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Proteases: A Beneficial Degradative Enzyme in Therapeutic Applications

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***Abstract*-** Proteases probably arose at the initial phases of protein development as simple degradative enzymes essential for protein degradation into its simpler form as amino acids in prokaryotic organisms. Proteases are an increasing group of enzymes that hold great potential. Proteases are produced by animals, plants, and microorganisms. Microorganisms play a dominant role in the field of proteases production. Their contribution in the life cycle of numerous pathogenic organisms has led them to become a probable target for emerging therapeutic agents in contradiction of life-threatening diseases. These enzymes are being utilized in the cure of respiratory tract issues, cardiovascular disease, inflammation, and cancer. Proteases promote healing process of tissue damage; it may be surgical or accidental damages, fractures or burns. Due to these special features, proteases are an emerging class of enzymes that possess diverse medical applications. Along with proteases, protease inhibitors are also played a very important role in disease control. Therefore protease inhibitors have drawn the attention towards their crucial role in the therapeutic application.

***Keywords*:** Degradative enzyme, Cardiovascular disease, Tissue damage, Medical applications, Cancer, Protease inhibitors.

I. INTRODUCTION

Proteases (also termed peptidases and proteinases) are capable of hydrolyzing peptide bonds which are found between amino acids in proteins. They can be found everywhere in nature and all living organisms, from microbes to animals, plants, and humans. Proteases have great medical and pharmaceutical importance due to their key role in biological processes and in the life-cycle of many organisms [7].

Proteases are degradative enzymes which accelerate the degradation of proteins. Investigations have demonstrated that proteases have the special ability to conduct highly specific and selective modifications of proteins such as activation of zymogenic forms of enzymes by limited proteolysis, blood clotting and lysis of fibrin clots, and processing and transport of secretory proteins across the membranes.

Proteases are wide-ranging proteolytic enzymes found in all animals, plants and microorganisms. There are many studies have been carried out for more than a century on their eminent property to promote degradation of certain peptides in particular proteins. Further evidence of their significance in various biological processes has been object of studies in all living organisms. Hence, proteases control the fate, localization and activity of numerous substrates, produce novel bioactive molecules, contribute to process cellular information and transmission of molecular signals [13].

Proteases have great catalytic activity and substrate specificity. Proteases are essential and most important constituents of all organisms on earth, including prokaryotes, fungi, plants and animals. These organisms can be cultured in huge quantities in a comparatively short period and they can also produce a large amount of desired product [4].

Proteases play an important role in numerous processes such as digestion, fertilization, growth, maturation, aging, and even death of the organism. They control several physiological processes by governing the activation of the formation and degradation of proteins. These enzymes are very significant and helpful in the replication and spread of viruses, bacteria and parasites, hereof they are amenable for an efficient transmission of diseases which are caused by these pathogens. Their participation in the life cycle of disease- causing organisms has led them to become a forceful target for evolving therapeutic agents against deadly diseases such as cancer and AIDS [1]. By means of structural and functional multiplicity, proteases complete an enormous array of critical functions ranging from intracellular protein recycling to nutrient digestion to immune system cascade amplification [9].

Present review article focused on the therapeutic application and sources origin of the proteases enzymes, and to know the how it plays the best role in controlling various medical disorder of human.

II. SOURCES OF PROTEASES

Proteases are widely distributed in nature and found in all living organisms such as animals, plants, and microbes. They are crucial for the cell growth and their activities.

Proteases from animals

The most prevalent proteases from the animals are trypsin, chymotrypsin, pepsin, and rennin. Trypsin is the chief digestive enzyme in the intestine; catalyze the degradation of proteins present in food. Chymotrypsin is secreted by the pancreas of animals and converted into an active form called trypsin. The obtained pure form of chymotrypsin is very precious and used only in diagnostic and analytical applications [21]. Another protease enzyme is pepsin; it is an acidic aspartic protease that is generally found in the stomach of almost all vertebrates. Pepsin attacks on internal peptide bonds found in the polypeptide chain. It has aspartate at their active site. A pepsinogen is an inactive form of pepsin. It is secreted by the chief cells of the stomach. When pepsinogen comes into contact with gastric juice, it activates and become pepsin. It is an important digestive enzyme and plays a most crucial role in protein digestion [5].

