Journal of The Gujarat Research Society

ISSN: 0374-8588
Volume 22 Issue 1, January 2020

Pharmacological Enzymes Produced By Microorganisms: A Viable Arena for Anti-inflammation

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ABSTRACT: ***Biopharmaceuticals is a new area that studies and uses biological organisms and their products for medicinal purposes. Enzymes are extraordinary biocatalysts that dramatically increase the pace of biological processes. They have a lot of unique characteristics, such a lot of catalytic potential, a lot of substrate specificity, and pH & temperature optima. They have a wide range of therapeutic uses because to these exceptional characteristics. They're progressively being used to address a wide range of illnesses, whether alone or in conjunction with other treatments. Plants, animals, and microbes may all produce useful enzymes. Easy separation, higher uniformity, better productivity, financial viability, better resistance, or candid manufacturing by recombinant DNA technology utilising microorganisms as parent cells are all benefits of enzymes separated from microorganisms. In addition, microbial enzyme are easier to modify and optimise than those derived from plants and animals. As a result, microbial enzymes have enticing properties and potential, and they are a significant subclass of advanced biopharma. Our focus on the therapeutic possibilities of microbial enzymes, as anti-inflammatory in this study. This data will assist in highlighting & further exploring their medicinal potential, which is rapidly spreading and improving wellness.***

KEYWORDS: ***Anti-inflammatory, Enzyme, Inflammation, Microbial, Potential, Therapeutic***

1. INTRODUCTION

Medicinal plants have been a useful source of therapeutic compounds for millennia, and several of today's medicines are natural chemicals produced from plants or their derivatives. However, because natural product-based drug development has its own set of challenges, the pharmaceutical industry has moved its attention to synthetic chemical libraries and high-throughput screening (HTS) for the discovery of novel therapeutic leads. Over decades, interest has been undertaken on identifying and developing therapeutic molecules to fight human diseases. Enzymes' potential as biopharmaceuticals has been boosted by recent advancements in biotechnology[1].

In 2008, the Austrian "Drugs from Nature Targeting Inflammation (DNTI)" collaboration was established, bringing together experts with expertise in a variety of fields relevant to natural product-based therapeutic development. The DNTI programme used a combination of computational techniques, ethno-pharmacological knowledge, phytochemical analysis and isolation, organic synthesis, plant biotechnology, or a wide range of in vitro, cell-based, as well as in vivo bioactivity models to identify & characterise natural products with anti-inflammatory activity. Various medical diseases have been linked to a decrease in enzymatic activity or a deficiency in the enzymes. Enzyme replacement by targeted administration has organically developed as a treatment for previously difficult-to-treat diseases. Enzymes have several benefits as biopharmaceuticals, including high substrate specificity and affinity, efficient catalysis with low toxicity, and few side effects. Enzymatic catalysis allows numerous targets, including prodrugs, to be converted into the desired products at the same time, allowing for the delivery of lower amounts of therapies[2].

1.1.A historic view on natural compounds as therapeutic possibilities:

The oldest written documents on plant medical uses date from 2600 BC, and they describe a complex Mesopotamian pharmaceutical system with over 1000 plant-derived remedies. Egyptian medicine goes back to around 2900 BC, but the "Ebers Papyrus" from around 1550 BC is the most important preserved record, including over 700 medicines, mostly of plant origin. Medicinal plants were solely used on an empirical basis at that period, with no mechanistic understanding of their pharmacological properties or active components. Anton von Störck, who researched toxic plants like aconite and colchicum, & William Withering, who researched foxglove for the treatment of edema, set the groundwork for the logical clinical examination of therapeutic herbs in the 18th century. Over the projection period, the market is expected to increase because to rising demand from end-use sectors such as food and beverage, biofuel, animal feed, and household cleaning. Furthermore, rising consumer health awareness has led in increased consumption of functional food items, which is likely to drive product growth over the coming years[3].

Microbial enzymes are a valuable resource for medicinal treatments since they are inexpensive, consistent, and easy to isolate. The major benefit of microbial enzyme production is that it produces large yields on low-cost media in a shorter amount of time. Furthermore, fusion proteins, PEGylation, point mutations, nanocarrier encapsulation, or other genetic modification methods can be used to increase the efficiency of microbial fermentation and provide an ongoing uniform supply of enzymes. Scientists across the world are realising the vast potential of microbial enzymes in therapeutics & biopharmaceuticals, resulting in a significant increase in the use of these enzymes as curative agents. The knowledge on therapeutic uses of microbial enzymes, such as anti-inflammatory agents, enzybiotics, fibrinolytic agents, anticancer agents, & digestive aids, is summarised in this study, which helps to emphasise & further investigate their potential as therapeutic agents[4].

