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Review Article

Role of Serine Protease and its Inhibitors in Human Disorders

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Abstract

Breakdown of proteins into amino acids occurs in presence of Protease enzymes. In case of Serine proteases, serine acts as nucleophile amino acid. Serpines are known for ability to inhibit serine proteases. Serpins are involved in coagulation, inflammation and complement activation. Protease-activated receptors (PARs) are cleaved by serine. Protease inhibitors are known for anti-HIV action as anti-viral agents. This review summarizes types of proteases and serine proteases. Role of four PARs (1 to 4) are discussed in brief. It also highlights importance of serine protease inhibitors in inflammation. Various anti-viral agents such as Atazanavir, Darunavir, Fosamprenavir, indinavir, Lopinavir, Saquinavir, Nelfinavir, Ritonavir, Tipranavir approved by US-FDA are discussed in this review.

Keywords: *HIV; Inflammation; PAR1; PAR2; Serine Protease*

Introduction

A protease is an enzyme that catalyses the breakdown of proteins into smaller polypeptides or single amino acids (also known as proteolytic enzymes, peptidases, or proteinases). Proteins' peptide bonds are cleaved by the process of hydrolysis, in which water breaks down bonds. Proteases are involved in a variety of biological processes, including protein digestion, catabolism (the breakdown of ageing proteins), and cell signalling. The pancreas and the stomach are the sources. It is widely accepted that proteolytic enzymes contribute to the breakdown of protein during the digestion of dietary protein. To carry out cell development and remodelling as well as the synthesis of new proteins, existing protein molecules must be dismantled. Recently developed compounds frequently require proteolytic digestion [1].

Serine protease

Proteases are enzymes that speed up the breakdown of peptidic covalent bonds. When Serine proteases, also known as serine endopeptidases, split peptide bonds in proteins, serine acts as the nucleophile amino acid at the location. They can be found in eukaryotes and prokaryotes alike. Serine proteases are categorised as either chymotrypsin-like (trypsin-like) or subtilisin-like based on their structural

