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Enzymes for Disease Treatment: A Review

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ABSTRACT

Background

Since ancient times, enzymes have been widely used in a variety of sectors. Unfortunately, until the late 1950s, when scientists finally discovered the gold mine, they were sitting on, their potential as medicines lay dormant. The use of enzyme therapy for the treatment of numerous diseases, such as lysosomal storage disorders, cancer, Alzheimer's disease, irritable bowel syndrome, exocrine pancreatic insufficiency, and hyperuricemia, has increased significantly during the past few decades. Gene therapy, the treatment of microbial infections, and wound healing are further uses for enzymes.

Keywords: Disease; Human study; Therapeutic; Treatment

Introduction

Since 6000 BC, enzymes have been unwittingly used in a wide range of industries. Even after Payen and Persoz described the first enzyme in 1833, enzymes were only employed commercially, and the majority of their potential remained untapped [1,2]. Yet, a clear image of the use of enzymes for therapeutic treatments slowly emerged with the development of better lab equipment and the separation of enzymes in pure form. We describe enzyme therapy as the use of biological globular proteins that catalyze key biochemical reactions in their natural state or when fused with particular chemicals that enhance their properties in order to cure diverse problems. According to PubMed metrics, enzyme therapy has developed into a fast-expanding subject in recent years, with more than 300 publications relating to «enzyme replacement therapy» alone published every year over the past ten years, as seen in (Figure 1).

The earliest widely known application of enzymes for medicinal purposes was in enzyme replacement therapy. Dr. Christian de Duve suggested in 1964 that enzymes might be used to treat lysosomal storage disorders [3]. Since its inception, enzyme replacement therapy has advanced significantly and is now used to treat a variety of enzyme deficiency disorders, including adenosine deaminase-severe combined immune deficiency [4], Gaucher disease [5], adenosine deaminase-fabry disease [6], Fabry disease [7], Pompe disease [8], Hunter syndrome, Hurler-Scheie syndrome [9], Sly syndrome [10], Morquio A syndrome [11], Tay-Sachs disease [12], Wolman disease [13], adenosine deaminasesevere combined immune deficiency [4], hypophosphatasia [14], metachromatic leukodystrophy [15], Sphingomyelinase deficiency [16], homocystinuria [17], Maroteaux-Lamy syndrome [18], alpha-mannosidosis [19], and ceroid lipofuscinosis type 2 [20].

The treatment of exocrine pancreatic insufficiency, which can occur in a number of disorders including cystic fibrosis, chronic pancreatitis, and celiac disease, with enzymes is known as pancreatic enzyme replacement therapy [21]. In addition, the therapeutic application of enzymes has expanded in the modern period to include gene therapy [22], the treatment of cancer [23], the healing of wounds [24], the enhancement of irritable bowel syndrome patients' lives [25], and the prevention of antibiotic-resistant microbial infections [26]. In this post, we go through the characteristics of several enzymes and how well they work to treat certain diseases. Based on the numerous disorders that they are used to cure; the enzymes have been divided into divisions. An update on recent advancements in enzyme research and their use as medicines is also provided in this article.

