

## Effectiveness Of Trypsin - Chymotrypsin as an Anti Inflammatory in Maxillofacial Trauma - A Double Blinded Randomised Clinical Trial

Research Article

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### Abstract

**Background:** Surgical treatment in patients with facial bone surgeries governs a meaningful extent of tissue trauma prompting prevalent postoperative portents of pain, facial swelling, and inconvenience. Those symptoms are a major disadvantage and affect the patient's quality of life. Patient satisfaction after treatment of mandibular fractures may be improved by reducing or eliminating these side effects. One way to do this is to prescribe medication such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAID), a combination of corticosteroids and NSAID or enzyme preparations like serratiopeptidase or trypsin chymotrypsin combinations.

**Materials And Methods:** A clinical prospective study was done in the postoperative period for patients with facial trauma (Para symphysis fracture of mandible). 30 patients divided randomly into 2 groups. Group 1: Placebo (Control group). Group 2: Trypsin chymotrypsin group (chymoral forte), TDS 30 mins before food for 7 days. Facial swelling was quantified by 2 linear distances (Tragus-pogonion). Pain was recorded by means of VAS scale. All the outcomes were measured on day 1, 3, and 7 postoperatively.

**Results:** Group 2 (chymoral forte) showed a significant reduction in Facial swelling postoperatively when compared to Group 2 (placebo) at all times. There was no statistically significant difference in pain reduction when comparing both groups.

**Conclusion:** Owing to anti-inflammatory, anti-oedematous, fibrinolytic, anti-infective, and analgesic effects, trypsin: chymotrypsin oral combination has emerged as a promising treatment to facilitate healing of traumatic injuries. Trypsin chymotrypsin combination always showed a significant reduction in swelling and pain postoperatively.

**Keywords:** Maxillofacial Trauma; Pain; Swelling; Fractures; Proteolytic Enzyme; Trypsin Chymotrypsin.

### Introduction

Maxillofacial region involves soft and hard tissues forming the face extending from frontale superiorly to the mandible inferiorly [1]. The face being the foremost exposed to a part of the body is especially susceptible to trauma. Trauma to the facial region causes injuries to skeletal components, dentition also as soft tissues of the face [2]. Injuries to the maxillofacial region are increasing in frequency and severity due to the heavy reliance on road transportation and therefore the increasing socio-economic activities of the population. During wound healing, the formation and remodelling of the extracellular matrix involves a series of events that occur during a sequential fashion [3]. The clot formed

during the method of healing consists mainly of fibronectin and fibrin. Afterward plasmin, breaks down the fibrin barrier to revive circulation. As a response to trauma the liver releases acute phase proteins like alpha 1 antitrypsin and alpha 2 macroglobulin which bind to plasmin and hence fibrinolysis is packed up [4]. Trypsin: chymotrypsin combination minimizes fibrinolytic pack up and therefore the severity of the inflammatory phase might be reduced.

Various other areas where use the enzyme can be made use of are:

- Resolves oedema post operatively and modulates inflammation associated with various conditions including accidental and surgi-

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cal trauma.

- Inflammation of a vein associated with thrombus, Thrombophlebitis.
- Gynaecological surgery such as vasectomies and caesarean post operatively.
- In dentistry specially for tooth extraction, periapical abscess and maxillofacial surgery. Implement in bronchitis for the reduction in viscosity of mucus and sputum.
- Fractures and dislocation, sprains and strains.
- In ocular trauma such as macular oedema, black eye, hyphema, uveal tract inflammation, subconjunctival haemorrhage, extra-ocular trauma.
- In ENT such as nasal fractures, para pharyngeal abscess.
- Conjunction with conventional therapy in treatment of patients with cancer of breast, lungs, head etc.

Previously our team has a rich experience in working on various research projects across multiple disciplines [5-48] Now the growing trend in this area motivated us to pursue this project.

The aim of this study is to evaluate the effectiveness of Trypsin-Chymotrypsin as an anti-inflammatory agent in maxillofacial trauma.