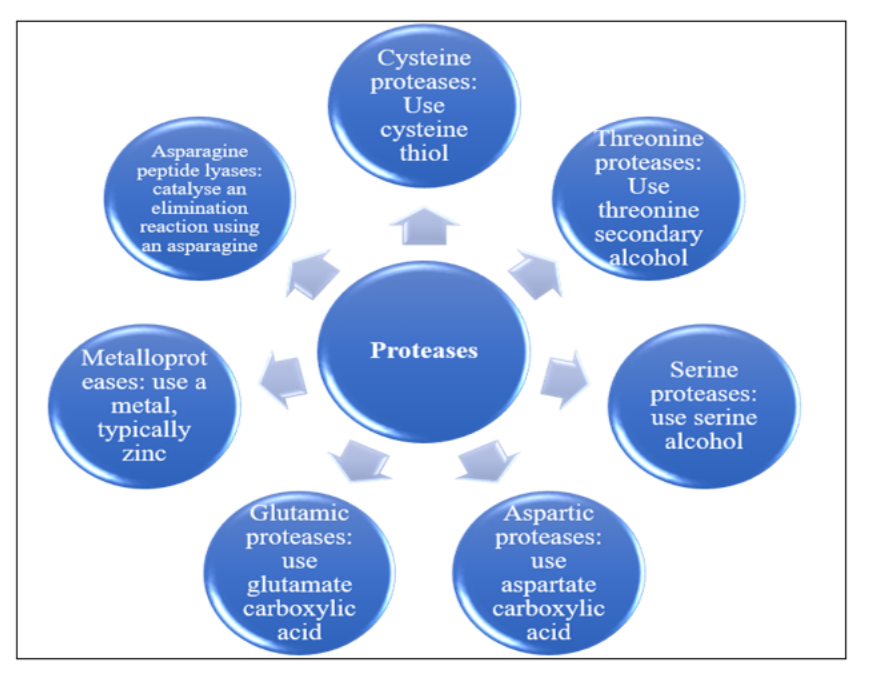

Figure 1: *Classification of proteases [2-4].*

properties. The mechanism of serine proteases is based on a serine nucleophilic base. The peptidic link that was the aim was broken. This function may be performed by cysteine, threonine, water molecules linked to metals, or aspartate. The group's nucleophilic property is frequently enhanced by the presence of a histidine that is kept in a "proton acceptor state" by an aspartate. The catalytic trio is made up of a triangle-shaped arrangement of the side chains of serine, histidine, and aspartate. The polypeptide substrate is bound by the cleft-shaped active site of serine proteases. Schechter and Berger labelled the amino acid residues of the polypeptide substrate (Pi,..., P3, P2, P1, P1', P2', P3',..., Pj) and their corresponding binding sub-sites (Si,..., S3, S2, S1, S1', S2', S3',..., Sj). The split happens between P1 and P1'.

Many inactive protease zymogens are produced and released; proteolysis then activates these zymogens. The structure of the enzyme's active site is altered as a result. Serine proteases behave in a certain way. Other proteases participate in signalling pathways, enzyme activation, and degradation processes in diverse cellular or extracellular compartments, whereas cascades of protease activations control complement and blood coagulation [5].

Classification

The MEROPS protease classification system recognised 16 superfamilies in 2013; each has many families. The catalytic triad or dyad is utilised by each superfamily in a different protein structure, proving the catalytic mechanism's convergence across time. The majority of proteases are S1 family members of the superfamily PA clan. P: superfamily made up of various nucleophile class families; S: exclusively serine proteases for superfamilies. Families are categorised within each superfamily based on the catalytic nucleophile (S: serine proteases) [6].

Superfamilies	Families	Examples
SB	S8, S53	Subtilisin (*Bacillus licheniformis*)
SC	S9, S10, S15, S28, S33, S37	Prolyl oligopeptidase (*Sus scrofa*)
SE	S12, S13	D-Ala-D-Ala peptidase C (*E. coli*)
SF	S24, S26	Signal peptidase I (*E. coli*)
SH	S21, S73, S77, S78, S80	Cytomegalovirus assemblin (human Herpes virus 5)
SJ	S16, S50, S69	Lon-A peptidase (*E. coli*)
SK	S14, S41, S49	Clp protease (*E. coli*)
SO	S74	Phage K1F endosialidase CIMCD self-cleaving protein (*Enterobacteria* phage K1F)
SP	S59	Nucleoporin 145 (Homo sapiens)
SR	S60	Lactoferrin (Homo sapiens)
SS	S66	Murein tetrapeptidase LD-carboxypeptidase (*P. aeruginosa*)
ST	S54	Rhomboid-1 (*Drosophila melanogaster*)
PA	S1, S3, S6, S7, S29, S30, S31, S32, S39, S46, S55, S64, S65, S75	Chymotrypsin A (Bostaurus)
PB	S45, S63	Penicillin G acylase precursor (*E. coli*)
PC	S51	Dipeptidase E (*E. coli*)

Table 1: *Families of serine proteases.*

Substrate specificity

Serine proteases are substrate-specific due to their unique structure, which consists of two beta-barrel domains that converge in the catalytic active site. These enzymes are classified as trypsin-like, chymotrypsin-like, or elastase-like depending on how specifically they target a substrate [7].

Trypsin-like substances

Trypsin-like proteases that come after positively charged amino acids cleave peptide bonds (lysine or arginine). The residue in the enzyme's S1 pocket at the bottom is related to this selectivity (generally a negatively charged aspartic acid or glutamic acid) [8].

Chymotrypsin-like

Chymotrypsin-like proteases have a more hydrophobic S1 pocket than do trypsin-like proteases. Tyrosine, phenylalanine, and tryptophan are examples of medium- to large-sized hydrophobic residues that are favoured.

