have been used to treat various diseases/disorders.

Keywords: Alginate lyase, Antioxidant enzymes, Asparaginase, Bromelain, Cardiovascular, Collagenase, DNAases, Gastrointestinal, Glutaminase, Hemocoagulase, Hyaluronidase, Lipases, Oncological, Pancreatic enzymes, RNAases, Serratiopeptidase, Streptokinase, Therapeutics, Tissue plasminogen activator, Urokinase

Introduction

Enzymes are widely used in medical diagnosis and their applications1. Recently, Jain et al.2 who reviewed the emerging prebiotic xylooligosaccharides (XOS) and their health benefits, discussed the enzymatic production of XOS including the role of xylanases. High dietary magnesium is known to modulate thyroid hormone synthetising enzymes, and thereby modify histoarchitecture of thyroid gland, resembling goitre3. Biocontrol potential of Streptomyces sp. (NII 1006 strain) from the Western Ghats, India has been correlated with extracellular hydrolytic enzymes, chitinase in particular4. Maachia et al.5 who studied biological control of grapevine diseases reported production of hydrolytic enzymes such as biase (chitin-1,4-chitobiosidase) and nagase (N-acetyl glucosamindase) by Bacillus strains B27 and B29. Velho-Pereira and Kamat6 have, in their review, tabulated enzymes from actinobacteria.

Enzymes are also used as therapeutic agents since they catalyse complex chemical reactions under appropriate physiological conditions. Initially, proteolytic enzymes have been used as supplements in gastrointestinal disorders7. Later, the use of enzymes has been extended for treating cancer and a diverse spectrum of diseases8. As such, not much information is available on the optimal application of therapeutic enzymes. This review focuses on the use of enzymes as therapeutic agents in cancer, pancreatic disorders, heart diseases, kidney diseases, respiratory disorders, etc. The focus is on two themes viz., enzymes presently used as therapeutic agents and enzymes having potential for future.

Enzymes presently used as therapeutic agents

Collagenase— Collagenase is a matrix metalloproteinase that breaks peptide bonds in collagen. Microbial collagenase hydrolyses native collagen and also other proteins and it is used in the debridement of dermal ulcers and burns9. Collagenase ointment is more effective than the petrolatum ointment for debridement of necrotic tissue10. Collagenase is used for enzymatic fasciotomy and it offers a potential advantage over nonspecific degradative enzymes by targeting collagen. Collagenase from Clostridium histolyticum is approved as a novel nonsurgical treatment for Dupuytren's contracture by the US Food and Drug Administration (USFDA). It provides a safe, effective alternative to surgery for patients with Dupuytren's contracture with the advantage of a quicker recovery with a minimal morbidity11,12. Streptomyces exfoliates
CFS 106, an isolate of cultivated field soil, has been shown to produce collagenase economically using cheap nitrogen sources such as soybean/feather meal. Collagen-rich matrix constitutes the main barrier to chronic total occlusion (CTO) crossing. Local administration of a human-grade purified collagenase degrades collagen CTO and it effectively facilitates guide-wire crossing in CTO. The oxygen–ozone combined collagenase injection for treatment of lumbar disc herniation shows significant reduction in pain and improvement in function and it can be considered as a viable option instead of surgery. Intravenous injection of type I collagenase digests collagen and can be used as a strategy to improve systemic gene delivery into tumors. Peyronies disease is an acquired connective-tissue wound-healing disorder of the tunica albuginea of corpus cavernosum and intralesional collagenase has been used for its treatment. It has recently been approved by USFDA under the name Xiaflex (Auxilium Pharmaceuticals, Malvern, PA, USA).