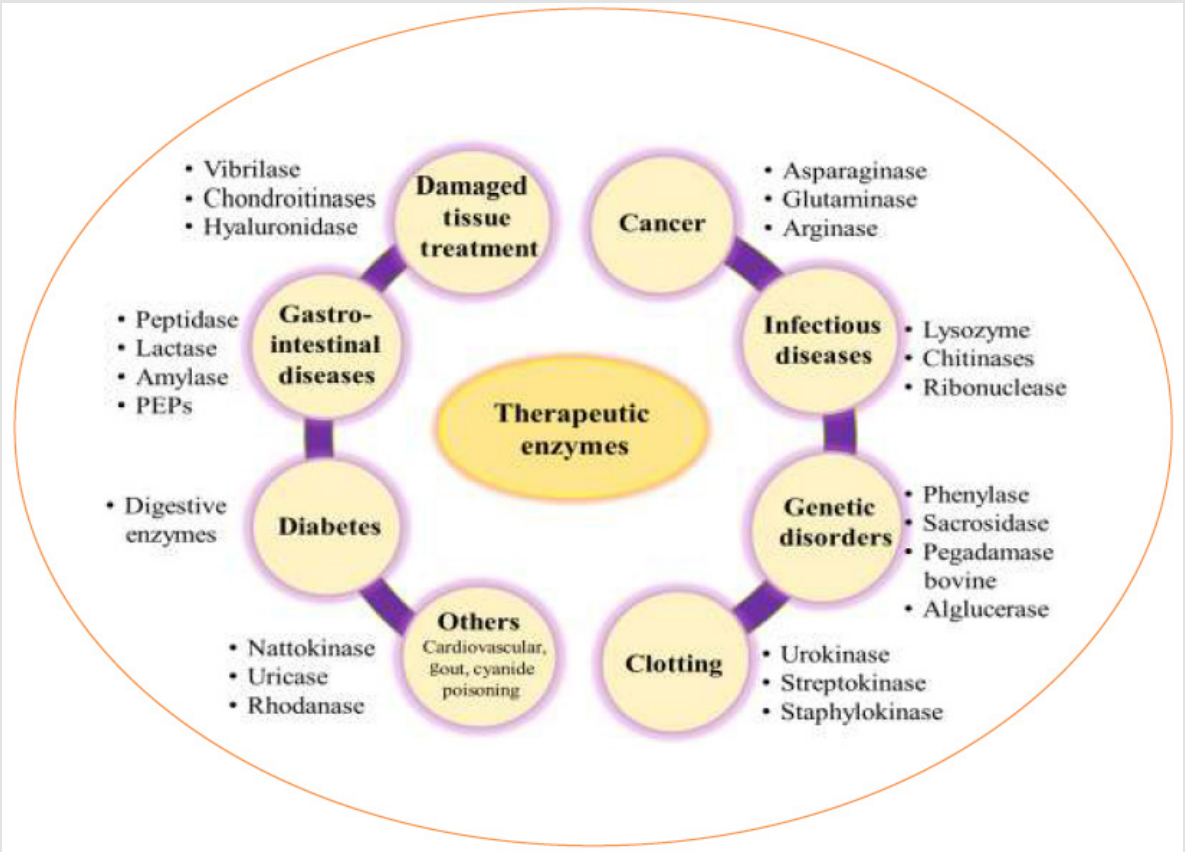

Figure 1: Disease treatment potential of enzymes.

Medicinal Value of Enzymes

Anti-Alzheimer's Disease: Alzheimer's disease is a serious illness that can cause someone to vanish long before they really pass away. The development of -amyloid peptide plaques and neurofibrillary tangles in the brain, which results in the deterioration of the nervous system, is the pathological condition linked with Alzheimer's disease. This buildup of amyloid plaques and neurofibrillary tangles causes extensive oxidative damage to neurons, which ultimately results in cell death. Dementia progresses and the cognitive system becomes severely dysfunctional as a result of neuronal loss. The proteolytic activity required to break down amyloid peptides in the brain into swiftly removed, nonneurotoxic chemicals has been found in numerous enzymes in recent years.

The term «amyloiddegrading enzymes» refers to these enzymes. Serine proteases, aspartyl proteases, cysteine proteases, and zinc metalloprotease enzymes are the several types of enzymes that have been utilized to treat Alzheimer's disease [22]. The Neprilysin family of enzymes is one of the zinc metallopeptidase enzyme families. Neprilysin enzymes have been seen to break down hydrophobic -amyloid plaques' N-terminal end into little peptides with fewer than fifty amino acid residues. The breakdown of these betaamyloid plaques was shown to be significantly reduced in mice whose expression of the enzyme Neprilysin was knocked off. Neprilysin, Neprilysin-2, Endothelin-Converting Enzyme-1, and Endothelin-Converting Enzyme-2 are enzymes from the Neprilysin family that have been linked to the elimination of -amyloid plaques in the brain. The insulin degrading family of zinc metallopeptidases, which differs from the Neprilysin family in terms of structure and catalytic function, has been discovered to be connected to the clearance of amyloid plaques from the brain. One of the enzymes in this family that has been proven to dissolve beta amyloid plaques is inulysin. Furthermore, it has been discovered that even these insulin degrading enzymes' inactive form aids in the breakdown of -amyloid plaques by acting as a chaperone. It has been noted that the angiotensin-converting enzyme cleaves the more harmful -amyloid-42 to the less harmful -amyloid-40.