Thrombin-like

It contains tissue-activating plasminogen, thrombin, and plasmin. They play a role in digestion, blood coagulation, and the aetiology of neurodegenerative diseases like Alzheimer's and Parkinson's dementia.

Elastase-like

Comparing proteases to trypsin- or chymotrypsin-like proteases, the S1 cleft of proteases is substantially smaller. As a result, alanine, glycine, and valine-rich residues are favoured.

Subtilisin-like

Prokaryotes contain the serine protease known as subtilisin. Subtilisin is not connected to the chymotrypsin-clan in terms of evolution, despite having a catalytic mechanism that uses a catalytic triad to produce a nucleophilic serine. Since the same mechanism evolved twice independently during evolution, this serves as the fundamental illustration used to show convergent evolution.

Catalytic mechanism

Before becoming active, many trypsin-like serine proteases must first undergo proteolysis into an inactive zymogen precursor [10]. The proprotein precursor is split between residues 15 and 16 at the same location in all known members of the family (Numbering of chymotrypsinogen). The nascent N-terminus alters the structure of the enzyme by forming an ion pair with the highly conserved D194, which organises the oxyanion hole and the substrate-binding site [11]. But in proteases like tissue-type plasminogen activator, Lys at position 156 forms an ion pair with D194 and confers a catalytically competent fold without proteolytic cleavage at residue [12].

The hydrolysis of the peptide bond by two tetrahedral intermediates is accomplished by nearly all Clan PA proteases using the conventional catalytic triad [13]. The catalytic S195's hydroxyl O atom engages H57 as an all-purpose base to attack the carbonyl of the substrate peptide link. The backbone N atoms of G193 and S195 stabilise the oxyanion tetrahedral intermediate, which together with the oxyanion hole creates the positively charged pocket in the active site. Ground and transition state stabilisation is aided by H-bonding interactions in the oxyanion hole, which contribute 1.5 - 3.0 kcal/mol [14]. The acyl-enzyme intermediate is created when the tetrahedral intermediate collapses, and H57 aids in maintaining the stability of the newly created N-terminus. The free polypeptide fragment is replaced by a water molecule, which then assaults the acylenzyme intermediate. The oxyanion hole stabilises the second tetrahedral intermediate along the pathway, and its collapse results in the formation of a new C-terminus in the substrate.

Serine proteases are multifunctional enzymes that frequently take part in cytokine synthesis that promotes inflammation as well as immune cell activation. They manage inflammatory response. A number of illnesses, including inflammatory arthritis, skin and lung inflammation, and neuroinflammation, are promoted by their dysregulation during inflammation. A number of serine proteases were chosen due to their importance in inflammatory illnesses and the widespread hunt for inhibitors. Small chemical compounds or peptide-based inhibitors created from natural protein inhibitors are used in inhibitor discovery strategies. The fact that a considerable number of recent patents for serine protease inhibitors, which are used to treat inflammation, have linkages to disorders affecting the skin and the retina, is particularly significant to note [15].

Numerous physiological and pathologic processes include serine proteases, a class of proteases. Numerous immune system components contain serine proteases, which are hypothesised to be a factor in inflammation. They have been studied as potential therapeutic targets in a variety of inflammatory diseases. The serine protease inhibitor Bowman-Birk protease inhibitor (BBI), which is made from soybeans, is heat- and acid-resistant. It is a fantastic alternative for oral delivery with little negative effects because of these characteristics. BBI has also been demonstrated to offer therapeutic advantages for inflammatory and cancerous conditions [16].

