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Serratiopeptidase: The Healing Enzyme

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Abstract: *Inflammation is still a major factor in the majority of diseases and physiological imbalances. Acute inflammation is a protective mechanism used by the immune system to remove the source of inflammation, and failure to resolve it leads to chronic inflammation. In other words, inflammation is a cleansing process that helps to maintain homeostasis by removing invading materials and noxious alterations. Serratiopeptidase, a proteolytic enzyme from the trypsin family, has a wide range of applications in the fight against inflammation. Nonsteroidal anti-inflammatory medicines (NSAIDs) are the most commonly used treatments to treat acute inflammation, either alone or in combination with other medications. These medications have a number of drawbacks, including side effects, adverse drug reactions, and so on. Enzyme-based anti-inflammatory medications have become more popular than chemical-based anti-inflammatory drugs as a result of these limitations and consequences.*

Keywords: Serratiopeptidase, Inflammation, Proteolytic enzyme, Enzyme therapeutics.

I. INTRODUCTION

Proteases are one of the three most important types of industrial enzymes, accounting for over 60% of all enzyme sales globally. Serrapeptase, also called serratiopeptidase, is a proteolytic enzyme that breaks down proteins into smaller components known as amino acids. It's made by bacteria in the digestive tracts of silkworms (Serratia marcescens E15), and it helps the emerging moth digest and disintegrate its cocoon. Intravenous trypsin was developed in the 1950s in the United States to alleviate inflammation caused by rheumatoid arthritis, ulcerative colitis, and atypical viral pneumonia, as well as post-surgical swelling and bruises produced by sports injuries [1, 2]. Serratiopeptidase was first used by the Japanese, according to accounts. According to published reports, serratiopeptidase was first used in Japan to treat inflammation in 1957. The growing efficacy of enzyme therapies has led to the oral administration of experimentally encapsulated enzymes such as trypsin, chymotrypsin, and bromelain [3]. Japanese and European researchers examined numerous enzymes for anti-inflammatory activity in the 1980s and early 1990s, and found that serratiopeptidase was the most effective of them in lowering the inflammatory response [4]. Serratiopeptidase is now widely utilised as an anti-inflammatory and pain treatment of choice in Japan and Europe [5]. Serratiopeptidase has therefore been used in Japan and Europe for about 40 years to treat pain and inflammation caused by arthritis, trauma, surgery, sinusitis, bronchitis, carpal tunnel syndrome, and painful breast swelling. Serratiopeptidase has been called the “miracle enzyme” or “super enzyme” due to its wide range of actions in the human body [6].

II. INFLAMMATION

Inflammation, both acute and chronic, causes the synthesis of physiologically active biomolecules such as interleukins, cytokines, and other short peptides such as kallikreins, which are linked to the immune system's fine tuning [7,8]. These pharmacologically active compounds also contribute to the creation of an optimal environment for tumour growth. Inflammation and associated physiological alterations in the brain and other neural tissues have been observed in the most demanding scenario [8].

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2.1 MECHANISM OF INFLAMMATION