## Materials And Method

A total of 30 electively posted surgical patients were selected. The patients were grouped into two categories: group I (n = 15) were given placebo in place of trypsin: chymotrypsin preparation, categorized as the control group/placebo group; group II (n = 15) patients were treated with oral preparation of trypsin:chymotrypsin in the ratio of 6:1 with an enzymatic activity of 200,000 A.U./tablet (tab. chymoral forte). These patients received 1 tablet of chymoral forte 3 times a day × for 7 days postoperatively. Patients diagnosed with fracture of parasymphysis of mandible were included in the study. The study being Double-blinded, the operating surgeon was not aware of the drug dispensed by the controller to the patient's postoperatively neither did the patients nor the investigators aware of the drug given. The codes of the drugs were disclosed to the investigator by the controller after the pain assessment.

Only clean and electively posted surgical cases were selected and patients with significant comorbidities like uncontrolled diabetes mellitus, hypertension etc. were eliminated from our study. The mean average age group of individuals taken in both the groups ranged from 20- 40years. Routine blood investigations like complete blood picture, urine routine and microscopy, renal functional tests, liver function tests, ECG, chest X ray was done to all the patients from both the groups prior to surgery. Patients with all the investigations within normal limits and a baseline hemoglobin

of greater than or equal to 10 were included in the present study. Intra operatively a single shot of third generation cephalosporins antibiotic, cefotaxime 1gm intravenously has been administered to all the patients from both the groups at the time of induction during anaesthesia. Post operatively a uniform antibiotic coverage of cefotaxime 200mg in tablet form (oral preparation) over a period 5 days was given to individuals of both placebo group and chymoral forte treated group. Facial swelling was quantified by 2 linear distances(Tragus-pogonion).Pain was recorded by means of VAS scale. All the outcomes were measured on day 1, 3, and 7 postoperatively.The statistical analysis was done using Statistical Package for Social Sciences (SPSS) Version 15.0 Statistical Analysis Software. The values were represented in mean ± SD.

## Results

Of all the 30 patients studied divided into 2 groups, we found that in Group 1 (PLACEBO), 15 patients with a mean age of 28.4 years, included 5 Females (33%) and 10 Males (67%) who received conventional therapy post-surgery. In Group 2 (TRYPSIN-CHYMOTRYPSIN)) 15 patients with a mean age of 31.6 years, included 9 Males (60%) and 6 Females(40%) as shown in Fig who received oral preparation of trypsin:chymotrypsin in the ratio of 6:1 with an enzymatic activity of 200,000 A.U./tablet (tab. chymoral forte).The mean value of swelling for Group 1 pre operatively was found to be 15.33cm (SD: 0.94),on day one mean distance was 16.53 cm (SD:0.96), on day 3 mean distance was 16.13 cm (SD: 1.03), and on day 7 mean distance was 15.57 cm (SD:0.93).The mean value of swelling for Group 2 pre operatively was found to be 14.57cm (SD:0.94),on day 1 mean distance was 15.36 cm (SD: 0.89), on day 3 mean distance was 15.13 cm (SD: 0.99), and on day 7 mean distance was 14.64 cm (SD: 0.95).Swelling was more in Placebo group receiving conventional therapy when compared to Study group receiving oral preparation of trypsin:chymotrypsin in the ratio of 6:1 with an enzymatic activity of 200,000 A.U./tablet (tab. chymoral forte),as shown in Table 1.Mean value of pain was more in group 2(Trypsin-chymotrypsin) compared to group 1(Placebo), as shown in Table 2.

## Discussion

Following an acute injury, there is a pointy rise within the levels of the protease inhibitors  $\alpha$ 1-antitrypsin and  $\alpha$ 2 macroglobulin [48]. These acute phase reactants inhibit several proteolytic enzymes, which if uncontrolled can lead to unregulated inflammation and impair healing. The order of affinity of  $\alpha$ 1antitrypsin with proteolytic enzymes is as follows: elastase>chymotrypsin>cathepsin G>trypsin>plasmin.9,10 Similarly,  $\alpha$ 2macroglobulin shows greatest affinity with cathepsin G. At now , it must be reiterated that

Figure 1. Gender distribution in the study.

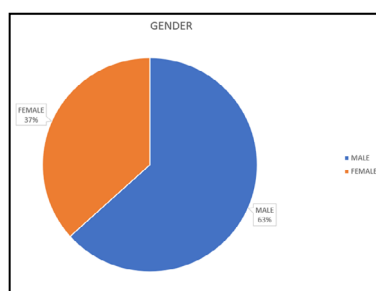


Table 1. Swelling measurements on 1st, 3rd and 7th day post operatively.