Serine proteases and serine/cysteine protease inhibitors help to preserve the epithelial barriers in the skin and lungs (serpins). One theory holds that an insufficient barrier makes it easier for allergens to flow through. Both exogenous proteases from allergens or bacteria and endogenous proteases like trypsin can trigger lysis of the epithelial barrier as a result of an imbalance of proteases and antiproteases. Members of the serpin protein superfamily are found in all living things, including viruses, plants, and animals. Serpins share 30% of their sequence with the archetype serpin and feature a three-sheet structure (A-C) with an exposed reactive loop that serves as a pseudo-substrate for the target protease (-1-antitrypsin). The protease modifies its conformation after joining the reactive loop, which causes it to become inactive [17].

Serine protease inhibitors

Serpins are a class of proteins that suppress the activity of serine proteases, commonly referred to as serine protease inhibitors. These proteins inhibit protease activity via a conserved mechanism involving a significant conformational shift [18-20]. The serpin simulates a substrate for its target serine protease using a peptide sequence known as the reactive centre loop. The connected protease transfers from the top to the bottom of the serpin molecule when the reactive centre loop ruptures. The serpin's -sheet A is simultaneously inserted with a fragment of the damaged reactive centre loop, inactivating the protease irreversibly [21,22].

Serpins are similar to serine proteases in that we are learning more about how they operate in both normal and pathological brain activity. The serpins that have been shown to inhibit the serine proteases addressed earlier are listed in table 1. Recent research have focused heavily on the roles of these serpins in brain development, function, and illness [18,19]. The next part will concentrate on two serpins, protease nexin-1 and neuroserpin, which have been shown to have significant effects on synaptic plasticity and cognitive function [23].

During homeostasis, inflammation, tissue injury, and the onset of cancer, protease activity needs to be minimised. This requires protease inhibitors, such as those from the Kunitz, Kazal, serpin, and mucus families. Protease inhibitors usually have other inherent qualities that help to decrease the inflammatory response in addition to their anti-protease activity, such as the regulation of cytokine synthesis, signal transduction, and tissue remodelling. We sought to summarise recent research on the Kunitz family of serine proteinase inhibitors and its connection to health and illness in this review [24]. Serpins are a class of structurally conserved proteins that inhibit serine proteases and are essential for a variety of biological activities, including blood clotting, complement activation, and inflammation. Serine protease inhibitors are also known as serpins. Serpins have recently been discovered in parasitic helminths, and it is thought that by inhibiting the host immune response, they support parasite survival and immunological control.

Ascaris spp., *Brugia malayi, Ancylostoma caninum, Haemonchus contortus, Trichinella spiralis, Trichostrongylus vitrinus, Anisakis simplex, Trichuris suis, Schistosoma* spp., *Clonorchis sinensis, Paragonimus westermani*, and *Echinococcus* Spp. are few species containing serpins and smapins (small serine protease inhibitors) [25].

Serine protease and serine protease inhibitors in inflammation

Serine proteases and inhibitors have a variety of applications. They have an impact on immune system development, tissue repair, and inflammation. Protease inhibitors can eliminate some allergens in their most basic and visible forms since many allergens are cysteine or serine proteases. Serine protease levels in the environment have been associated with asthma [26]. The protease activity of class 1 allergens can break down complement factor C5 into its active components, which is thought to be a factor in the development of airway hyper-responsiveness [27].

It is believed that serine proteinase inhibitors are crucial for maintaining the epithelial barrier. Netherton's syndrome results in the loss of the epidermal barrier protein and reduced epithelial integrity [28]. The discovery of anomalies in the filaggrin protein, an epithelial protein required for barrier function, has brought attention to the importance of epithelial integrity in the development of eczema and asthma. It was found that filaggrin gene mutations were present in 9% of the populations under study and were associated with atopic dermatitis and asthma that co-occurred with atopic dermatitis [29].