1.2.Anti-inflammatory enzymes:

Inflammation is a common immunological response that occurs when cellular homeostasis is disrupted, allowing for survival during infection, tissue damage, or contamination. Immune cells move to the site of tissue damage in an orderly sequence regulated by cytokines, chemokines, & acute phase proteins during the acute inflammatory response. This acute phase reaction appears to be sufficient to address the injury and initiate the process of healing in some cases[5].

Numerous research have been conducted throughout the years to develop ways to reduce acute and chronic inflammatory reactions. Enzymatic anti-inflammatory medicines have recently surpassed chemical anti-inflammatory therapies in popularity. NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are the most common treatments used to treat acute inflammation. They can be used alone or in combination with other drugs. These NSAIDs, on the other hand, have a number of drawbacks, including side effects. Enzyme centered anti-inflammatory medicines have been created to overcome the limits of traditional pharmaceuticals, and they are becoming increasingly popular these days. They also have benefits such as high efficiency and substrate specificity[6].

Injections of trypsin intravenously and intramuscularly were found to alleviate symptoms of rheumatoid arthritis, ulcerative colitis, postsurgical edoema, and sports injuries in the 1950s in the United States. Because of the therapeutic effectiveness of these enzymes, trypsin and chymotrypsin are now used as oral medicines. Since inflammation has been linked to a variety

of dangerous, debilitating, and incurable diseases, enzymes might come to the rescue as anti-inflammatory medicines[7].

1.3.Serratiopeptidase:

Serratiopeptidase (Serratia E15 protease, EC 3.4.24.40) is a novel enzyme that is proving to be an effective anti-inflammatory. It is a trypsin-like protease with a molecular mass of around 52 kD. Because it contains zinc in its structure, it is also known as a metalloprotease. Serratiopeptidase, also known as serrapeptase, was first identified from Serratia spp., an enterobacterium found in the silkworm Bombyx mori. Serratiopeptidase is gaining popularity across the world as a dietary supplement or a medicinal agent, with regulatory status varying by country. In Canada, for example, it is legal to use it to treat pain and swelling & to take it as a dietary supplement. It is authorized for the treatment of acute pain in India & is used as a pharmaceutical agent in conjunction with other medications. However, the FDA has authorized it as a New Dietary Ingredient in the United States.

Serratiopeptidase has an unfavorable effect on the mobility of immunological cells. It attracts lymphocytes to the inflamed area. Serratiopeptidase has recently been demonstrated to decrease bradykinin, histamine, and serotonin-induced capillary permeability, breakdown aberrant proteins & exudates, and promote the absorption of destroyed products into blood & lymph. It also stimulates wound healing & can help to restore & mend inflamed skin caused by trauma. In contrast to NSAIDs, serratiopeptidase controls immune cell migration from lymph nodes to damaged tissue. This unusual method of action, along with its broad substrate specificity, clearly indicates that this one-of-a-kind serine protease can maintain homeostasis. Its proteolytic nature allows it to clean and mend wounds.

1.4.Collagenase:

Collagenase (EC 3.4.24.3) is a one-of-a-kind protease capable of hydrolyzing natural collagen in a specific manner. It features a saddle-shaped tertiary structure, and the active site contains a Zinc moiety. The side chains having 2 histidines, 1 glutamate, and a water residue tetrahedrally coordinate the zinc moiety, as its water molecule hydrogen linked to another glutamate residues. It was found to be efficient in breaking type I & type III collagen, which are the main collagen types seen in PD plaques. It spared type IV collagen found in adjacent connective tissue arteries & veins, decreasing PD plaques while leaving surrounding vasculature, elastic tissue, & axon myelin sheaths unharmed. Collagenase is a well-tolerated, less painful, & effective therapy for a variety of diseases, according to new research.

Clostridium histolyticum-produced collagenase is used to disintegrate burn scars instead of harsh surgical debridement. Debridement is the process of removing damaged or dead tissue in order to provide improved treatments and active healing. Surgical & mechanical debridement techniques are less precise and unpleasant. This enzyme destroys necrotic dead tissues in a painless & selective manner. It promotes wound healing by releasing collagen-derived peptides, which stimulate macrophage chemotaxis & cytokine production, promoting wound healing. Dupuytren's disease (DD) is a fibroproliferative condition defined by the development and subsequent contracture of specific sections of the palmar aponeurosis, resulting to significant limitations in hand use in later stages of the disease.

