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Protease Activated Drug Development-A Review

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ABSTRACT:

Protease is referred to as a group of enzymes whose catalytic function is to hydrolyze peptide bonds of proteins, they are also called proteolytic enzymes or proteinases.The action of proteases was thought to be restricted to digestive, extracellular modelling and tissue reshaping purposes, mainly by proteolytic activities throughout Homeostasis and Interstitial molecules. development also in aberrant maladaptive circumstances, during disease pathogenesis. Proteases can also be involved in various aspects of human biology. Proteases, for example, digest food proteins in the small intestine to allow amino acid absorption.Other processes mediated by proteases include immune function, blood coagulation, bone formation, maturation of prohormones, programmed cell death, and the recycling of cellular proteins that are no longer needed.Proteases are not restricted to only digestive and tissue reshaping purposes, but are also essential as essential factors for physiological immune responses to the diseases. Proteases are essential. This activation may be directed by the destruction of indirect pathogens or phagolysosomes, through activating checks pattern recognition receivers such as over head receptors.. Unfortunately, excess production of proteases that can also lead to excess tissue inflammation and damage maladaptive host responses. Protease-activated prodrugs can be exploited or destroyed to improve drug delivery. This review was prepared with an intention to discuss the use of proteases in drug development.

INTRODUCTION

Proteases play an essential and fundamental role through the regulatory mechanism, proteolysis, in many biological and pathological processes. Proteolysis is an irreversible regulatory mechanism and now it is known for its selectively cleave specific substrates. Additionally, multimeric and multi catalytic proteases exist to degrade multiple intracellular proteins, called proteasomes, essential, and significant for biological processes (López-Otín and Hunter, 2010).The human degradation is composed of at least 569 proteases that are spread over 5 widths and that form a complete list of proteases synthesized by human cells classes metalloproteinases, serine, cysteine, threonine, and aspartic proteases(López-Otín and Matrisian, 2007). The covalent catalysis includes serine, cysteine and threonine proteases. The nucleophile of a catalytic site is part of the specified amino acid.Increasingly controlled actions, proteases play an important role in the replication and transcription of DNA, in cell proliferation & differentiation, in angiogenesis, in neurogenesis, in ovulation, in fertilization, in wounds repair, in stem cell mobilisation and the activation of 3 nucleophiles. blood coagulation, inflammation, immunity, senescence, necrosis 4 and apoptosis.(López-Otín and Bond, 2008) Therefore, proteolytic actions have deregulated modifications in proteolytic actions underlie many diseases like cancer and neurodegenerative, cardiovascular disorders, that is the ability to degrade extracellular matrices. Because proteases are strongly associated with cancer progression, specifically invasion and metastasis. Intracellular proteases such as lysosomal cysteine proteases, such as destroying certain foreign bodies and endocytized proteins, also participate in more defensive processes. With strong evidence of protease involvement in diseases, proteases serve an important and essential role in drug development. Some therapies have been developed and supervised to target and inhibit dysregulated proteases and proteasomes, in particular for the suppression of tumors.Proteasome inhibitors have been successful in the treatment of hematological malignancies and have been tested as therapeutic agents in the 5 clinics for over 10 years (Orlowski and Kuhn, 2008). The first inhibitor, bortezomib has been used as a treatment for relapsed mantle cell lymphoma and multiple myeloma. However, the usage of

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such expansive protease inhibitors has shown a lack of success overall (Turk, 2006). Therefore, more specific and significant protease-inspired therapies have been attempted.Firstly, the recombinant of engineered protease types can replace defective protease but is constrained by the large doses required to achieve this effect. Second, gene-therapy approaches targeting protease genes can intrinsically proper protease activity can be improved. This approach has been shown to work in blocking prostate cancer in lentiviral-mediated neprilysin gene transfer(Horiguchi *et al.*, 2007). Third, an indirect approach is to hamper protease inhibitors to reduce or decrease protective (anti-tumor) proteases. Proteases that can sensitize cancer cells, as seen in Karikari, are thus activated to induce apoptosis or drug treatments,for the inhibition of caspase inhibitors to induce apoptosis in pancreatic cancer(Karikari *et al.*, 2007). Fourth, proteases can serve as biomarkers for prognosis of tumor diagnosis. The presence of protective and regulated proteases can predict good clinical prognosis but their absence can indicate the need for different and various treatments. Dysregulated proteolytic activities can signify disease that can be progressive. An effective detection technique is the use of protease activatable or stimulated probes (Zhu *et al.*, 2011; Jang and Choi, 2012; Kim and Kim, 2012; Yhee *et al.*, 2012). Molecular beacons or Activatable probes can also help in signaling typically by fluorescence, the detection of proteases after the protease degrades the linkage between the dye and a quencher.iIn this way, as seen by Karikari, et al, proteases are activated which can sensitize cancer cells to induce apoptosis or drug treatments that is activated or stimulated. Using a similar approach, protease-activated prodrugs (PAPs) can be exploited or destroyed to improve drug delivery to areas where protease expression, like in malignant tissues, is higher than in normal tissues.