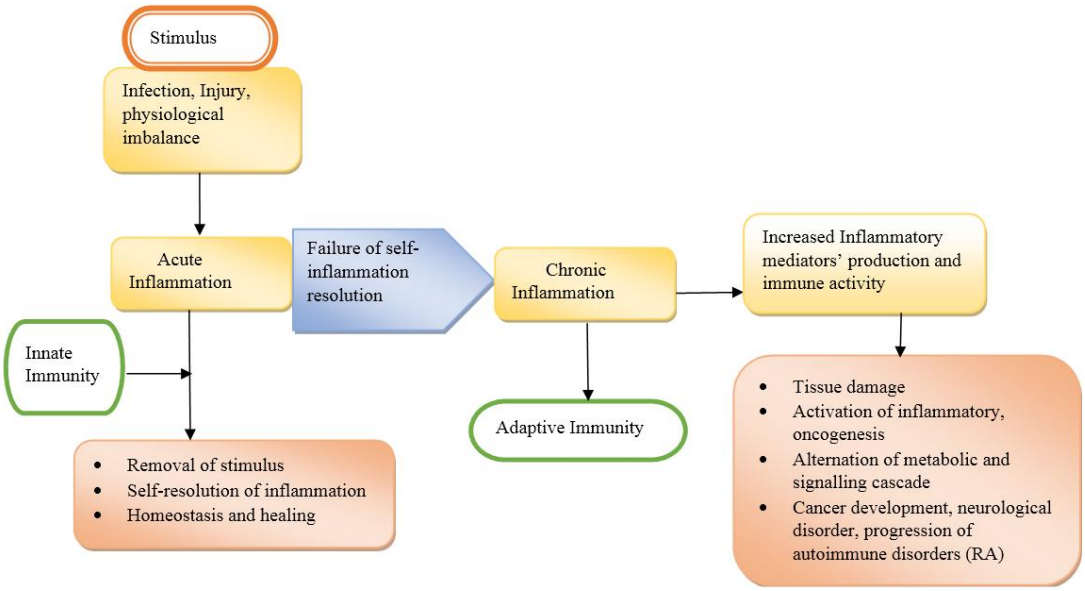

Figure 1: A detailed overview of various causes resulting in inflammation. Inflammatory mediators are produced by both external and endogenous causes, and these mediators further disrupt tissues of normal homeostasis by influencing blood and lymph flow.

2.2 RESOLUTION OF INFLAMMATION

Every physiological system contains both supportive and anti-inflammatory chemicals, and tissue homeostasis is achieved when the two are in balance [16]. Polyunsaturated fatty acids (PUFAs)-derived lipid mediators are a major component in the resolution of inflammation. Serratiopeptidase and other comparable enzymes (enzymes) indirectly aid in the clearance of inflammation in this case.

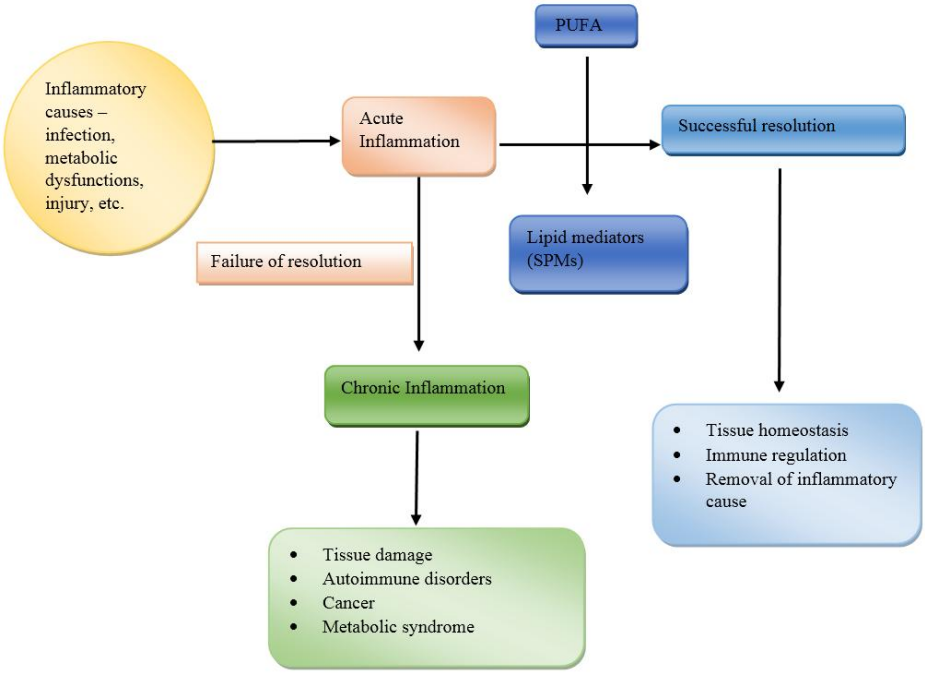

Figure 2: Scheme of resolution of inflammation: causes, acute and chronic inflammation

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III. ENZYMES AS THERAPEUTICS

Enzymes play an important part in the biological world by acting as a biocatalyst [9]. Activity enzymes have been utilised in industries, agriculture, research, and development for decades because of their broad substrate affinity and powerful catalyst [10,11]. Since the last few decades, various enzymes have met our therapeutic needs in cancer treatment, the treatment of blood vascular problems, the treatment of enzyme deficiency disorders, and as an anti-inflammatory drug substitute [12,13]. It's interesting to note that of the different enzyme groups, one termed serine protease has shown remarkable promise in modern medicine. Serine proteases are found in a wide range of organisms, including animals, plants, and microorganisms. Tissue plasminogen activators, either from animal or microbial sources, are the most efficient strategy to heal vascular diseases [14,15].