One example of an endogenous protease that is significant in the acute allergic reaction and has the ability to trigger epithelial lysis via proteolysis is mast cell tryptase. Tryptase is associated with the allergic inflammatory response on multiple additional levels. The human airway smooth muscle contractile response is elevated when tryptase stimulates the protease-activated receptor 2 (PAR-2) on mast cells [30]. In addition to myocyte proliferation [31], cytokine generation by human airway smooth muscle cells [32], mast cell chemotaxis, and

bronchial hyperresponsiveness are only a few of the biological processes that tryptase stimulates. Tryptase inhibition has been shown to have an impact on the allergic reactions late stage [28]. Mast cell myositis, an unique aspect of allergic asthma, is significantly influenced by tryptase [33].

The immunological responses to dust mite serine and cysteine protease allergens provide some mechanistic clues into how abnormalities in protease homeostasis could particularly drive allergy reactions, such as a TH2 cytokine shift and IgE activation. The cysteine proteases Der p1 and Der f1 are found in house dust mites, and they regulate TH2 and IgE in various ways. Der p1 eliminates CD23 from B cells' surface, blocking an inhibitory feedback mechanism that typically controls the manufacture of IgE [34]. Increased soluble CD23 from cleaved CD23 induces increased interleukin (IL)-4-mediated IgE production [35]. The pulmonary serpin-1-antitrypsin has been demonstrated to prevent Der p1 from cleaving CD23 [34]. The fact that household dust mites produce more IgE in response to bystander allergens emphasises how crucial proteases are in controlling how atopy develops [36]. IgE production is encouraged by house dust mites. Additionally, according to research by Reiling KK., *et al*. house dust mite protease can cleave the IL-2 receptor (CD25) on T cells, blocking a significant TH1 cytokine and increasing the production of IL-4 and decreasing the production of IFN- by T lymphocytes [37]. By selectively cleaving the reactive centre loop through a thiol-dependent mechanism that catalytically inactivates serpin -1-antitrypsin, der p1 lowers the amount of defence against destructive proteases [38].

The cysteine protease Der f1 proteolytically activates the PAR receptors on eosinophils, causing activation, degranulation, and superoxide generation [39]. This is similar to an allergic reaction. Der p1 affects airway epithelial cells through the extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) pathways, increasing constriction and delaying relaxation responses [40]. Furthermore, it has been shown that exposure to dust mite allergens causes the production of cytokines and chemokines by keratinocytes and airway epithelial cells, which may aid in the development of allergies [41]. It has been proven that utilising Cystatin A, an antiprotease, reduces the IL-8 response in keratinocytes and builds an immunological defence against mite proteases [42]. According to studies on mice, intranasally delivered Der p1 that is proteolytically active causes significant inflammatory cell infiltration of the lungs and systemic IgE production [43].

Protease activated receptors

The amino termini of the four GPCRs, referred to as protease-activated receptors (PARs) (PAR 1-4), are cut by serine proteases such thrombin, plasmin, and trypsin. This cleavage reveals a novel amino terminal that functions as a tethered ligand to activate the receptor. Since it has been demonstrated that active PARs bind to several G proteins and the signalling cascades that are linked to them, it is possible that activating PARs may have pleiotropic effects. Short peptide sequences that imitate the tethered ligand can potentially activate PARs in addition to the aforementioned serine proteases. These short agonist peptides have been used to study the roles of PARs in the many cell types where they have been identified.

For the four members of the PAR family, there are known ligands, known agonist peptides, and known activating serine proteases in the CNS. The structure, activation, and signalling of PARs, as well as their general characteristics, have all been thoroughly reviewed [44,45]. A few recent reviews have also discussed the involvement of PARs in numerous areas of CNS development, neuroprotection, and neurodegeneration. This section will go through how we now perceive the function of PAR in synaptic plasticity, learning, and memory [46-48].