Proteases from plants

Plants also produce a variety of proteases. Proteases obtained from the plants are extensively used in drug and the food industry. Certain proteases, such as Papain and Bromelain are basically involved in numerous processes such as brewing, meat softening, milk-clotting, cancer treatment, digestion and viral disorders [16].

Pineapple and papaya are the best fruits which contain a large amount of proteases. Pineapple fruit comprises a variety of protease enzymes collectively called Bromelain. Bromelain is very helpful to cure a wide range of health issues, such as inflammatory disease, blood clotting problem in veins, indigestion, tissue damage and cancer.

Papain is a plant proteolytic enzyme which is obtained from papaya fruits. It is generally extracted from the unripe papaya fruit. In unripe papaya fruit, it is present in high quantity rather than ripped fruit.

Proteases from microorganisms

Microorganisms are the best option for the many products because they are present everywhere in nature and can produce the desired product in relatively high quantity rather than plants and animals. Microorganisms are preferred over the others for the large-scale production of proteases due to their fast growth and simplicity of life. Proteases are produced by bacteria, fungi and also by viruses [21].

III. THERAPEUTIC APPLICATIONS OF PROTEASES

Proteases perform a great variety of roles, ranging from the cellular level to the organ and organism level, to yield systematic maintenance or regulation of the body's functions. They are liable to do many complex processes which are involved in the typical physiology of the cell as well as in abnormal pathophysiological circumstances. Their participation in the life cycle of disease-causing organisms has led them to become a probable target for emerging therapeutic agents against deadly diseases such as cancer and AIDS.

Useful in inflammatory disease

Proteases play a vital role in inflammatory diseases. It is well known for their anti-inflammatory activity. Bromelain is a type of protease enzyme which is usually obtained from pineapple plants. It is extracted from the pineapple fruit and stem cells [22].

Bromelain is also used to regulate expression of mRNAs encoding pro-inflammatory cytokines by human immune cells. Bromelain cut specific molecules found on the cell surface that affect migration and activation of leukocyte. It inhibits the signal transduction between immune cell and colon epithelial cell lines. Eventually, the inflammatory response interrupts [11]. It is a non-toxic compound with beneficial values. Bromelain is most prominent to overcome the inflammation and reducing swelling. Bromelain is a natural anti-inflammatory agent, that's why it has many uses. In patients, who are suffering from arthritis, it may decrease the inflammation that responsible for joint pain. It is also supportive in relieving the pain, tingling, numbness, and loss of sensation in fingers [2].

Useful in treatment of blood clots related to stroke

Cardiovascular disease is a major cause of death. Thousands of people die every year from cardiovascular disease than from any other cause. So it's a demand of today to overcome such types of disease so that people can live their life happily. In the human body, there are many types of proteins are present. Sometimes the performance of few proteins is considered as fatal for the human being. Proteins play a great and vital role in any of living organism because they all require proteins for their cellular functions. Therefore Proteins are the critical components for organisms. As well protein production, the degradation of proteins is also significant, as this is the way to recycle dysfunctional or injured proteins and release the amino acids to produce new proteins [6]. A protein called fibrin participates in the process of blood clotting. It is a necessary process of the body but occasionally it is the cause of death by the cardiac stroke. The most common form of cardiac stroke happens when a blood clot blocks a coronary artery that feeds the heart muscle. The principal reason for stroke arises when a

blood clot blocks, an artery bringing blood to the brain. Formation of vascular blood clots is also a principal cause of death in cancer patients because cancer cells make circumstances that favor clotting. There are some factors responsible to increase the risk of coagulation of blood, such as–deficiency of nutrients in the diet, lack of workout, chronic inflammation, excess free radical damage, and aging. One of the key target molecules of proteases is fibrin. Fibrin is a derivative of fibrinogen. It is an insoluble protein that plays a primary role in the formation of blood clots. In the process of blood clot removal, serine protease plays a significant role. A serine protease is a plasminogen activator which activates the plasminogen into plasmin. After that this activated plasmin do the actual task of blood clot dissolution. Plasmin involves in fibrinolysis. It acts on fibrin protein and breaks down it [23].