Prodrugs are derivatives of drug molecules that can undergo a transformation by an enzyme, environmental stimulation chemical, to release the active parent drug (12). Just as activatable probes, prodrugs in their native state are inactive should be stimulated in order to form the drug but only after a stimulus releases an active drug. In this way, prodrugs are an extremely significant approach to increase selectivity and efficacy of chemotherapy, reducing the toxic effects on healthy cells. By chemical conjugation, prodrugs improve all pharmaceutical properties of the parent drug, such as its solubility, permeability, stability, and 12-13 or instability, previously unsuitable drugs for clinical purpose usage can now be utilized. It has been estimated in distribution about 5-7% of drugs currently approved worldwide are classified as ever-larger prodrugs. (Rautio *et al.*, 2008; Mahato, Tai and Cheng, 2011). Since prodrugs can overcome major and important hurdles of drug formulations like poor solubility, amounts of prodrugs are approved and improved every year 14. Prodrugs are made up of the parent drug conjugated with a pro-moiety, like a polymer or peptide substrate by a cleavable linkage and/or a targeting moiety for specific delivery like an antibody. Common functional groups used to modify prodrugs 12 for superior properties, called specifically protease-cleavable, pro-moieties, cleavable prodrugs. Using this strategy, the prodrug only achieves its active form when the enzyme of interest, for which the moiety is its, cleaves substrate it. Therefore, the drug is released at a specific and significant location where the enzymes are over-expressed. (Stella, 2004)Adipose tissue is the first site of storage for extra energy as triglyceride and it helps in synthesizing a number of biologically active compounds that regulate the significant metabolic homeostasis.(Ponnulakshmi *et al.*, 2019).The stained techniques that are proven SG-GNPs increase the reactive oxygen species and decreased the mitochondrial membrane potential(Wu *et al.*, 2019) enzyme showed activity is detergent even after 1 hour of incubation, the determination of staining activity is also studied as a content(Rengasamy *et al.*, 2016). Non-alcoholic steatohepatitis (NASH), is an essential component of Non-alcoholic fatty liver disease (NAFLD) spectrum that can be used by enzymes too, which progresses to end-stage liver disease, if not diagnosed and treated properly. (Mohan, Veeraraghavan and Jainu, 2015). Obesity in children has also become a regular problem like cough and cold. The drugs from protease may also be helpful in preventing obesity.(Shukri *et al.*, 2016) Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Ariga *et al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy *et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and

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Antony, 2018; Manohar and Sharma, 2018; Menon *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan *et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy *et al.*, 2019; Gheena and Ezhilarasan, 2019; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar *et al.*, 2019; Sharma *et al.*, 2019; Siddique *et al.*, 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

Protease During Apoptosis:

The importance and essentials of proteases during apoptosis are becoming increasingly apparent. Since apoptosis contributes to a variety of disease processes, understanding, protease roles and their inhibitors could provide the sight for pathogenesis of the conditions and their inhibitors might provide sight in pathogenesis of the conditions and suggest novel therapeutic strategies. We discuss the involvement and role of proteases,protease inhibitors and substrates that appear to be the participants in the apoptotic process(Patel, Gores and Kaufmann, 1996). One of the early indication through proteases could be essential riggers for apoptosis that came from the studies on proteins found in the cytoplasmic granules of the cytotoxic T- lymphocytes and the natural killer cells, both of which kill by binding to the target cells and inducing apoptosis within the so-called kiss of death. Purification of the constituents of the cytotoxic T lymphocyte and the natural killer granules yielded perforin, a pore-forming protein, as well as a series of serine proteases, has the unusual property of cleaving at Asp residues. Exposure of target cells to be purified through the preparation of performing B in the combination was sufficient to induce apoptosis.