Pancreatic enzymes—Insufficiency of pancreatic enzymes leads to indigestion and inadequate absorption of fat, protein and carbohydrate, causing steatorrhoea and creatorrhoea resulting in abdominal discomfort, weight loss and nutritional deficiencies. This serious condition, known as exocrine pancreatic insufficiency caused by chronic pancreatitis, cystic fibrosis, pancreatic cancer and pancreatic surgery, can be treated by pancreatic enzyme replacement therapy. Pancreatic enzyme replacement therapy with delayed-release of pancrelipase is now becoming a standard practice since it significantly improves the coefficients of fat and nitrogen absorption as well as clinical symptoms. Currently used pancreatic enzyme supplements contain a mixture of protease, lipase and amylase, known as pancreatin. Bovine pancreatic enzymes appear to be a better alternative compared to porcine and human pancreatic extracts. Pancreatic enzymes in the form of enteric-coated mini microspheres are useful in treating patients with Celiac disease. Centella asiatica (L.) extract that demonstrated higher pancreatic lipase inhibitory activity has been shown helpful in managing hypolipidemic and hypoglycemic effects. Pancreatic enzymes can also be used as supplements in the treatment of indigestion, constipation and bloating.

Recently, Somaraju and Solis-Moya have evaluated the efficacy and safety of pancreatic enzyme replacement therapy in children and adults with cystic fibrosis. The results show that enteric-coated microspheres score over enteric-coated tablets in terms of stool frequency, abdominal pain and fecal fat excretion. However, it requires more evidence on the long-term effectiveness and risks associated with pancreatic enzyme replacement therapy, relative dosages of enzymes needed for people with different levels of severity of pancreatic insufficiency, optimum time to start treatment and variations based on differences in meals and meal sizes.

Lipases—Lipases catalyse the hydrolysis of triacylglycerol and phospholipids and they are obtained from bacterial, fungal, plant and animal sources. Acinetobacter haemolyticus TA106 from healthy human skin under optimized medium has been shown to produce lipase with maximum activity of 55U/mL. A recent theoretical analysis by Foukis et al., has proposed suitable equations for effective production of immobilized lipase. Lipases have earlier been used in the treatment of gastrointestinal disturbances and dyspepsia. Similase and Vitaline® are high-potency plant enzyme supplements that support digestion of protein, carbohydrates and fats. Microbial lipases show significant lipolytic activity and they are stable against proteolytic hydrolysis as well as bile salts resulting in higher lipolytic activity. Oral pancreatic enzyme preparation containing highly stable lipase constitutes a good candidate for enzyme substitution therapy. The pancrelipase formulations (Creon®, Zenpep® and Pancreaze®) are approved effective treatments for pancreatic enzyme insufficiency. They provide symptomatic relief, prevent morbidity and improve quality of life. Another futuristic development is the restoration of a patient’s own bioengineered lipase production with gene therapy for treating lipoprotein lipase deficiency.

Hyaluronidase—Hyaluronidases are glycosidases with both hydrolytic and transglycosidase activities and they catalyse the hydrolysis of hyaluronic acid, lower the viscosity and increase tissue permeability. Hyaluronidase, as an enzymatic component of snake venom, has been discussed by Gomes et al. In ophthalmology, hyaluronidase is most often used as an adjunct to local anaesthesia for retrobulbar, peribulbar and sub-Tenon’s block. It decreases intraocular pressure, reduces distortion of the surgical site, decreases incidence of post operative strabismus and limited local anaesthetic myotoxicity.
Hyaluronidase liquefies the vitreous haemorrhage as demonstrated in a phase III trial in diabetic patients and it can be used as an alternative or adjunct to conventional mechanical vitrectomy. Hyaluronidase is used therapeutically in combination with other drugs to speed up delivery and absorption and to diminish discomfort due to subcutaneous or intramuscular injection of fluid, to increase the effectiveness of local anaesthesia and as a spreading factor to improve better penetration of chemotherapeutic drug into tumors. Hyaluronidase treatment destroys the hyaluronate coat surrounding tumor cells and allows lymphocytes to approach the tumor membrane to enhance the cytotoxic action of immune response. Further, hyaluronidase disrupts intercellular adhesion and chemosensitizes tumor cells by a mechanism, independent of increased drug penetration in cancer chemotherapy. Hyaluronic acid levels are elevated in several cancers and its degradation using hyaluronidase has been shown to enhance the action of various chemotherapeutic agents in patients. Hyaluronidase facilitates penetration and decreases interstitial fluid pressure, permitting anticancer agents to reach malignant cells. Moreover, it has been proposed that hyaluronidase may itself have intrinsic anticancer activity.