Moreover, it has been observed to cleave -amyloid-40 in particular locations. The mono-carboxypeptidase enzyme angiotensin-converting enzyme has been seen to cleave-amyloid-43 to produce amyloid-42. Matrix metalloproteinase-2 and matrix metalloprotease

9 have been seen to cleave neurofibrillary tangles [27] serine protease known as plajin can break down amyloid fibrils and plaques. Little amounts of an oligopeptidase enzyme termed acyl-peptide hydrolase are created by cells via a poorly understood mechanism. After the 13th, 14th, or 15th amino acid, this enzyme has been seen to break both oligomeric and monomeric -amyloid plaques. In mouse models, the cysteine protease enzyme cathepsin B has been shown to lower the concentrations of -amyloid in the brain. It has been noted that the zinc ectopeptidase enzyme glutamate carboxypeptidase breaks down amyloid plaques in the brain into amyloid-14, amyloid-18, and amyloid-35 [28].

Anti-Cancer Activity: An extremely fatal terminal condition known as pancreatic carcinoma causes aberrant cell division in pancreatic cells, which results in the growth of metastatic tumors. Precancerous lesions that develop into pancreatic carcinoma can be roughly categorized as pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, and mucinous cystic neoplasms. The type of pancreatic intraepithelial neoplastic lesions most frequently seen to develop into metastatic tumors are these. Due to their size and rapid growth into carcinomas and metastases to other tissues, these lesions are also difficult to identify and do not give enough time for therapy. A propensity for pancreaticancer has been linked to mutations in a number of genes, including KRAS, TP53, SMAD4, ATM, BRCA1, BRCA2, PALB2, PRSS1, p16/CDKN2A, MLH1, and STK11 [29].

Hepatocellular carcinoma is a highly typical metastatic malignant tumor that can result in tissue necrosis and organ failure in the liver by causing a number of clinical alterations. Hepatitis C infection, excessive alcohol consumption, and aflatoxin B1 exposure are a few of the most prevalent risk factors [30]. Melanomas are cutaneous malignant metastatic tumors with a high mortality rate that have been on the rise recently. These cancers are brought on by a confluence of hereditary and environmental factors. Exposure to ultraviolet light is one of the main causes of melanoma. Lesions on the skin that show uneven borders and changes in pigmentation and hue are indicative of melanoma. In a 1999 study, it was discovered that including proteolytic enzymes in the diet helped patients with pancreatic cancer live longer.

The study's small sample size, however, makes it difficult to draw many conclusions [31]. Hepacid is a polyethylene glycosylated arginine deiminase enzyme that is injected intramuscularly and is being researched as a therapy for hepatocellular cancer. Another polyethylene glycosylated arginine deiminase-derived enzyme used to treat metastatic melanoma is called melanocid. Both of these enzymes break down and limit the amount of arginine, an essential amino acid required for the growth of cancerous cells [32]. Although arginine deiminase enzymes have been shown to have a considerable impact on mice, their usage in humans is still restricted due to their brief serum half-life. Furthermore, due to their microbial origin, these enzymes have been found to have a significant immunogenicity in mammals.

Despite the fact that the enzymes were seen to have a considerable impact on certain patients during clinical trials, the outcomes were incredibly uneven, and they were also seen to have a number of undesirable side effects, including higher ammonia levels. These genes, which produce the arginine deiminase enzyme, have been identified from a variety of bacteria, including Streptococcus sangria, Mycoplasma arginini, and Pseudomonas aeruginosa, and are primarily overexpressed in Escherichia coli BL21 cells [33]. The disorder known as acute lymphoblastic leukemia is brought on by the malignant transformation and proliferation of lymphoid progenitor cells. Many physical symptoms, including anemia, thrombocytopenia, weight loss, leukopenia, fever, bruising propensity, hepatosplenomegaly, and night sweats, are used to describe this illness [34].

This kind of leukemia can now be treated using the enzyme L-asparaginase. This enzyme breaks down L-asparagine into ammonia and L-aspartate, which causes cell death. Unfortunately, using this enzyme for treatment has a number of disadvantages, including toxicity and cell resistance to the enzyme. Erwinase and Oncaspar are the two enzymes that have been approved for use in the management of acute lymphoblastic leukemia. L-asparaginase is an enzyme, and oncaspar is a polyethylene glycosylated version of it. The enzyme is polyethylene glycosylated, which improves stability and plasma retention duration while lowering immunogenicity and proteolysis [35]. Acute lymphoblastic leukemia is being treated with Erwinase, a different L-asparaginase enzyme made from Erwinia chrysanthemi [36].