More clear data of proteases could be involved centrally in controlling the mechanism of cell death that has emerged from nematode studies. A series of genes that can control various elements of the programmed cell death process in this worm have been identified, two of which, ced-3 and ced-4, are required for cell death during development. The third line of evidence for a role for proteases in apoptosis comes from studies that have explored the effects of diverse protease inhibitors on apoptosis induced by a variety of agents.(Martin and Green, 1995).This can be said as an example, The current studies, we established that sesame deactivates STAT-3 translocation, thereby decreases the elevated expression of, cyclin-D1, Bcl-2, and diminished expression of Bax, caspase-9 and 3 in FTC-133 cell lines. Conclusively, sesame hampers thyroid cell expansion and initiates apoptosis by hindering STAT-3 translocation.(Ma *et al.*, 2019).*Garcinia mangostana* is extensively used in most of the Indian herbal pharmaceuticals and nutraceuticals, that is used worldwide for many diseases(Priya, Jainu and Mohan, 2018)

Role Of Proteolytic Enzymes:

The most prevalent genetic expansion was the trypsin, which yielded the enzymes responsible for digestion, blood coagulation, fibrinolysis, growth, fertilization, apoptosis, and immunity. This expansion 's success lies in a highly efficient fold that combines catalysis and regulatory interactions. Complexity added stems from the recent observation of the trypsin fold 's significant conformational plasticity. The Proteases arose from the earliest stages of protein evolution as the simple destructive enzyme necessary for the catabolism of proteins and amino acid generation in primitive organisms. Studies of the proteases based on the original for several years Roles which are blunt protein-associated aggressors. The realization, however, that beyond these unspecific degrading functions, proteases act as sharp scissors and catalyze highly which are specific proteolytic processing reactions and produce new protein products, inaugurated a new era in protease research.(Neurath and Dixon, 1957) The current success of the research in the group of the ancient enzymes derived mainly from a large collection of findings demonstrating their relevance in the control of the multiple biological processes in almost all living organisms. Proteases thus regulate the destiny, localization and activity of many proteins, modulate protein-protein interactions, create new bioactive molecules, contribute to the processing Proteases affect DNA replication and transcription, cell proliferation and differentiation, tissue morphogenesis and remodeling, heat shock and the unfolded protein responses as a direct effect of the various actions;of cellular information and also generate, transduce and amplify the main molecular

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signals.Angiogenesis, neurogenesis, ovulation, fertilization, healing of wounds, activation of stem cells, homeostasis, coagulation of the blood, swelling, immunity, autophagy, senescence, necrosis and the primary cycle called apoptosis. In line with these important and essential roles of proteases in the cell behavior and survival and death of all organisms, there are multiple pathological conditions underlying changes in proteolytic systems as cancer, neurodegenerative disorders, and inflammatory and cardiovascular diseases(Turk, 2006). Many proteases play an important and major focus of attention for the pharmaceutical industry as potential drug targets or as diagnostic and prognostic biomarkers. Proteases are important in plants and help to process, mature or destroy specific protein sets in response to developmental indications or variations in environmental conditions (García-Lorenzo *et al.*, 2006). Many infectious microorganisms require proteases for replication or use as virulence factors proteases which have facilitated the development of protease-targeted therapies for diseases of great relevance and need to human life such as AIDS(Turk, 2006)The proteases are also essential tools of the biotechnological industry because of their usefulness as biochemical reagents or in the manufacture of the numerous products.(Saeki *et al.*, 2007)

This exceptional diversity in protease function results directly from the evolutionary invention of a multiplicity of enzymes that exhibit a variety of sizes and forms.In terms of specificity, diversity is also a very important and essential common rule.Some proteases exhibit an exquisite specificity towards a single protein peptide bond (e.g. angiotensin-converting enzyme); however, most proteases are relatively non-specific to substrates, and some are overtly promiscuous and indiscriminately target multiple substrates (e.g.proteinase K).Proteases also follow different and different strategies to establish a suitable location in the cellular geography and, in most cases, operate in the context of complex networks consisting of distinct proteases, substrates, cofactors, inhibitors, adapters, receptors and binding proteins, which may provide an additional level of interest but also a complexity for the study of proteolytic enzymes. (Cera and Di Cera, 2009)