IV. SERRATIOPEPTIDASE

Serratiopeptidase is an endopeptidase with a molecular weight of around 60 kilodaltons. It is a more powerful caseinolytic agent than any other alkaline or neutral protease. Silkworms provide this potent proteolytic enzyme. Serratia peptidase, or Serrapeptase, is another name for serrapeptidase. The enzyme comes from the bacteria Serratia E 15 and HY-6, which grow in the silkworm's gut wall. It is important for silkworm morphological change [17]. It aids in cocoon proteolysis and moth emergence. Non-living tissues, blood clots, cysts, arterial plaque, and inflammation in all forms are all susceptible to this enzyme.

4.1 PRODUCTION

Serratiopeptidase is produced commercially by fermenting Serratia marcescens culture. This enzyme is secreted in the highly selective medium by the controlled fermentation of Serratia sp. The recovery procedure includes a variety of filtrations, concentrations, and processes to make the enzyme suitable for pharmaceutical uses, before being dried to a fine free-flowing powder [18,19]. The potential catabolite suppression on serratiopeptidase synthesis was demonstrated using a glucose fed-batch culture [20].

4.2 MECHANISM OF ACTION OF SERRATIOPEPTIDASE

Serratiopeptidase digests or breaks down toxins and inflammation-related protein debris. This enzyme has extraordinary therapeutic properties, including the ability to breakdown non-living tissue. It has no effect on healthy tissue and cells since it does not use living tissue as a substrate. Serratiopeptidase is implicated in inflammatory mediator degradation, swelling suppression, fibrinolysis activation, immunological complex reduction, and proteolytic alteration of cell-surface adhesion molecules that direct inflammatory cells to their targets [16]. Proteolytic enzymes have analgesic properties because they cleave bradykinin, a messenger molecule implicated in pain signalling. According to another view, peptidases like trypsin may operate as accelerators of the inflammatory process, decreasing its duration [21] rather than as anti-inflammatory agents. It works in three ways to reduce inflammation [22,23]:

- It breaks down fibrin, an insoluble protein by-product of blood coagulation.
- It thins the fluids produced by inflammation and injury, allowing them to drain more quickly, speeding up the tissue repair process.
- It relieves pain by preventing the release of pain-inducing amines known as bradykinin.

4.3 PHARMACOKINETICS

Serratiopeptidase is an acid labile enzyme, which means it is destroyed by stomach acid if taken unprotected. Enterically coated pills, on the other hand, allow the enzyme to pass through the stomach intact and be absorbed in the intestine. Serrapeptase is discovered in trace levels in urine, indicating that it is carried directly from the colon to the bloodstream [24,25]. It's ideal pH and temperature are 8.5-9.5 and 40°C (stable at 40°C but rapidly loses action at 60°C in 10 minutes).

4.4 PROPRIETARY NAMES

Aniflazime, Aniflazime, Bidanzen, Brasan, Cipzen, Dailat, Danzen, Danzen (FM), Danzyme, Dasen, Dazen, Denzo, Enziflur, Eze, Flanzen (FM), Infladase, Kineto, Korzen, Lergan, Medi zyme (FM), Podase, Rodase (FM), Septirose (FM),

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Seraim, Seramed, Serato-M, Serradase, Serrano, Serrao, Serrapep, Serrason, Serrazyme, Serrin, Sinsia, Sumidin, Unizen, Unizen (FM), Verolin.

4.5 ROLE OF SERRATIOPEPTIDASE

Cystic Breast Disease -

Serrapeptase has also been used in the successful treatment of fibrocystic breast disease. 85.7 percent of the patients receiving serrapeptase reported moderate to marked improvement. No adverse reactions to serrapeptase were reported. Thus, serrapeptase was concluded to be a safe and effective method for the treatment of breast engorgement [26,35].

Sinusitis/Bronchitis

Serratiopeptidase (30 mg/day orally for four weeks) was tested on the elasticity and viscosity of nasal mucus in adult patients with chronic sinusitis by Japanese researchers. Serratiopeptidase improved bronchopulmonary secretion removal by decreasing mucus viscosity [36]. In individuals with laryngitis, catarrhal rhinopharyngitis, and sinusitis, serratiopeptidase caused a considerable and rapid relief in symptoms after 3-4 days. 97.3 percent of patients treated with serrapeptase had excellent or good therapeutic efficacy, compared to only 21.9 percent of patients treated with a placebo [37]. Serratiopeptase and other proteolytic enzymes [38] have also been shown to aid in the dissolution of sputum in patients with bronchial asthma [27,39].