Asparaginase—Asparaginase is an amino-hydrolase converting asparagine to aspartic acid and ammonia, which leads to cell death. It has been used for the treatment of acute lymphoblastic leukemia (ALL) for nearly 30 years. Three types of asparaginase are currently available viz., native asparaginase; pegylated asparaginase (PEG-asparaginase) derived from *Escherichia coli*; and third one from *Erwinia chrysanthemi* (crisantaspase) and bacteria derived enzyme has been found to have the lowest toxicity among a large variety of similar enzymes with known antitumor activity. It is also used as a model enzyme for development of new drug delivery system. *Bacillus aryabhattai* ITBHU02 has been reported to be a potential source for production of L-asparaginase. Genetic algorithm (GA) optimized yield has been shown to be 7.8% higher than RSM based optimization. Actinobacteria, such as *Streptomyces caesuis*, *S. cyaneus*, *S. exfoliates* and *S. phaeochromogenes* have been shown to be potential producers of glutaminase free L-asparaginase with better therapeutic properties.

Leukemic cells require a high amount of asparagine for their proliferation and depend on body fluid asparagine. Administration of L-asparaginase results in depletion of circulating serum asparagine and kills tumor cells. Healthy cells are unaffected as they synthesize asparagine intracellularly with L-asparagine synthetase. L-asparaginase, in combination with other drugs and radiotherapy, has shown great success in the treatment of ALL. Achievement of complete remission in patients is observed with a few side-effects including pancreatitis, coagulation abnormalities and allergic reactions. Sometimes, tumor cells may develop resistance to L-asparaginase. To overcome this difficulty, the drug is modified by pegylation or immobilization, and also treatment protocols can be modified to increase the efficiency of the drug. PEG-asparaginase is widely used for the treatment of children with ALL. It is less immunogenic and has a longer half-life than native *E. coli* asparaginase, which makes it a potent drug with reduced number of doses.

Glutamine reduction is also necessary for optimal anti-leukemic activity of asparaginase. Indeed, both *Escherichia coli* and *Erwinia chrysanthemi* asparaginases possess glutaminase activity also and their administrations have shown to reduce serum glutamine level by deamidating glutamine to glutamate and ammonia. Emadi et al. have reported that asparaginase products deserve a second look particularly in non-ALL malignant blood disorders.

*L-glutaminase*—L-glutaminase is an amidohydrolase that catalyzes the hydrolysis of L-glutamine into glutamate and ammonia. Cancer cells, especially lymphatic tumor cells, cannot synthesize L-glutamine, and require a large amount of L-glutamine for their rapid growth. Hence, the use of L-glutaminase deprives the tumor cells from L-glutamine and causes selective death of L-glutamine dependant tumor cells. L-glutaminase has been used as an efficient anti-retroviral agent in treating acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) as it lowers L-glutamine levels in both serum and tissues for prolonged periods. This results in substantial reduction in serum reverse transcriptase activity of the HIV with improved long-term survival benefits. L-glutaminase alone or in combination with asparaginase is mainly used in treating cancer, specifically ALL. It is also a therapeutic agent for retroviral diseases. *Achromobacter glutaminasificans* glutaminase–asparaginase is chemically modified by
succinylation, and the succinylated enzyme has broader antitumor activity than *E. coli* asparaginase.\(^{44}\)

**DNA and RNA enzymes**— Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) enzymes can be used to study gene function and treat diseases in which gene products are involved. They can be used to block the expression of specific genes in cells and thereby prevent certain diseases. RNA enzymes can be delivered to the cells either endogenously as gene-encoding ribozymes or exogenously as preformed ribozymes. These enzymes can cleave mRNAs and thereby inactivate abnormal gene expression. It is applicable to any disease where a specific gene product can be linked to the initiation and/or perpetuation of the disease. Deoxyribonuclease (DNAse), obtained from Bacillus sp. and Nocardia sp., degrades DNA and it has been investigated as a mucolytic agent for the treatment of chronic bronchitis.\(^{45}\) The increased viscosity of pleural pus in patients with pleural empyema is attributed to high concentrations of DNA resulting from the breakdown of phagocytes, bacteria, and other intrapleural cells.\(^{46}\) Streptodornase, a mixture of four DNAse enzymes, reduces the viscosity of pus by the digestion of DNA, whereas commercial human recombinant DNAse digests DNA and decreases the viscosity of pleural empyema pus without causing allergic reactions known to occur with streptodornase.\(^{46}\) Commercial Pulmozyme® (Dornase α), a DNAse, liquefies accumulated mucus in the lung and also diminishes pulmonary tissue destruction in cystic fibrosis patients.\(^{45}\) Chemically modified DNA enzymes can cleave RNA in the absence of divalent metal ions and such RNA-cleaving DNA enzymes have potential therapeutic applications as antibacterial and antiviral agents.\(^{47}\)