Drug Targets In Inflammation And Pain:

The activation of a novel class and the importance of receptors coupled with G proteins have shown that proteases signal to cells: protease-activated receptors (PARs).The receptors are expressed in a wide range of cells, which ultimately and significantly are all involved in mechanisms of the inflammation and pain. Numerous studies have been considered that play an important role of PARs in cells, organ systems, highlighting the essential fact that PAR activation results in signs of the inflammation.(Ossovskaya and Bunnett, 2004) A growing body of evidence that is discussed suggests that these receptors, and the proteases that activate them, interfere with inflammation and pain processes.Chemotherapy is successful but still faces challenges including non-selectivity and high toxicity, as the pillar in the treatment of various and differs in cancers for several decades. Increasing selectivity is therefore a key step in improving the clinical efficacy of chemotherapy. The prodrug is one of the most important and promising approaches to increase the selectivity and efficacy of a chemotherapy drug. The classical prodrug approach is to improve pharmaceutical properties by basic chemical modification (solubility, stability, permeability, inflammation, delivery, etc.) There are numerous selective formulations of prodrugs that were designed to improve the selectivity of chemotherapy drugs. Various tumor-targeting ligands, ligand-associated transporters, and polymers may be incorporated into a tumor-enhancing prodrug.(Russell and McDougall, 2009).Prodrugs may also be activated or induced by enzymes that are expressed specifically at a higher tumor level , resulting in selective anti-tumor effect.leading to a selective anti-tumor effect. This can be achieved by conjugating the enzyme to a tumor-specific antibody or delivering a vector expressing the enzyme inside the tumor cells.(Vergnolle, 2009)

Protease In Cardiovascular Health And Disease:

The platelet is involved solely in the formation of clots, and is now known as a key mediator in

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various other processes such as inflammation, thrombosis, and atherosclerosis.Also, the antiplatelet agents have become paramount in the prevention or precautions and management of various and different cardiovascular diseases. However, the currently most widely used anti-platelet drugs, aspirin, and clopidogrel, have also been shown to decrease and reduce the risk of serious vascular events only by approximately one quarter. Similarly, oral glycoprotein IIb/IIIa antagonists have been associated and involved with excess mortality, thus restricting the use-age of parental glycoprotein IIb/IIIa antagonists to the treatment of acute clinical conditions(Badimon, Padró and Vilahur, 2012).For the prevention of cardiovascular diseases, therefore, there is still a clinical need for antiplatelet drugs with greater antithrombotic efficacy but with safety profiles that allow long-term preventive administration. A wide range of physiological and pathological responses in cardiovascular systems have been shown to influence thrombin signaling with the protease-activated receptors (PARs). Thus, interference with PARs appears to be a promising strategy for developing new antiplatelet agents with higher efficacy.(Packer, Hiramatsu and Yoshikawa, 1999).In vitro has been performed to establish the contribution of proteolytic enzymes to the ETHOLOGY of cardiovascular disease. The contribution of several MMPs to ECM degradation in cardiovascular diseases has been highlighted in several excellent and elaborated reviews.MMPs do not only play an important role in protein but also-required for ECM degradation; other proteases like cathepsin cysteine proteases are needed as well. Cathepsin of the cysteine protease family is present in lysosomes and endosomes and degrade intracellular or endocytosed proteins. These cathepsins have been proven to play an important and significant role in cardiovascular diseases. Another review article was focussed on the essential role of the cysteine protease family of the cathepsins in cardiovascular disease(Lutgens *et al.*, 2007). Historically, the PARs have been recalcitrant in the development of peptidomimetic antagonists with recent PAR1 drug candidates based on natural products now undergoing large-scale clinical studies, the treatment of patients with acute coronary syndromes. In an orthogonal approach, PARs have been blocked on the inside of the cell with the use of cell-penetrating for preventing singling to an internally located G protein.(Leger, Covic and Kuliopulos, 2006)