1.5.Superoxide Dismutase:

As byproducts of regular aerobic metabolism & as external stimulus reactions, all aerobic organisms create reactive oxygen species (ROS). One of the most important defence

mechanisms is Superoxide Dismutase (SOD), which is found in virtually all cells. SOD (EC 1.15.1.1) is a metalloenzyme that is found everywhere. Its structure is made up of an 8-stranded betabarrel that, together with the two surface loops, keeps the active site firmly in place. In a back-to-back manner, two subunits are firmly linked via mostly hydrophobic and a few electrostatic contacts. The capacity of enzybiotics to eradicate antibiotic-resistant bacteria is their most significant and noticeable benefit.

Superoxide anions, hydroxyl radicals, & hydrogen peroxide are among them. These serve as oxidative stress mediators. Inflammation, carcinogenesis, neurological diseases, and ageing can all be caused by reactive oxygen species (ROS). To counteract the effects of ROS, cells have evolved a complex set of antioxidant defense systems. SODs are also used in cosmetic compositions to reduce skin damage caused by free radicals. Microbes are proving to be a cost-effective source for the synthesis of various SODs. Aerobic bacteria with increased oxygen demand, such as Corynebacterium glutamicum, have been found to produce high amounts of SOD.

1.6.Application:

- Analytical tests: Diabetics monitor their glucose levels using strips of paper fertilised with aldohexose enzyme.
- The presence of enzymes where they are not supposed to be may also make it easier to detect a disease. Enzyme's seep into the circulation when the liver is sick or injured, for example. The presence of these enzymes in the blood will indicate liver damage.
- Therapeutic accelerators: Enzymes are commonly employed as medications to treat individuals with enzyme shortages, such as the use of blood coagulation factors to treat bleeder's disease, or the use of proteases to breakdown fibrin to prevent the formation of hazardous blood clots. Nuclease might be a possible medical treatment for monogenic disease, however it's unclear how well it's been commercialised and used therapeutically.
- Proteases are used to clean wounds, which speeds up the healing process.
- Manufacturing of pharmaceuticals: Complex medicine's chemical synthesis is typically difficult, thus companies use enzymes to accomplish chemical transformations.
- Enzymes are used in a semi-therapeutic fashion to assist digestion and complement the pancreas' natural amylase, lipase, and protease. Lactase deficiency causes the enzyme lactase to be lost. Lactase supplements can help these people prevent stomach discomfort.
- Enzymes must generate the most intriguing therapeutic agents for the treatment of metabolic disorders since they are specialised biological catalysts.

Various medical diseases have been linked to a decrease in enzymatic activity or a deficiency in the enzymes. Enzyme replacement by targeted administration has organically developed as a treatment for previously difficult-to-treat diseases. Enzymes have several benefits as biopharmaceuticals, including high substrate specificity and affinity, efficient catalysis with low toxicity, and few side effects. Enzymatic catalysis allows numerous targets, including prodrugs, to be converted into the desired products at the same time, allowing for the delivery of lower amounts of therapies[6].

2. LITERATURE REVIEW

Ashok Pandey et. al. [8] described that for almost a century, enzymes were utilised as industrial catalysts. Because of the benefits of intense synthesis via fermentation at high productivity and

under regulated circumstances, microorganisms had gradually supplanted animals and plants tissues & fluids as enzyme sources. Enzymes from any source might well be produced in microbial hosts, including higher organisms, non-culturable bacteria, and metagenomic pools, thanks to genetically engineered. Protein engineering techniques, on the other hand, enabled the development of enzyme variations with better properties as process catalysts. Fermentation is now the primary method for producing enzymes, and it will remain so for the foreseeable future. The pillars of biocatalysts advancement include impressive developments in fermentation technology, molecular biology, bioinformatics, material sciences, nanotechnology and process control.

Ángela J. Espejo-Mojica et al. [9] explained that LSDs were generated by a build-up of partly degraded substrates within the lysosome as a result of a lysosomal protein's function being lost. Mammalian cells were used to make recombinant lysosomal proteins because of their ability to carry out post-translational changes comparable to those seen in native human proteins. Several investigations had demonstrated that bacteria (e.g., E. coli) and yeasts may produce active recombinant lysosomal proteins. Despite the fact that protein folding and PTMs were a major concern for the production of these enzymes in microorganisms, the findings show that differences in glycosylation (i.e., the presence or absence of a different structure) did not prevent the production of active enzymes or cellular capture in the case of recombinant enzymes produced in yeasts.