Schmidts *et al.*\(^{48}\) have investigated and suggested the use of DNA enzymes as potent novel drugs for the treatment of inflammatory diseases such as atopic dermatitis. The two challenges regarding the dermal application of DNA enzymes are the large molecular weight and the sensitivity to DNAases as part of the natural skin flora. To overcome these limitations, they have developed a suitable nano-sized drug carrier system, promising for topical application of DNA enzyme.

Ribozymes are RNA molecules possessing specific catalytic activity and they are capable of catalyzing highly sequence-specific reactions determined by RNA-RNA interactions between the ribozyme and its substrate molecules.\(^{49}\) The key to the recognition of and binding to the substrate molecule and the subsequent cleavage reaction resides in the RNA molecule. The capacity of ribozymes to specifically inactivate other RNAs has made ribozymes very promising molecular tools and potential gene suppressors with important applications.\(^{50}\) Ribozymes have been targeted against a myriad of genes, including oncogenes and drug resistance genes, viral diseases such as AIDS, viral hepatitis, mumps virus etc and cellular diseases viz., Alzheimer’s disease, cancer, diabetes, rheumatoid arthritis, etc.\(^{50}\)

RNA-based therapeutics are investigated for diseases ranging from genetic disorders to HIV infection to various cancers. The emerging drugs include therapeutic ribozymes, aptamers, and small interfering RNAs (siRNAs), demonstrating the unprecedented versatility of RNA. Hammerhead ribozymes are catalytic RNA molecules capable of inducing the site-specific cleavage of a phosphodiester bond within an RNA molecule.\(^{51}\) Thus, they can be used to reduce the intracellular level of a specific mRNA coding for a protein which affects cellular metabolism or environment, causing disease. Nucleic acids are potentially immunogenic and typically require a delivery tool to be utilized as therapeutics. Hence, improved synthetic delivery carriers and chemical modifications of the RNA therapeutics are necessary.\(^{51,52}\) Hepatitis C virus genome is present exclusively in RNA form during replication. Various nucleic acid-based therapeutic approaches targeting the hepatitis C virus genome, such as ribozymes, aptamers, siRNAs, and antisense oligonucleotides, have been suggested as potential tools against hepatitis C virus.\(^{53}\)

**Urokinase**— Urokinase or urokinase-type plasminogen activator (uPA) is a serine protease which converts plasminogen to plasmin, thus promoting fibrinolysis. uPA, as a thrombolytic agent, is used to treat of pulmonary embolism, acute myocardial infarction, severe or massive venous thrombosis, ophthalmic clot and hemorrhage and peripheral arterial occlusion.\(^{54}\) It is also administered intrapleurally to dissolve fibrinous adhesions thereby improving the drainage of complicated pleural effusions and preventing pleural loculations.\(^{55}\) ActiVase is the first recombinant enzyme drug approved by the USFDA in 1987. Urokinase is presently marketed as Kinlytic™ and used as a thrombolytic drug in infarction. It is a life saving,
therapeutically important fibrinolytic enzyme used in the treatment of many disorders requiring dissolution of blood clots. Prolonged thrombolysis with low-dose urokinase could be an alternative approach to therapy in patients with massive pulmonary embolism.