Bacterial Protease:

Bacterial proteases are a wide variety of enzymes with diverse and necessary functions in cell viability, stress responses and pathogenicity. Although their perturbation is clear and offers the potential for antimicrobial drug development, both as traditional antibiotics and also anti-virulence drugs, they are not yet the target of any clinically used therapeutics. Here we describe the potential for and recent progress in the development of compounds targeting bacterial proteases with a focus on AAA+ family proteolytic complexes and signal peptidases. Caseinolytic protease belongs to AAA+ family of proteases, a group of multimeric barrel-shaped complexes whose activity is tightly stimulated or regulated by associating AAA+ ATPases.(Brötz-Oesterhelt and Sass, 2014) .The possibility of chemical disturbance of these complexes is followed by compounds targeting ClpP for inhibition, activation of its associated ATPase. The SPs are also a proven target for antibiotics. Chemical inhibitors have successfully targeted both the Type I and Type II SPs responsible for the cleavage of targeting peptides during protein secretion. The threat of pan-antibiotic resistance continues to develop and other bacterial proteases provide an arsenal of new developmental antibiotic targets(Culp and Wright, 2017).

Extracellular Protease In Pathophysiological Process:

Primary targets are the Proteases that constitute drug discovery. In the present review, because of the differential expression, we focus on extracellular proteases (ECPs) in many pathophysiological processes, including cancer, cardiovascular conditions, and inflammatory, pulmonary, and periodontal diseases. Many novel ECP inhibitors are currently under clinical review and in the coming years and decades we should anticipate a strong and essential high in new therapies focused on protease inhibition. Because the activity of a targeted protease is directly blocked, one can take

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advantage of differential expression in disease states to deliver therapeutic or imaging agents selectively.Latest experiments in selective production of metalloproteases (Matrix metalloproteinase, adamalysins, Pappalysins, Neprilyzine, Metallocarboxypeptidases and Glutamate Carboxypeptidesis II) in the compound, serine proteases (elastases, factors of coagulation, activators of plasminogen tissue / urokinase system, kallikreins, tryptase, dipeptidyl peptidase IV) and cysteine proteases (cathepsin B) are essential(Cudic and Fields, 2009).

Role Of Proteolytic Enzyme In Diseases:

Chronic inflammatory lung diseases such as cystic fibrosis and emphysema are classified by higher-than-normal levels of pulmonary proteases. While these enzymes play important and meaningful roles such as the killing of bacteria, their dysregulated expression or activity could affect inflammation. For effective resolution of pulmonary disease infection, the effectiveness of endogenous control mechanisms can put an end to this over exuberating protease activity in vivo.The function of the pulmonary antiproteases is to fullest this essential role. In addition to their anti-protease activity, protease inhibitors in the lung also often have other intrinsic properties that contribute to microbial killing or termination of the inflammation process (Greene and McElvaney, 2009).

Protease In Cancer Drug Development:

Many diseases such as cancer and neurodegenerative and cardiovascular conditions are caused by deregulated changes in proteolytic behavior (Choi *et al.*, 2012)). While protease inhibitors against hypertension and viral infections have been successfully developed, there have been failures in people as far as cancer drugs are concerned. Progress in cancer profiling now makes us more aware that the tumor is weakening a dynamic network called the protease system that decides the global outcome of the exploitation by individual nodes. Identification of which tumor micro-environmental proteases are effective in treating cancer through use of Protease-Activated Medicines (PAPs). This concept for Metallo, cysteine, and serine proteases is illustrated here. PAPs are currently not only present as small molecular adducts containing a cleavable sequence of substrates and a latent medication Also produced as different nanoparticles and different kinds. Although PAPs for treatment are the subject of the study, it is evident that protease-activating sensors and nanoparticles are also important imaging devices, including also manufactured as various and different types of nanoparticles. Although the emphasis of the review is on PAPs for treatment purposes, it is clear that protease activatable probes and nanoparticles are also powerful tools for imaging purposes, including tumor diagnosis and staging, as well as visualization of tumor imaging and creating during microsurgical resections.(Vandooren *et al.*, 2016). Bionanotechnology has a pivotal role in the development of novel therapy, applications of gold nanoparticles (AuNPs) in the treatment of cancer, with the help of enzymes.(Ke *et al.*, 2019).Glioma is the prime cause of cancer allied mortality in adolescent people and it accounts for about 80% of all malignant tumors.(Li *et al.*, 2020).Disclosure of ultraviolet (UV) radiation is the feature of the environment to cause redness of the skin, inflammation, photoaging, and skin cancer(Chen *et al.*, 2019). Biosynthesis of Zinc oxide nanoparticles (ZnONPs) from natural plants stands as a promising nano-drug delivery system also helpful in cancer therapeutics.(Wang *et al.*, 2019).The results proposed the anticancer effect of ZO toward DMBA-induced mammary cancer in SD animals and Michigan cancer foundation-7 mammary cancer cells.(Gan *et al.*, 2019)The mace extract is seen that cytotoxic activity and induced apoptosis through the modulation of the target genes Bcl-2 in the KB cell lines, suggesting the potential of mace as a candidate for oral cancer chemoprevention(Rengasamy *et al.*, 2018). The cytotoxic effect on oral cancer cell line due to the presence of anticancer constituents in the berries, in which oral cancer also play a significant role in life (Ramya, V and Gayathri, 2018).In pineapple, an extract is effective in treating agent in case of oral cancer in a natural way instead of harmful treatments.(Menon, V and Gayathri, 2016).