Antidiabetic Effect: In glucose hemostasis, the enzyme glucokinase is crucial. A protein called glucokinase regulatory protein controls its function [37]. Transcriptional factors control glucokinase activity in the pancreas, whereas glucokinase regulatory protein controls it in the liver. The first stage in the metabolism of glucose is catalyzed by the enzyme glucokinase, and mutations in this enzyme are linked to young-onset diabetes with maturity. High levels of this enzyme and enhanced glucose tolerance were caused by a high-carb diet [38].

Anti Cardiovascular Diseases: In the world, cardiovascular disease (CVD) is the leading cause of death. This severe disease is thought to be treatable by ERT. First, urokinase is an enzyme whose substrate is plasminogen, an inactive form of the serine protease plasmin. This enzyme turns plasminogen into plasmin, which sets off a proteolytic cascade that takes part in the extracellular matrix's breakdown during thrombolysis (ECM). Many vascular disorders can be treated with the use of this procedure [39]. Second, the enzyme nattokinase promotes fibrinolytic activity by inactivating plasminogen activator inhibitor 1 [40].

Troubleshooting Enzyme Treatments: For a variety of diseases, enzymes have been employed as therapeutic medicines [41-43]. Studies on the potential of enzymes as therapeutic agents and on the metabolic pathways involved in many diseases have benefited from advancements in both biotechnology and protein engineering [44]. Recombinant enzymes have consequently become new therapeutic options for a variety of disorders, including cancer and genetic anomalies (LSD, CF, etc.) [44,45]. Enzyme treatments must overcome enzyme fast clearance in vivo, undesired off-target interactions, and patient immune response to become commonly used medications.

The most amazing therapeutic enhancement strategies to date include the encapsulation, molecular alteration, and active monitoring of immune response. Applying the enzyme medication directly to the intended tissue is one of the simplest strategies to avoid undesirable off-target reactions. Deoxyribonuclease has been administered via eye drops for individuals with dry eye illness [46] in this context, and urokinase has been delivered via catheter to dissolve intraluminal clots [47]. Other strategies, such as enzyme encapsulation and modification as well as monitoring of patients' immune reactions, are being developed, though, to overcome the specific limitations [48-60].

Conclusion

Many disorders are treated with enzyme therapy. There are various stages of clinical trials for some enzymes. Pharmaceutical companies are now producing safer, less expensive enzymes with increased potency and specificity thanks to advancements in biotechnology [61-78]. Enzymes and medications have the potential to work synergistically to treat a variety of ailments and lessen the adverse effects of specific medications [79-84]. Such biochemical leads can be developed for therapeutic evaluation thanks to the high degree of specificity of enzymes and the fast-growing competence in macromolecular chemistry (Table 1).

Table 1: Enzyme therapy research as per published literature.

Findings/outcomes	Study type	Date of publication	Disease	Pharmacological action	Reference
A combination of pine bark extract and nattokinase prevents venous thrombosis in long-haul flights	Human Study	Sep 01, 2003	Thrombosis	Platelet aggregation inhibitors	48
A high lipase pancreatic enzyme is superior to regular pancreatin in adult cystic fibrosis patients	Human Study	Dec 01, 1994	Cystic fibrosis	Anti- cystic fibrosis	49
A polyenzymatic formula improves stable angina pectoris	Human Study	May 01, 2009	Angina pectoris	Ani Angina pectoris	50
AGM possibly improves insulin sensitivity and β-cell function and reduces liver damage and inflammation in prediabetic adults	Human Study	Jul 04, 2021	Prediabetes	Anti- inflammatory	51
An oral enzyme application is well-tolerated and improves postoperative symptoms and quality of life in breast cancer patients	Human Study	Aug 01, 2006	Breast cancer	Anticancer	52
An oral enzyme preparation used as an additive therapy in patients with multiple myeloma significantly prolongs survival time	Human Study	Jul 01, 2001	Multiple myeloma	Anticancer	53
Benefits of a food supplement containing Boswellia serrata and bromelain for improving the quality of life in patients with osteoarthritis	Human Study	Oct 31, 2019	Osteoarthritis	Osteoprotective	54
Bromelain has anti-platelet properties	Human Study	Feb 01, 2006	Thrombosis	Anti platelet	55
Bromelain has antimetastic protential as demonstrated in lung cancer cells	Human Study	Jan 01, 1988	Lung cancer	Antimetastatic	56
Bromelain has no difference in reducing symptoms of mild-to- moderate knee OA after 4 weeks when compared with diclofenac	Human Study	Sep 30, 2016	Knee	Anti- inflammatory	57
Bromelain is effective in treating postoperative edema after third molar surgery	Human Study	Sep 01, 2010	Edema	Analgesic	58
Bromelain may benefit children diagnosed with acute sinusitis	Human Study	Mar 01, 2005	Sinusitis	Ant sinusitis	59
Bromelain may benefit patients with postoperative constipation	Human Study	Sep 01, 2007	constipation	Anti constipation	60
Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults	Human Study	Dec 01, 2002	Knee	Analgesic	61