Tek Chand Bhalla [10] described that Since antiquity, man had used microbes to make wine, bread, cheese, and other products without realising that microbes were involved. Communication, education, transportation, & globalisation were all rapidly altering the socioeconomic landscape in which we live. Emerging conveniences had been added in response to new difficulties in food, medicine, & the environment. Microbes, products, & microbial processes would play a critical role in meeting these issues in the future years. Microbe-related genetic, metabolic engineering, & protein programmes would produce more efficient microbial systems, resulting in the availability of high-quality goods within the reach of the average person. In the foreseeable future, the scope of applied microbiology would expand dramatically.

3. DISCUSSION

Medicinal plants have served as a helpful medical supply for thousands of years, and some of today's medications are natural or derivative substances generated by plants. However, because the creation of natural medicinal products has its own problems, the pharmaceutical market has focused on synthetic chemical libraries and high-performance screening (HTS) for new therapeutic leads. Different medical conditions were related to a reduction in enzyme activity or enzyme insufficiency. Organically specified replacement of enzymes for previously difficult to deal with illnesses has been created as a therapy. Enzymes offer several advantages, including high sustratum specificity and affinity, efficient, low toxicity catalysis, & minimal adverse consequences. Numerous objectives such as pro-medicines, such as enzyme catalytic, can be simultaneously transformed into the required products, allowing less therapy.

Because microbial enzymes are cheap, constant and easy to isolate, they are a significant resource for therapies. The main advantage of the manufacture of microbial enzymes is that they generate high yields in a shorter period on cheap cost medium. In order to enhance the effectiveness of microbial fermentation and provide a continuing uniform supply of the enzymes, fusion, PEGylation, point mutations, nanocarrier encapsulation, or other genetic modification methods. Globally, scientists realise that in therapies and biopharmaceuticals,

microbial enzymes have a huge potential and this leads to a substantial growth in usage in the treatment of these enzymes. In this study, which helps highlight and further explore their potential as therapists, we have summarised information of the therapeutic application of microbial enzymes such as anti-inflammatory agents, enzybiomics, fibrinolytic agents, anti-cancer agents & digestive aids.

Inflammation is a typical immune response to cell homeostasis that can be survived during infection, tissue injury or contamination. Due to several years of study, techniques of reducing chronic and acute inflammatory responses have been developed. Recently, enzymes have overcome the popularity of pharmacological anti-inflammatory therapy. The most frequent therapies for acute inflammation are NSAIDs (Non-Steroidal Anti-Inflammatory Medicines). They can be taken alone or with additional medicines. On the other hand, these NSAIDs have several disadvantages, including adverse effects. The use of enzymes in contemporary medicine as anti-inflammatory drugs originated from 1950s and has been reported in USA where trypsin might alleviate the symptoms of RTA, ulcerative colitis, postoperative edoema and sports injury, if administered intravenously and intramuscularly. The successful use of these enzymes in treatment led to the use via oral therapy of trypsin and chymotrypsin. Because inflammation is involved in numerous noxious, debilitating and uncurable dis-eases, enzymes are a major rescue agent.

3.1. Precautionary measures:

Upon inflammatory situations, use proteolytic enzymes between meals; Do take additional folate, which inhibits folate absorption over time, with long lasting pancreatin supplementation; Consider adding bromelain to a glucosamine-containing supplement bromelain seems to have the impact of glucosamine (strengthen); Do bromelain carefully following heat exposure it has shown a varied action. Don't take additional blood thinning products in proteolytic enzymes; If you have a history of allergy to pineapple or heart palpitation, do not use bromelain; Do not take bromelain with potato protein or soybean products—these foods might affect the efficacy of the enzyme.

4. CONCLUSION

Microbial enzymes have enormous medicinal potential and are extremely important. The synthesis of therapeutic enzymes by bacteria is both cost effective and environmentally beneficial. They may be useful in the treatment of a variety of human disorders, such as the use of fibrinolytic enzymes in the treatment of myocardial infarction, pulmonary clotting, and venous stroke, the use of enzybiotics in the treatment of infections, cancer treatment with amino acid degrading enzymes, wound and inflammation treatment with anti-inflammatory enzymes, and easier digestion of food with digestive aids. The requirement of the hour is to evaluate novel enzymes as well as to upgrade and improve current ones. To reap their benefits over chemical therapeutic agents & in the treatment of many human diseases, the isolation, control, overproduction, & uses of these microbial enzyme biopharmaceuticals should be studied to their full potential.

The ability to transport enzymes to the body is important for the development of medicines. In order to bind to their potential substrates, catalytically active enzymes must be in their natural forms. Their development as treatments is hampered by their fragile structure. PEGylation, nanocarriers and nanoparticle encapsulation, and the creation of mutant variations utilising recombinant DNA technology have all developed as complementing methods that have

allowed researchers to overcome some of the challenges associated with enzyme structure and function.

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