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Future For Protease:

The applications of proteases in the industry and therapeutics have Therapeutics have evolved quite steadily in the past two decades and have expanded exponentially. The market and future protease markets will continue to expand new protein engineering strategies and techniques.The new method to specifically control human protease activities for clinical applications is apoptotic caspase activation with engineered, kle molecule-activated proteases. Furthermore, a modern technique for the site-specific targeting of drugs and tumor imaging can be developed in diseased tissues taking advantage of proteolytic activities of protéases. Protease development can be predicted to be a multidisciplinary future with several significant advances with synthetic biologies, computer architecture, crystallography and screening technology. It may be so incredible that some of the proteases, enzymes which cleave other proteins or even catalytically, makings of the largest single-family of enzymes, constituting the human genome is estimated at 2 percent. Proteases are aspartate, cysteine, glutamate, métallo, serine and threonine, which are consistent within each member of each group in six groups on the basis of the characteristic mechanisms.based on characteristic mechanistic features consistent within each member of a group. Proteases carry a wide range of critical features from recycling intracellular proteins to nutrient digestion and immune system cascades to amplification through structural and functional diversity(Li *et al.*, 2013).

DISCUSSION:

Prodrugs are the derivation of drug molecules that can undergo a transformation by an enzyme in an environment stimulation chemical to release the activity of parent drug (Rautio *et al.*, 2008). Just as activating a bill probe, prodrugs in their native state are inactive and should be stimulated in order to form the drug but only after a stimuli release and active drug. In this way, prodrugs are an extremely significant approach to increase selectively and efficacy of chemotherapy, reducing the toxic effects on healthy cells.

By chemical conservation, products improve all pharmacological properties of the parent trucks, such as its solubility, permeability, stability, and instability are previously in suitable drugs for clinical purpose usage can now be utilized. It has been estimated and distribution about 5 to 7 percent of drugs currently approved worldwide are classified as ever-larger prodrugs (Rautio *et al.*, 2008; Mahato, Tai and Cheng, 2011),. The common functional groups used to modify pro-drugs, for superior properties, called specially pro-drugs Cleavable, Prom-moieties, cleavable raw drugs. Using this strategy, the prodrugs only achieve its active form when the enzyme of interest, for which there propriety in its Cleves substrate.

Therefore, the drug is released at a specific and significant location where the enzymes are overexpressed (Stella, 2004). Protease also follows different and various strategies to establish the appropriate location in the cellular geography and in most cases operate in the context of complex networks compressing distant A new level, however, of interest and complexity, can be achieved by proteases, substrates, cofactors, inducers, adapters, receptors and binding proteins in proteolytic enzyme study (Cera and Di Cera, 2008).Limitations of this study are Homogenous, Future scope there can be many updates and discoveries of proteases and also many books about proteases that can be reviewed.Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

CONCLUSION:

Protease is used as important for many processes and activities, the referred reviews are mostly in important topics that are in drug development in proteases.

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