Useful in repair and cleaning of tissue damage

All types of tissue damage, such as surgical or accidental damages, fractures, and burns, promotes a physiological process of healing, which eventually leads to the structural and functional renovation of the injured tissues. The process of injured tissue repairing can be classified into four successive stages—hemostasis and coagulation, inflammation, proliferation, and remodeling. If the progression is broken up or stopped during any stage, it leads to impaired healing and development of a chronic wound. Such types of chronic wounds are responsible for significant morbidity, mortality, and poor quality of life. So, rapid and effective supervision of acute tissue injury is required to prevent it from developing to a chronic wound. Trypsin, it is an active form of chymotrypsin, is an oral proteolytic enzyme preparation which has been used for the clinical purpose for a long time. It provides better and faster retrieval of acute tissue damage than numerous of the other existing enzymes [18].

Useful in egg fertilization

Proteases play an important role in eggs fertilization in throughout echinoderms. Echinoderm is the common name given to any member of the phylum Echinodermata of marine animals. Proteases help in eggs fertilization as well as block any subsequent sperm. During the fertilization egg and its associated somatic cells are released attractants which are attracts the sperm towards the egg. Once the sperm becomes close to the egg, usually the extracellular matrix then stimulates the sperm, enabling it to penetrate the matrix and reach the cell surface, hereafter the sperm and egg are now able to fuse. After the fusion however egg immediately changes their strategies and then employs its resources to block any subsequent sperm. There are so many secretory vesicles presents nearby the plasma membrane of egg, called cortical granules are stimulates and release their contents towards surface membrane [8]. Cortical granules generally contain serine protease. The contents of cortical granules are variable with species. After fusion the serine protease accomplish at least two distinct molecular tasks. First task is in cleaving the tethers of the extracellular matrix to the egg cell surface. Severing this link, the so-called delaminase, enables the extracellular layer to detach and lift off the cell surface to remove subsequent sperm from the egg surface. The second task by this protease is to cleave egg cell surface receptors for sperm and in that way sperm unable to access the egg and cannot complete the fusion process. In this way serine protease avoids polyspermy and plays best role in egg fertilization [12].

Useful in food indigestion disorder

Enzymes play a vital role in human health and well-being. Our digestive tract depends on many different types of proteolytic enzymes to help break down our food proteins present in the variety of foods such as dairy, meats, eggs such as [19],[7]. Proteolytic enzymes are a type of digestive enzyme that split the protein into short peptides or amino acids. In the digestive tract, the stomach is the first compartment, which is chemically active towards proteins. Its acidic pH serves three major functions: it sterilizes the ingested material, denatures food protein and activates local proteolytic enzymes [10]. Protein digestion initiates in the stomach with the help of an acidic protease called pepsin, which is secreted in the stomach. Pepsin is acid stable protease and it is able to break down the large polypeptide chains. Thereafter proteases present in the pancreatic juices and intestine break down the polypeptide chains into small peptide units and individual amino acids. In this way remaining short form of the protein is absorbed and utilized by the cells. Proteases that break down amino acids from the ends of the polypeptide protein chains are called exopeptidases, whereas those that cleaves internal bonds within the peptide chain are termed endopeptidases [21], [17]. Pepsin split proteins into short fragments to increase its availability for sequential digestion. When taken on an empty stomach, proteolytic enzymes pass into the bloodstream and become Systemic enzymes. Systemic enzymes are enzymes that work outside of the digestive system and contribute in the reactions inside our body's cells.