Streptokinase— Streptokinase (SK), a bacterial extracellular enzyme, is a single-chain polypeptide that exerts fibrinolytic action indirectly by activating the circulatory plasminogen. SK is used for intravenous administration immediately after the onset of a myocardial infarction in patients, thus reducing the amount of damage to the heart muscle. SK stimulates a cascade system responsible for the production of active plasmin, a proteolytic enzyme which digests fibrin, the main structural component of blood clots. It is usually administered only when the first heart attack occurs. SK, used in intrapleural fibrinolytic therapy, is known to accelerate drainage of loculated effusions in complicated empyema. Intrapleural streptokinase is an effective and safe adjunct in facilitating drainage in parapneumonic Intrapleural streptokinase is an effective and safe adjunct in facilitating drainage in parapneumonic

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Serratiopeptidase— Serratiopeptidase is a proteolytic enzyme prescribed in various specialties such as surgery, orthopaedics, gynaecology and dentistry for its anti-inflammatory and analgesic effects. It is reported to possess antiatherosclerotic effects due to its fibrinolytic and caseinolytic properties and also can be used as a health supplement to prevent cardiovascular morbidity. Serratiopeptidase has been found useful in patients suffering from acute or chronic inflammatory disorders of ear, nose or throat such as laryngitis, catarrhal rhino-pharyngitis and sinusitis. It is orally effective equivalent to diclofenac sodium in both acute and chronic phases of inflammation.

Apart from the two common conventional drugs for inflammatory disorders viz., corticosteroids and nonsteroidal antiinflammatory drugs, serratiopeptidase derived from non-pathogenic enterobacteria Serratia sp E-15 has anti-inflammatory and anti-edemic activity in a number of tissues. Serratiopeptidase is reported to exert a beneficial effect on mucus clearance by reducing neutrophil numbers and altering the viscoelasticity of sputum in patients with chronic airway diseases. Al-Khateeb and Nusair have investigated the ability of serratiopeptidase to reduce postoperative swelling, pain and trismus after third molar surgery and reported significant reduction in the extent of cheek swelling and pain intensity in 2nd, 3rd and 7th post-operative days. Serratiopeptidase hydrolyses bradykinin, histamine and serotonin responsible for the edematic status, reduces swelling and improves microcirculation and expectoration of sputum. The antibiofilm property of the enzyme may enhance antibiotic efficacy in the treatment of staphylococcal infections.

Lysosomal hydrolases— Lysosomal hydrolases deficiency causes lysosomal storage diseases (LSDs). It can cause impaired intracellular turnover, degradation and disposal of a variety of substrates present in lysosomes, including sphingolipids, glycosaminoglycans, glycoproteins and glycogen. The accumulation of these substrates in the endosome/lysosome elicits complex, secondary biochemical and cellular events that ultimately lead to cell and tissue damage. The pathology of LSDs is typically characterized by the variable association of visceral,
that detoxify cellular organic peroxides and hydrogen peroxide by oxidation. Heme oxygenases have both antioxidative and antiinflammatory properties whereas peroxiredoxins play an important role in removing hydrogen peroxide. 

Cytochrome c oxidase— Immuno globulin G-degrading enzyme of Streptococcus pyogenes is a cytochrome c oxidase which cleaves immuno globulin G (IgG) with a unique degree of specificity in the hinge region. Pathogenic IgG antibodies constitute an important clinical problem contributing to the pathogenesis of a number of autoimmune conditions and acute transplant rejection.

Amyloid β-protein (Aβ) cleaving proteases— Aβ is degraded by a diverse set of proteolytic enzymes viz., Aβ-degrading proteases such as zinc metallo-proteases, serine proteases and cysteine proteases. Aβ is the main component of amyloid plaques, which accumulates abnormally in the brains of patients with Alzheimer's disease. Leissring has detailed the involvement of specific Aβ cleaving proteases in the etiology and potential treatment of Alzheimer's disease. The Aβ-cleaving proteases are referred as novel class of enzymes that may serve as therapeutic agents.

L-lysine α-oxidase— L-lysine α-oxidase belongs to the group of oxidases of L-amino acids. It was first isolated from Trichoderma viride and later from T. harzanium Rifai. This enzyme catalyzes mainly oxidative deamination of L-lysine resulting in a decreased level of the essential amino acid L-lysine and producing α-keto-ε-aminocaproic acid and hydrogen peroxide. This possibly provides the basis for the unique properties of L-lysine α-oxidase viz., cytotoxic, antitumor, antimetastatic, antiinvasive, antibacterial, and antiviral activities, as well as immunomodulating effect.