PAR1

Experiments in several cell types demonstrate that PAR1 can connect to the intracellular signalling pathways Gq/11, Gi/o, G12/13, and their associated ones [44,45]. Increased PAR1 expression, NGF secretion, neurite retraction, and astrocyte proliferation are a few effects of PAR1 activation on the CNS [46]. It has been observed that different neuronal and glial populations in the cortex, basal ganglia, striatum, and nucleus accumbens of mammalian brains express PAR1 [49,50]. Significant PAR1 expression is seen in the hippocampus and amyg-

dala, two regions of the brain that are crucial for memory and learning. According to evidence from numerous studies, astrocytes in the hippocampus of rodents and humans both express a significant amount of PAR1 [49-51].

Since both the mRNAs for prothrombin and plasminogen are expressed in the brain [49,52], the previously identified tPA/plasmin signalling system is a strong candidate to act as a PAR1 regulatory system [50,53]. The involvement of PAR1 in neuronal damage following ischemia or traumatic injury has been extensively studied, as may be expected given the prior considerations of thrombin, tPA, and plasmin. PAR1 ablation or pharmacological suppression reduced infarct volume in ischemia and hypoxia conditions. [50]. In a cortical stab wound model after traumatic brain injury, PAR1 activation produced astrogliosis related with the development of glial scarring [54].

Similar neuroprotective effects of PAR1 inhibition or deletion were seen in dopaminergic nerve terminals in the striatum of Parkinson's disease-modeling mice [55].

Research on PAR1 suggests that it supports normal brain function in a variety of ways. Dopaminergic neurons' activation of PAR1 in nicotine and morphine dependence models regulated nicotine-induced dopamine release, conditioned location preference, and hyperlocomotion [56,57]. In the hippocampus, it has been found that PAR1 activation affects synaptic responses. It has been shown that PAR1 activation increases NMDAR-mediated currents in whole-cell recordings from CA1 pyramidal cells [53,58].

Additionally, in hippocampus extracellular field recordings, this improved NMDAR response helped LTP develop [59]. These findings imply that synaptic plasticity and NMDAR-dependent memory formation may be modified by PAR1 activation. Research has shown that loss of PAR1 causes learning and memory deficits in passive avoidance, cued fear conditioning, and contextual fear conditioning tasks using PAR1 knockout mice [60]. In LTP tests, slices from PAR1 mutant animals showed noticeably reduced levels of theta-burst-produced LTP, highlighting the significance of PAR1 function [61].

Surprisingly, the maximal amount of potentiation obtainable with repeated theta-burst stimulations is lowered irreversibly by ablation of PAR1. In addition to showing that basal baseline synaptic transmission and short-term plasticity in PAR1 knockout animals are not aberrant, we also discovered that the expression levels of AMPAR and NMDAR subunits are not altered in PAR1 knockout mice. These lines of evidence, along with an earlier finding that NMDA-evoked current responses are normal in PAR1 mutant animals, point to PAR1 as a novel regulator of neuronal activity-dependent plasticity [58].

PAR2

Neurons and glia in the brain contain the PAR2 protein, which is highly expressed, particularly in the cortex, amygdala, and hippocampus [62,63]. PAR2 has been demonstrated to relate to Gq/11 and Gi/o when it is activated. Recent research have begun to look at how PAR2 activity affects synapse behaviour and function, despite the fact that little is known about how PAR2 functions in the brain. Mesotrypsin and Neuropsin, which were described in a previous section, are two potential candidates as endogenous PAR2 activators in the brain [45,64,65]. In a transient ischemia/reperfusion scenario, the infarct volumes of PAR2 deletion animals were considerably larger than those of PAR1 ischemia experiments, indicating that PAR2 activation has a neuroprotective effect [66].

PAR2 activation was found to be neuroprotective against seizures in an *in vivo* electrical amygdala-kindling seizure model [62]. Moreover, in an *in vitro* model of kainite-induced neurotoxicity [67]. In a rat strain with high baseline levels of anxiety, a systemic injection of a PAR2 activating peptide reduced performance in the test-retest version of the elevated plus maze and the Morris water maze [68]. Slice electrophysiological research has shown that the administration of a PAR2 activating peptide can change synaptic transmission and neuronal excitability, which may assist to explain these problems [69]. These findings show that the benefits and drawbacks of activating PAR2 must be carefully balanced [23].

