



## Review Article

# Role of orally administered enzymes in dental practice: A review

Abhishek Sharma<sup>1,\*</sup>, Vishal Thakur<sup>2</sup>, Asusa Cicilia Loli<sup>3</sup>, Sonali<sup>3</sup>, Dania Fatima<sup>4</sup>

<sup>1</sup>Dept. of Prosthodontics Crown Bridge and Implantology, Himachal Institute of Dental Sciences, Paonta Sahib, Himachal Pradesh, India

<sup>2</sup>Dental Surgeon at Ekdant Dental Clinic, Himachal Pradesh, India

<sup>3</sup>Dept. of Prosthodontics Crown Bridge and Implantology, Bhojia Dental College and Hospital, Bhud, Baddi, Himachal Pradesh, India

<sup>4</sup>Dept. of Prosthodontics Crown Bridge and Implantology, Kalka Dental College and Hospital, Meerut, Uttar Pradesh, India



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## ABSTRACT

For the better anti-inflammatory or analgesics effects of drugs; enzymes have been widely used in the medical field either it may be arthritis or fracture of the bone or it may be oedema. Along with anti-inflammatory action these drugs have anti-oedema properties, healing properties and fibrinolytic properties as like trypsin-chymotrypsin. In this article we are going to discuss about the importance or applications of these enzymes either alone or in combination with other NSAIDS in the field of dental practice.

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## 1. Introduction

Dentistry is the branch of medical science dealing with the investigation, treatment, and prophylaxis of the ailments of teeth and oral cavity. Dental problems have increased in frequency as one of the effects of the modern lifestyle and so dental visits have become common nowadays. Although, dentistry includes operative or surgical procedures mostly. However, for a majority of dental ailments, dentists still rely on medications, either alone or as part of preoperative/postoperative management. These include anesthesia, analgesics, antibiotics, dietary supplements, steroids or anti-anxiety drugs, etc. And now these days for the better anti-inflammatory or analgesics effects of drugs; enzymes have been widely used in dentistry also and in this discussion, we are going to give a review on few of the enzymes these includes serratiopeptidases, chymotrypsin, etc.

### 1.1. Role of individual enzyme as a drug

#### 1.1.1. Serratiopeptidases

Serratiopeptidase is a proteolytic enzyme that is produced by non-pathogenic enterobacterium *Serratia* sp. And this microbe was first isolated from silkworm's intestine to allow the dissolution of its own cocoon.<sup>1</sup> It has been used for years for reducing inflammation and pain due to surgery, trauma, and other inflammatory conditions. Serratiopeptidase acts as an anti-inflammatory agent to pacify mild to moderate pain and inflammation. Common conditions associated with pain and inflammation include arthritis, trauma, surgical wounds and fibromyalgia and in many other diseases in general practice. Additionally, SP helps to reduce fluid retention in affected areas, which contributes to proper drainage and faster recovery. LOXs are key enzymes which catalyze the biosynthesis of SPMs and non-specific inhibition of NSAIDs affects native inflammation resolution. New generation NSAIDs are effective as COX-II specific but their clinical applications remain questionable

\* Corresponding author.

E-mail address: [abhi16febabhi1992@gmail.com](mailto:abhi16febabhi1992@gmail.com) (A. Sharma).

and so researchers find more concern on enzyme-based agents and are seeking more specific drugs like anti-inflammatory agents like serratiopeptidases and similar enzymes which indirectly assist resolution of inflammation without affecting the LOX-catalyzed SPMs production. The action of SP reported in the research works is their direct effect on the movement of immune cells. Enzyme regulates recruitment of PMNs and other lymphocytes at the site of inflammation and also SP reduces capillary permeability induced by histamine, bradykinin, and serotonin; and breaks down abnormal exudates and proteins thus, facilitates the absorption of decomposed products through blood and lymphatics.<sup>2,3</sup> SP has also been shown to increase the clinical activity of many antibiotics including the ampicillin, cephalexin, minocycline and it can also be useful in dental infections since the activity of antibiotics will get enhanced along with anti-inflammatory action of SP. In dentistry it has also anti-inflammatory, anti-endemic and analgesic effects, it is widely used after removal of wisdom tooth, postoperatively after maxillofacial surgeries and in TMJ arthritis. Also, SP were found to improve trismus in a better way than corticosteroids.<sup>4</sup> Although, SP has antiedemic, analgesic, fibrinolytic and caesinolytic properties its application in post-op oral surgeries or maxillofacial trauma has satisfactory results but due to its fibrinolytic activity the use SP in dental abscess is controversial or we can say it is generally not recommended to prescribe the SP in dento-alveolar abscess as it can further lead to the spread of the infection into deeper spaces and may lead to more complication. The reason for these complications is that an abscess is surrounded by haemorrhage, fibrin and inflammatory cells and around the necrosed part fibrin gets deposited in the form of membrane and thus, it also separates the dead part from the living. The wall of the abscess is formed by the effused and organized fibrin and sometimes the fibrin wall is not strong enough; in those cases the pus finds its way into surrounding cellular texture and results into a diffuse abscess.<sup>5</sup> SP can be prescribed either as a single salt with dosage of 5, 10, 15 mg BD or TDS or as fixed dose combination with other NSAIDs like PCM & aceclofenac (325 + 100 +15 mg), diclofenac (50 + 10 mg), etc. The usual adult dose of SP ranges from 15 to 60 mg per day. The concomitant use of SP with aspirin should be avoided as anticoagulants interacts with SP and might reduce its effects and the general consideration that should be taken to take this medicine is to take with food to avoid the GI upset. Like other drugs, SP too have few adverse effects that may include anorexia, GI upset, skin rashes, epistaxis.