Chondroitinase ABC (ChABC)— ChABC (glycosaminoglycan lyases) degrades chondroitin sulphate and the closely-related glycosaminoglycan hyaluronan which can be used for functional recovery in the damaged central nervous system (CNS). It is used for treatment of spinal injuries to promote regeneration of injured spinal cord and also acts by removing the accumulated chondroitin sulfate that inhibits axon growth. Chondroitin sulphate proteoglycans (CSPGs) are potent inhibitors of growth in the adult CNS and use of ChABC reduces the CSPG inhibition of spinal cord injury and promotes regeneration of injured axons, plasticity of
uninjured pathways and neuroprotection of injured projection neurons. Denholm et al. have reported that removal of CSPGs by chondroitinase AC and B inhibits tumor growth, neovascularization and metastasis.

Alginate lyase— Alginate lyases catalyze degradation of alginate, a complex copolymer of alpha-L-guluronate and beta-D-mannuronate. Lyases have been isolated from a wide range of organisms, including algae, marine invertebrates, and marine and terrestrial microorganisms. For more than two decades, alginate lyases are promising therapeutic candidates for treating mucoid Pseudomonas aeruginosa infections. The mucoid P. aeruginosa strains frequently isolated from cystic fibrosis patients have alginate exopolysaccharide which acts as a barrier against host’s immune defense and antibiotic treatment. It is reported that alginate lyase capable of degrading alginate polymer can be used in combination with antibiotics for the treatment of cystic fibrosis.

Hemocoagulase— Hemocoagulase is an enzyme complex isolated from snake venom which is known to possess coagulative and antihemorrhagic property. It accelerates the conversion of fibrinogen to fibrin polymer and promotes the interaction of platelets with fibrin clot. The clot thus formed is resistant to plasmin. Thus, it reduces the bleeding time, enhances cell division and hastens wound healing. Topical hemocoagulase solution has been used in oral and maxillofacial surgery as a hemostatic agent and promoter of wound healing.

Hemocoagulase is suggested to play a good hemostatic role in the hemorrhagic capillary in abdominal incision, in cases of cleft palate and septum deviation during plastic surgery, and in the control of intraocular bleeding during vitreous surgery. Prophylactic use of hemocoagulase in mechanically ventilated neonates is effective against pulmonary hemorrhage.

Jun-Min et al. have conducted phase III clinical trial to evaluate the effect of hemocoagulase agkistrodon obtained from chinese moccasin snake venom. It is found to possess good hemostatic and coagulative function and is safe for arresting capillary hemorrhage during abdominal surgery.

Bromelain— Bromelain is a crude, aqueous extract obtained from the pineapple (Ananas comosus Merr.) containing a mixture of proteolytic enzymes, referred to as sulfhydryl proteases. They are considered to have a range of beneficial properties such as anti-inflammatory, analgesic, antithrombotic and fibrinolytic.
effects\textsuperscript{31,88}. Bromelain is used for acute inflammation and sports injuries and also used an alternative treatment to NSAIDs for patients with osteoarthritis\textsuperscript{94}. Bromelain and papain, the two natural proteolytic enzymes are used to neutralize snake envenomation\textsuperscript{31}.

Pillai et al.\textsuperscript{95} have demonstrated that bromelain has the potential of being used as an effective anticancer agent for malignant peritoneal mesothelioma. During the treatment of patients with burn wounds, surgical escharotomy may cause considerable blood loss. Debridase, a bromelain derived enzymatic agent, is capable of lysing the burn eschar within 4 h, obviating the need for surgical debridement. It has an affinity to burned necrotic tissue and does not damage healthy skin\textsuperscript{96}. Deep burns are associated with the formation of an eschar, which delays healing and increases the risk of infection. A synopsis of enzyme therapy is given in Table 1.

Conclusion

Enzyme therapy is used in the treatment of cardiovascular, oncological, intestinal, viral and hereditary diseases. Some enzymes are in different phases of clinical trials. Biotechnological progress has encouraged pharmaceutical companies to produce safer and cheaper enzymes with improved potency and specificity. Enzymes in combination with drugs have potential to induce synergistic effect for treatment of various diseases and to reduce the side-effects of particular drugs.

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