Microbial Infections

Another essential property of serrapeptase is that it increases antibiotic delivery, allowing higher concentrations of antimicrobial drugs to reach the infection site. Bacteria often go through a process known as biofilm development, which results in antibiotic resistance. To prevent this bacterial immunity, many methods for suppressing biofilm-embedded microorganisms were tested. Proteolytic enzymes, according to one study conducted by Italian experts, could considerably improve the activity of antibiotics against biofilms. Serratiopeptidase significantly increases the efficacy of the antibiotic ofloxacin and inhibits biofilm formation in antimicrobial susceptibility tests [40,28]. Serratiopeptidase enhances antibiotic dispersion, which leads to strong antibacterial effects [41].

Carpal Tunnel Syndrome -

Carpal tunnel syndrome is an inflammatory disorder (musculoligamentous strain) of the hand and wrist that causes severe, long-term discomfort, inflammation, and dysfunction. Serratiopeptidase reduced inflammation and pain in carpal tunnel syndrome patients in a limited experiment. Sixty-five percent of the patients had improved clinically. There were no major side effects [29,41].

Dentistry

Serratiopeptidase helps in better control over dental infections and inflammation. This has been found to be effective in combination with tetracycline delivered as periodontal gel[42] .

Cardiovascular Implications

Hans A. Nieper, an internist from Hannover, Germany, was the first to investigate the effect of serrapeptase on plaque build-up in the arteries. Plaque is formed when fatty substances, cholesterol, cellular waste materials, calcium, and fibrin (a blood clotting ingredient) are deposited on the inner lining of arteries. Excess plaque causes a partial or complete blockage of blood flow through an artery, leading to arteriosclerosis, or artery hardening, and a stroke or heart attack as a result. Still, further research is needed in this area, as Nieper's research suggested that serrapeptase's protein-dissolving action will break down atherosclerotic plaques over time [42].

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4.6 CLINICAL SIGNIFICANCE OF SERRATIOPEPTIDASE

S. No	Clinical use	Symptoms	Remarks	Symptoms treated	Effects	Reference
1.	Cystic breast disease	Breast engorgement	More than 88% persons reported marked improvement	Reduction in breast pain, swelling and induration	No adverse reactions reported	26
2.	Sinusitis/bronchitis	Hypersecretion of thick mucus	More than 97% persons reported marked improvement	Reduction in the viscosity of the mucus improving the elimination of bronchopulmonary secretion	Effective in laryngitis, catarrhal rhinopharyngitis and sinusitis	27
3.	Microbial infections	Biofilm-embedded bacteria	More than 87% persons reported marked improvement	Significant improvement in rhinorrhoea, nasal stuffiness and paranasal sinus shadows	Effective in perennial rhinitis, chronic rhinitis with sinusitis or chronic relapsing bronchitis	28
4.	Carpel Tunnel syndrome	Musculoligamentous strain of the hand and wrist	Sixty five percent of the patients showed clinical improvement	Improvement in pain and inflammation	No adverse reactions reported	29
5.	Arteriosclerosis	Partial or complete blockage of the blood flow through an artery	Significantly effective	Improvement in blood flow through an artery	Due to protein dissolving action of serrapeptase	30
6.	Periodontal disorders	Periodontitis	Better relief than antibiotic alone	Serratiopeptidase improves microcirculation and reduce pain	Effective in scaling in root planning	31
7.	Osteoarticular infections	Pain in joints, difficult movement	Better relief than antibiotic alone	Reduction in pain and swelling	Resolution due to anti-inflammatory activity	32

4.7 DOSAGE

- Adults: The suggested dosage for the treatment of inflammation and pain is 1-3 10mg tablets three times per day on an empty stomach, whereas arterial blockage requires three tablets twice daily for the first month and subsequently three per day.
- Children and Animals: It is safe for children and animals to use. 1-3 pills per day is the recommended dosage. These tablets can be chewed because they are tasteless. In fact, chewing 1-2 pills for youngsters with mucus difficulties such colds can cure a sore throat in around 30 minutes.

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- Treatment time: Although most symptoms go away in 1-2 weeks, it is recommended that you stay on the medication for 3-4 months before getting a second opinion. Serrapeptase can be administered at a low dose, 1-2 per day for health maintenance.