### 1.1.2. Trypsin- chymotrypsin

Both TC are a family of serine proteases, and these two types of proteases originally synthesized in the pancreas in the inactive form of zymogen precursors (trypsinogen and

chymotrypsinogen) for the purpose of stopping unnecessary cellular activity and controlling when and where enzyme activity occurs. These active forms of enzymes also aid in the digestion of food. TC give the body the extra boost it might need for smoother digestion of proteins as well as for reducing inflammation and fighting infection. TC provides better resolution of inflammatory symptoms and promotes speedier recovery of acute tissue injury than several of the other existing enzyme preparations.<sup>6</sup> The role of TC in healing at tissue injury site is given below in a figure.

### 1.2. Thus, the clinical activities of TC include

- Fibrinolytic activity - TC breaks down the fibrin barrier thus improving and restoring circulation, resolving edema, hematoma and pain, promoting phagocytosis to remove the debris an accelerate recovery.

- Reduction in Plasmin Inhibitor levels within 3-5 days to post-surgery.

- Release of Intestinal Plasminogen activators - Studies have shown that TC brings about release of Plasminogen activators from the intestinal mucosa and those are absorbed into the systemic circulation along with TC thus, contribute further to bringing about fibrinolysis; thereby increasing tissue circulation and decreasing edema.

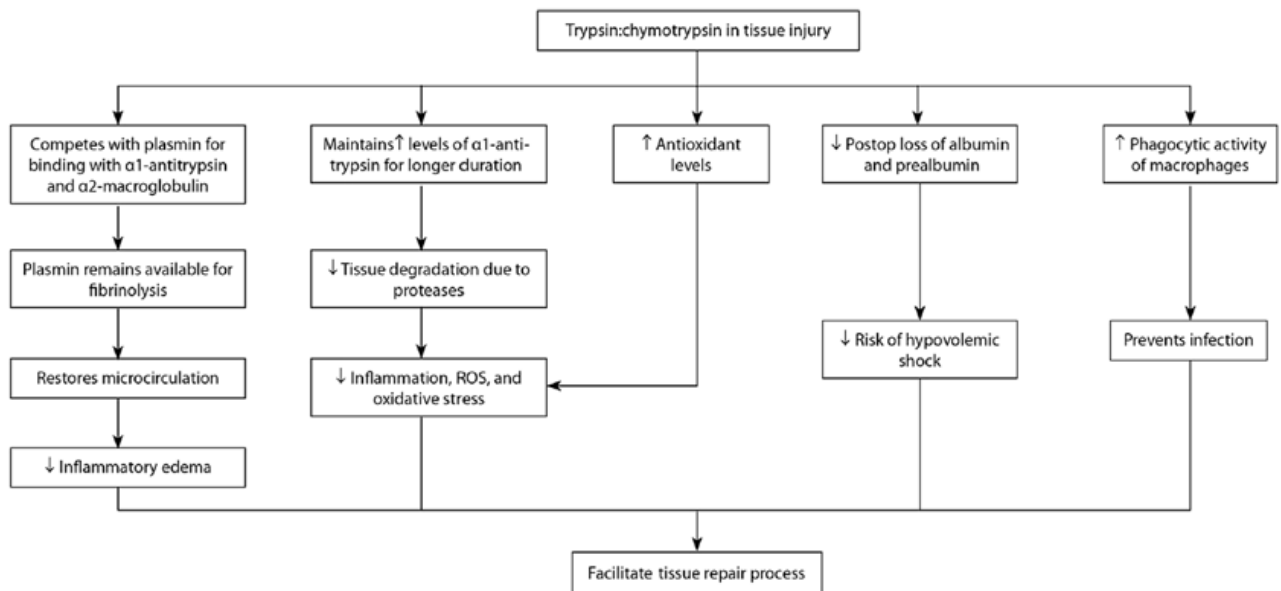
Due to these antioxidant, anti-inflammatory, antifibrinolytic, antiedema properties these can be indicated in dentistry in number of ways-

- Post-operative wounds,
- Oedema and hematoma caused after LA injection,
- Prevention of inflammation of the surgical stitches,
- After tooth extraction especially in case of impacted teeth or wisdom tooth,
- Peri-apical abscess (where SP might have negative effects) (5),
- Maxillofacial surgery,
- Post-traumatic oedema,
- Soft tissue injury & maxillofacial fractures and dislocation after trauma,
- TMJ arthritis
- Oral ulcers – due to its antioxidant & healing properties by removing the dead tissues.