PAR3 and PAR4

Despite the fact that PAR3 and PAR4 have been found in the brain in numerous studies, little is known about how they alter synapse behaviour and function [47,48,70]. Thrombin can cleave PAR3 at low doses and PAR4 at high ones, according to studies in a variety of cell types. Surprisingly, responses are not triggered when PAR3 is created alone using peptides that match the anticipated tethered ligand sequence, suggesting that PAR3 does not appear to signal on its own. However, at low thrombin concentrations, PAR3 and PAR4 form heterodimers, and it appears that PAR3 acts as a cofactor for PAR4 activation and signalling through Gq/11 coupling [44,45,71]. PAR4 expression was dramatically increased in both neurons and glia in ischemia models, much like it was in the studies on PAR1 [72,73]. In addition, PAR4 deletion mice have recently shown reduced infarct sizes in a transient ischemia/reperfusion situation [23,74].

Drugs and description

Alteplase: In unexpected occurrence of an ischemic stroke, pulmonary embolism, or myocardial infarction, a recombinant human tissue plasminogen activator is utilised to treat them. Low molecular weight human urokinase, also referred to as urokinase, is used to clean IV lines and treat pulmonary embolism and myocardial infarction [75].

Reteplase: Used to treat acute ischemic stroke, myocardial infarction, and pulmonary emboli. It is a pure form of human tissue plasminogen activator [76].

Anistreplase: Recombinant human tissue plasminogen activator used to treat myocardial infarction and pulmonary emboli when they happen abruptly.

Tenecteplase: A recombinant human tissue plasminogen activator that has been modified and is used to treat myocardial infarction and pulmonary emboli when they occur abruptly [77].

The protein used to treat haemophilia A and B is recombinant human coagulation factor VII.

Streptokinase: A pure fibrinolytic bacterial protein that dissolves thrombus in the treatment of pulmonary embolism, myocardial infarction, and venous thromboembolism [78].

Desmoteplase: Being studied for use in treating cerebral ischemia and strokes [79].

Ancrod: An anticoagulant created from the Malayan pit viper's venom, which has been purified. Inactive plasma fibrinogen is what makes it function. Not currently being utilised or promoted in any country [80].

Fibrinolysin: Aid in the healing of minor burns, superficial wounds, ulcers, surgical wounds, and superficial hematomas.

Anti-HIV Protease inhibitors approved by US FDA

Atazanavir: An version of the aza-dipeptide shows potent anti-HIV properties. In cell culture, the EC50 for atazanavir ranges from 2.6 to 5.3 nM. It is unique because it has a big phenylpyridyl P1 group that is asymmetric with respect to its benzyl P1′ group. Given that atazanavir has a strong oral absorption, it is dosed once daily as a combination of 300 mg atazanavir and 100 mg ritonavir [81]. This drug has less negative effects compared to other protease inhibitors [82,83]. Atazanavir also had no effect on insulin sensitivity or serum lipid levels [83,84]. However, some patients using atazanavir therapy had a noticeably higher prevalence of proximal tubulopathy [85].

Darunavir: The newest HIV protease inhibitor on the market was approved in 2006. Darunavir inhibits the growth of drug resistance by establishing hydrogen bonds with the HIV protease's structural core [86]. Darunavir and Amprenavir have very similar chemical struc-

tures, with the P2 group bis-tetrahydrofuran replacing the tetrahydrofuran group in Amprenavir. Darunavir can now form more hydrogen bonds with the HIV protease's Asp 29 residues because to this modification [87]. Darunavirhas a high potency inhibitory effect against HIV-1 and HIV-2, and its EC50 is as low as 1-2 nM [87,88]. Ritonavir and darunavir may be taken together [89]. Minor toxicities such rash, diarrhoea, nasopharyngitis, and nausea are linked to the usage of darunavir [90].