Consumption of nattokinase was associated with a reduction in both systolic and diastolic blood pressure	Human Study	Dec 31, 2015	Hypertension	Antihypertensive	62
Effective management of atherosclerosis progress and hyperlipidemia with nattokinase	Human Study	Dec 31, 2021	Cardiovascular	Cardioprotective	63
Enzyme therapy was found to be as effective to pharmaceutical intervention for herpes zoster	Human Study	Feb 10, 1995	Shingles	Ant shingles	64
Nattokinase combined with red yeast rice, but not nattokinase alone, has potent effects on blood lipids in human subjects with hyperlipidemia	Human Study	Jan 01, 2009	Hyperlipidemia	Anticholesteremic	65
Nattokinase decreases plasma levels of fibrinogen, factor VII and factor VIII in human	Human Study	Mar 01, 2009	Clotting	Anti-clotting	66
Nattokinase effectively shrinks the nasal polyp tissue through fibrin degradation	Human Study	Sep 30, 2017	Rhinosinusitis	Anti Rhinosinusitis	67
Nattokinase lowers systolic and diastolic blood pressure in human subjects	Human Study	Jun 01, 2010	Hypertension	Hypotensive	68
Nattokinase supplementation is an effective way to manage the progression of atherosclerosis and potentially may be a better alternative to statins	Human Study	Jul 10, 2017	Atherosclerosis	Anti-atherogenic	69
OPERA was able to improve CIPN symptoms in a prospective series of patients treated with neurotoxic chemotherapy	Human Study	Feb 28, 2017	Neuropathy	Chemoprotective	70
Pancreatic enzymes improve muscle healing after intense exercise.	Human Study	Aug 27, 2008	Muscle injury	Anti muscle pain	71
Pancreatic enzymes reduce symptomatic response of healthy subjects to a high fat meal indicating they may be beneficial in irritable bowel syndrome	Human Study	Feb 01, 2006	Bloating	Anti bloating	72
Pancreatic enzymes, particularly Lipase, may have a therapeutic role in the treatment of Rosacea	Human Study	Sep 01, 2007	Rosacea	Anti rosacea	73
Pancreatic insufficiency may be a cause of persistent symptoms, e.g. diarrhea, in adult celiac disease and may be ameliorated with pancreatic enzymes	Human Study	Feb 01, 2007	Celiac Disease	Anti celiac disease	74
Sodium alginate, sodium bicarbonate, bromelain and essential oils have therapeutic value in the treatment of functional dyspepsia	Human Study	Jun 01, 2009	Dyspepsia	Anti dyspepsia	75
The combination of serenoa repens, selenium, lycopene and bromelain are beneficial in patients with chronic bacterial prostatitis	Human Study	Oct 04, 2016	Bacterial	Antibacterial	76
The polyenzymatic therapy Wobenzyme improves symptoms in patients with recurrent obstructive bronchitis (COPD)	Human Study	Oct 01, 2005	Bronchitis	Anti bronchitis	77
The polyenzymatic therapy Wobenzyme reduces inflammation and intra-abdominal adhesions in children undergoing abdominal operations	Human Study	Jan 01, 2006	Abdominal disease	Antiinflammation	78
These results showed the effectiveness of bromelain on episiotomy pain and wound healing	Human Study	Feb 29, 2016	Perineal trauma	Analgesic	79
This study thus clearly supports the clinical relevance of treatment of postoperative conditions with bromelain	Human Study	tSep 05, 2016	Tooth extraction	Antiinflammation	80

Data Availability

All of the required data will be available upon request to the corresponding author.

Authors' Contributions

The author wrote the review article alone.

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Conflicts of Interest

There are no conflicts of interest.

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