Combination of TC enzyme may consist of purified proteolytic enzyme concentrate providing 50,000/1,00,000/2,00,000 armour units of Trypsin and Chymotrypsin in the ratio 6:1. And it is possibly safe up to the dosage of 800,000 units per day of this combination up to 7-10 days.

Adverse effects include –

- Gastric upset
- Corneal edema
- Allergy or anaphylaxis with symptoms include itching, shortness of breath. swelling of the lips or throat, shock, loss of consciousness, and death (rare).<sup>8</sup>



**Fig. 1:** Mechanisms of beneficial effects of trypsin: chymotrypsin in tissue repair.<sup>7</sup>

The contraindication of this combination includes – hypersensitivity, congenital cataracts, peptic ulcers, patients below 20 years as lens vitreous adhesion may not be responsive to chymotrypsin lysis, severe hepatic & renal impairment. The drug is similar to SP that to avoid concomitant use with anticoagulants like heparin, clopidogrel, aspirin (6). Although, TC are mostly tolerable by the population with less adverse effects, but still dentist must go through a thorough medical and drug history of the patient before prescribing them. TC can be prescribed as in trypsin-chymotrypsin alone or can be given in a fixed dose with rutins, BR, NSAIDs.

### 1.3. Bromelain

BR Bromelain is a proteolytic enzyme present in the plant of pineapple (*Ananas comosus*). It has been used for a long time in traditional medicine in South-east Asia, Kenya, India, and China because of its anti-inflammatory, anti-fibrinolytic, anti-thrombotic, and anti-edema properties.<sup>9</sup> BR is used as an adjunct in the treatment of soft tissue inflammation and oedema associated with trauma and surgery, and also as an anti-inflammatory and analgesic agent in treating the symptoms of arthritis, thus, it can be used in TMJ arthritis, after 3<sup>rd</sup> molar extraction with combination with rutins, trypsin or with NSAIDs. The analgesic and anti-inflammatory effects are reportedly due to inhibition of the arachidonic acid pathway of inflammation by selectively decreasing thromboxane generation, changing the ratio of thromboxane/prostacyclin (in favor of prostacyclin), and inhibiting PGE2 in addition to the direct effects on the nociceptors. Other reported anti-

inflammatory mechanisms of action of bromelain include inhibition of bradykinin at the site of inflammation via depletion of the plasma kallikrein system, and limiting the formation of fibrin by reduction of clotting cascade intermediates. Bromelain has also demonstrated anti-inflammatory action by inhibiting COX-2 expression and PGE2 production in murine microglial cells and human monocytic leukemia cell lines.<sup>10</sup> The efficacy of BR was studied in oral cancer cell line Ca9-22 and SCC25 cells to develop safer and superior anticarcinogenic agents and the treatment with BR inhibited the growth and proliferation of oral cancer cells, and induced apoptosis in Ca9-22 and SCC25 cells via various pathways and G1 cell cycle arrest. Thus, it can be hoped that BR will be developed as an anticarcinogenic medicine in future.<sup>11</sup> BR may cause nausea, vomiting, and diarrhea. Metrorrhagia and menorrhagia have occasionally occurred. Hypersensitivity reactions have been reported and have included skin reactions and asthma.<sup>11</sup>

## 2. Conclusion

From the overall discussion it can be concluded that the use of enzyme therapy through oral route has good results in the anti-inflammatory, analgesics role specially more with tissue healing has been observed in studies as well as in our clinical experience with the use TC especially with NSAIDs. But we can't ignore the role of other drugs too since BR have also been found to have an anticarcinogenic properties especially in case of oral cancer. Also, clinically it has been found that different people respond well to different combinations of these enzymes either it may be

diclofenac + SP or TC + Diclofenac or BR + Rutins + trypsin. And the most important in prescribing these enzymes with other medicine is mainly dependent upon patient selection in dental or medical practice.

### 3. Abbreviations

SP = serratiopeptidases, LOX = lipo-oxygenase, COX = cyclo-oxygenase, TC = trypsin-chymotrypsin, SPM = specialized pro-resolving mediators, BR = bromelain, NSAID = nonsteroidal anti-inflammatory drugs.

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### 5. Conflict of Interest

The authors declare they have no conflict of interest.

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### Author biography

**Abhishek Sharma**, Senior Resident

**Vishal Thakur**, Private Practitioner

**Asusa Cicilia Loli**, Post Graduate 2nd Year Student

**Sonali**, Post Graduate 2nd Year Student

**Dania Fatima**, Post Graduate 3rd Year Student

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