Fosamprenavir: It is the phosphate ester prodrug of amprenavir. It prolongs the time that amprenavir is available by being converted by the body to the active ingredient amprenavir. Because Fosamprenavir is a slow-release version of Amprenavir, fewer pills are required than with standard Amprenavir [91]. It is recommended to take 100 mg of ritonavir and 1,400 mg of fosamprenavir twice day. Clinical studies revealed that Fosamprenavir has a profile that is safer than Amprenavir [92].

Indinavir: It effectively blocks both HIV-1 and HIV-2. The disadvantage is the quick decline in circulating indinavir concentration. Low plasma levels of indinavir frequently result in treatment failures [93]. Its low solubility could result in kidney stones. Due to indinavir's rapid onset of action, 800 mg must be taken every 8 hours. Due to these issues, second-generation protease inhibitors have replaced indinavir.

Lopinavir: The core of lopinavir is a hydroxy ethylene dipeptide isostere and shares structural similarities with ritonavir. In lopinavir, the 5-thiazolyl P2 group of ritonavir is swapped out for a phenoxyacetyl group, and the 2-isopropylthiazolyl P2′ group is swapped out for a six-member cyclic urea. The inhibitory efficiency of lopinavir against drug-resistant HIV-1 protease subtypes is significantly enhanced by swapping the P2 and P2′ groups [94].

Lopinavir inhibits the activity of the HIV protease with an EC50 of 17 nM. Adult patients receive ritonavir 100 mg and lopinavir 400 mg orally twice daily. Insulin resistance and systemic hypersensitivity are side effects of lopinavir [84].

Nelfinavir: Saquinavir and nelfinavir share a DIQ group at their one terminal ends of the molecules. At the opposite terminal, it has a 2-methyl-3-hydroxybenzamide group. 1,250 mg of nelfinavir should be taken orally twice day. The most frequent adverse effects of nelfinavir are diarrhoea and nausea [95].

Ritonavir: The HIV protease inhibitor ritonavir was initially developed to boost the concentrations of other HIV protease inhibitors by blocking cytochrome P450 3A4 [96]. Ritonavir disrupts the cytochrome P450 3A4 isoenzyme's ability to operate, which affects how other protease inhibitors are metabolised. Increased HIV protease inhibitors usually lower the toxicity and side-effect profile of the HAART regimen. A less frequent dosage is preferred for patients on ritonavir-increased protease inhibitor regimens. Common side effects include nausea, vomiting, lack of appetite, diarrhoea, and numbness in the hands and feet.

Saquinavir: In MT4 cells, saquinavir's average 50% effective concentration (EC50) against HIV-1 is 37.7 nM. In 2003, the US Food and Drug Administration [97]. It is given at a dosage of 1000 mg along with ritonavir (100 mg). Saquinavir side effects are quite uncommon [98]. Saquinavir is a protease inhibitor, although it is not recommended because of its poor absorption [99].

Tipranavir: It is the only HIV protease inhibitor that isn't peptidomimetic. Due to the evolution of resistance to traditional protease inhibitors, it inhibits the HIV-1 protease. Although the structure of tipranavir differs from prior inhibitors in terms of its contact residues, it shares several characteristics with other HIV protease inhibitors. Tipranavir has an EC50 of 30 - 70 nM and prevents HIV-1 isolates from proliferating. The dosage is roughly 500 mg of the drug and 200 mg of ritonavir twice daily. Intracranial haemorrhage and decompensated hepatitis are two instances of adverse effects that are more severe when compared to the side effects of other protease inhibitors [100].

Conclusion

The review concluded role of Serpins in inflammation and as an anti-viral agents. Further emphasis on individual agent as serine protease inhibitor may prove to be important in treatment of viral infections.

Conflict of Interest

No conflict of interest exists.

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