4.8 INTERACTIONS

Serratiopeptidase is inhibited by Ni++, Mg++, Cd++, and Cu++, while serratiopeptidase is inactivated by EDTA. The addition of Zn++, Mn++, and Co++, on the other hand, restores activity. In the presence of di-isopropyl fluorophosphates or p-chloromercuribenzoates, the enzyme is not inhibited. When a medication is taken with an anticoagulant, the anticoagulant action may be amplified [2, 20].

4.9 CONTRAINDICATIONS [24]

- Patients with blood coagulation disorder
- Patient with severe hepatic/ renal disorders
- Hypersensitivity

4.1. ADVERSE DRUG REACTIONS

- Hypersensitivity: infrequently hypersensitivity reaction such as rash and redness may occur.
- Digestive: diarrhoea, anorexia, gastric discomfort, nausea or vomiting.
- Haemolysis: rarely bleeding tendency such as epistasis and blood sputum may occur. A case of pneumonitis, subepidermal bullous dermatosis and acute eosinophilic pneumonia due to Serrapeptase was also reported.

V. THERAPEUTIC APPLICATION OF SERRATIOPEPTIDASE

Serratiopeptidase has a significant history of medicinal usage, particularly as an anti-inflammatory enzyme-based medication. Several studies have suggested that the enzyme, alone or in conjunction with other medications, can help with sinusitis and bronchitis, atherosclerosis, carpal tunnel syndrome, rheumatoid arthritis, and other autoimmune illnesses [5]. Serratiopeptidase alters cell-surface adhesion molecules as well. Inflammation and the influx of immune cells into injured tissues are caused by these cell surface adhesion molecules, both directly and indirectly [29]. Proteolytic enzymes like serratiopeptidase, according to an Italian study, can significantly improve the effectiveness of antibiotics against biofilm and can even prevent biofilm formation. Several antibiotics activity, including ampicillin, ciclacillin, cephalexin, minocycline, and cefotiam, have been shown to be enhanced by serratiopeptidase [33].

Serratiopeptidase has been examined in clinical situations for allergy conditions, and it has been proven to lower the thickness and viscosity of mucus, as well as improve its removal by bronchopulmonary secretions [16]. Serratiopeptidase has been used as an expectorant in the past, but because it is a proteolytic enzyme, it can replace histamine and antihistamines as an expectorant for mutants. Serratiopeptidase was also utilised in the successful treatment of fibrocystic breast disease to assist reduce swelling and pain, with 25% of patients reporting moderate to remarkable improvement with no adverse effects [33]. The use of serratiopeptidase to break down atherosclerotic plaque is another fascinating area. Khateeb et al. have demonstrated the role of serratiopeptidase in the management of ortho-dental inflammatory syndrome [33] . The enzyme may be efficient in clearing accumulation of fatty substances, cholesterol, cellular waste materials, calcium, and fibrin on the inside of the arteries as it digests non-living tissue and keeping live tissue alone. Serratiopeptidase's fibrinolytic (clot-removal) activity may also aid with thicker blood, an elevated risk of stroke, and phlebitis/thrombophlebitis.

VI. CONCLUSION

Finding optimal medicines for autoimmune diseases and disorders is the most difficult. In chronic situations or both, symptomatic alleviation of inflammation has been provided for decades through the use of synthetic drugs such as NSAIDs and steroids. As previously said, inflammation is a complex immunological response triggered by a variety of stimuli that may not be healed by ordinary medications. As a result, the majority of anti-inflammatory medicines are linked to serious side effects and drug responses. These medications are associated with symptom alleviation rather than cure.

The utilisation of biological molecules such as proteins (enzymes) as treatments has become one of the most important areas of modern medicine in the last decade. Several enzymes, such as t-PA and staphylokinase as clot busters and L-

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asparaginase as an anticancer medication, have been permitted for clinical usage for a variety of life-threatening diseases and conditions. On the other hand, a serine protease derived from microbial sources has shown great potential in the treatment of numerous types of inflammation and inflammatory illnesses. Serratiopeptidase is a serine protease with a molecular weight of 60 kDa that has been extensively studied for its anti-inflammatory properties. Many disorders have been related to the use of enzymes in the clinic, including arthritis, sinusitis, inflammatory bowel disease (IBD), and bronchitis. For a long time, this proteolytic enzyme has been reported to be useful in a variety of disorders, specifically during surgical events, although there is a lack of study evidence and literature. The current study highlights the enzyme's potential as a broad-spectrum anti-inflammatory medication with few side effects and consequences.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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