Useful in prevention of cancer

By researcher, several pathways have been proposed to clarify the anticancer properties of Bromelain. They have suggested that proteolysis by Bromelain is a main pathway to control cancer. Bromelain has been found to have usual anti-cancer properties. It promotes apoptotic cell death and stopping tumor development. [14].

Some studies showed that Bromelain has improved protection against breast and lung cancer, and it affects malignant peritoneal mesothelioma, it is a rare cancer which is caused by asbestos exposure. It is also declared that the presence of Bromelain increased the death rate of cancer cells expressively. According to research, Bromelain has the

potential to be the most effective therapeutic agent in treating malignant cancer [15].

IV. PROTEASE INHIBITORS

Protease inhibitors have established increasing attention as beneficial tools not only for the study of enzyme structures and reaction mechanisms but also for possible application in pharmacology. Particular and selected protease inhibitors are potentially very powerful inhibitors for the controlling and inactivating the specific proteases which involved in the pathogenic activity in human. The activity of proteases can be regulated by Protease Inhibitors that can block the active site of protease. The activity of proteases in the life cycle of microorganisms is very important. If any chemical that affects the action of proteases means it directly affects the life cycle of microorganisms. Thus the protease inhibitors may act as a barrier for microbial infection [20].

Proteases and protease inhibitors have been progressively known as significant factors in the physiopathology of human diseases. Protease inhibitors are molecules that inhibit the function of proteases. Several naturally occurring protease inhibitors are proteins. These inhibitors inhibit the distribution of cancer cells and have an inhibitory outcome on tumor growth. Thus protease inhibitors are emerging as potential therapeutic tools to treat cancer [3].

An HIV-1 protease is essential for the reproduction and maturation of HIV in particular infected patient. The protease inhibitor inhibits the activity of HIV-1 protease, that's why HIV cannot complete the life cycle properly. This is one of the best possibilities to break the development of the AIDS in a patient. Thus, the HIV-1 protease inhibitors, included amprenavir, tipranavir or darunavir, are the extremely dynamic antiretroviral therapy [1].

Latest studies have discovered the role of Protease inhibitors in the inhibition of numerous pathogenic protozoa, such as Leishmania and Trypanosoma. These protozoa contain cysteine protease. This protease plays a most important role in the differentiation of parasite and influencing the host's immune system. Consequently, cysteine proteases are the significant virulence factor of protozoan parasites [20].

That's why with proteases, protease inhibitors are also very crucial in controlling the life-threatening diseases in human and animals. Therefore protease inhibitors have drawn the attention towards their crucial role in the therapeutic application.

V. CONCLUSION

The present review fundamentally centered on the therapeutic uses of the proteases. Proteases have been utilized for a broad assortment of therapeutic applications in the medicinal field. It plays the helpful and pivotal part in human and also animals and plants. It completes quickly numerous biological processes, such as digestion disorders, wound healing, cardiovascular diseases, and blood clots dissolution. Proteases help in eggs fertilization in echinoderms and block the subsequent sperms. It also helps in the inflammatory process, which causes pain in joints, and gives relief to the arthritis patients. Therefore proteases are a most emerging group of enzymes and have a great future as a various therapeutic class with miscellaneous clinical applications. Besides the therapeutic applications of proteases, protease inhibitors are also an emerging group of proteinaceous molecules which are very helpful in controlling the activity of pathogenic microorganisms that cause deadly diseases, such as HIV.

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Lakhan Kumar is a research scholar and pursuing Ph.D. in Microbiology from School of Studies in Microbiology, Vikram University, Ujjain (M.P.), India. He is doing his research on isolation and screening of proteolytic fungi from the soil. He is performing his research under the guidance of Dr. S.K. Jain (Reader, School of Studies in Microbiology, Vikram University, Ujjain (M.P.) India).

Dr. Sudhir Kumar Jain is appointed as a reader in School of Studies in Microbiology, Vikram University, Ujjain (M.P.) India. He has excellent grasp of research in Mycology and also in other filed of Microbiology. Many candidates had completed their Ph.D. under his supervision and guidance. He has very polite and friendly nature towards the people especially for research scholar.