Group	TR-PG PREOP		TR-PG DAY 1		TR-PG DAY 3		TR-PG DAY 7	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Group 1	15.33	0.94	16.53	0.96	16.13	1.03	15.57	0.93
Group 2	14.57	0.94	15.36	0.89	15.13	0.99	14.64	0.95

Table 2. VAS score on 1st, 3rd and 7th day post operatively.

Group	VAS DAY 1		VAS DAY 3		VAS DAY 7	
	Mean	SD	Mean	SD	Mean	SD
Group 1	5.33	0.58	3.33	0.58	1.33	0.58
Group 2	4.43	0.76	2.93	1	0.79	0.8

plasmin causes fibrinolysis, and its inhibition prevents fibrinolysis. Therefore, a steep rise in  $\alpha 1$  antitrypsin and  $\alpha 2$  macroglobulin following acute injury results in a period of fibrinolytic shutdown, with consequent maintenance of inflammatory response and edema and delay in repair [50].

Oral combination of trypsin: chymotrypsin targets this early stage of inflammation. Since  $\alpha 1$ -antitrypsin shows greater affinity for trypsin and chymotrypsin compared to plasmin, oral supplementation of the enzyme complex ensures that plasmin remains available for fibrinolysis and therefore the period of fibrinolytic shutdown is shortened [51]. As a result, local microcirculation is restored, inflammatory edema is cleared, and tissue repair is facilitated. The activity of proteolytic enzymes and their degradative effects are countered, resulting in reduction in inflammatory milieu, ROS and oxidative stress, and faster healing.

Ravi kumar et al studied the efficacy of trypsin:chymotrypsin (Chymoral) in accidental soft tissue injuries. The study included 156 patients presenting in the casualty department with bruises, lacerations, hematomas, and sprains. The conclusion drawn was that trypsin:chymotrypsin treatment in patients with accidental soft tissue injuries hastens the healing process and significantly reduces the recovery time [52]. This above mentioned study results are in accordance with the results of the present study.

Brakenbury and Kotowski also demonstrated that trypsin: chymotrypsin treatment improved the recovery rate in patients with ankle sprains. A double-blind randomized controlled trial involving 252 patients with sprains of the medial/lateral ligaments of the ankle that were immobilized using either below-the-knee plaster cast or an elastic bandage applied from the toes to below the knee. The results suggest that trypsin: chymotrypsin treatment hastens the recovery of accidental soft tissue injuries [53]. The above-mentioned study also is also in accordance with the results of the present study.

A multicentric study investigated the efficacy and safety of trypsin: chymotrypsin (Chymoral Forte) in patients with traumatic injuries from accidents, surgeries, burns, and others. It concluded that trypsin: chymotrypsin treatment in patients with surgical injuries, accidental injuries, and burns effectively resolves inflammation and improves healing [54]. The efficacy and safety of trypsin: chymotrypsin in accidental injuries, surgical and orthopaedic injuries,

burns, and sciatica has been corroborated by a substantial and largely consistent body of evidence from clinical trials. Our institution is passionate about high quality evidence-based research and has excelled in various fields [55-65].

## Conclusion

Trypsin: chymotrypsin combination hastens repair in surgical patients, shows high bioavailability without losing its biological activities as an anti-inflammatory agent. These properties help in resolving signs and symptoms of inflammation, tissue injury and facilitate the repair process. It also demonstrates analgesic effects and reduces the pain related to healing. It's thus concluded that trypsin: chymotrypsin treatment in patients hastens the healing process and reduces the recovery time. Overall, the use of trypsin:chymotrypsin in patients with acute injury reduces inflammation which in turn facilitates rapid healing

## References

- Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care. *Adv Skin Wound Care*. 2012 Jul;25(7):304-14. Pubmed PMID: 22713781.
- Basu S, Shukla V. Complications of wound healing. *In: Measurements in wound healing*. 2012: 109-144.
- McCarty SM, Percival SL. Proteases and delayed wound healing. *Adv Wound Care*. 2013 Oct 1;2(8):438-47.
- White MJ, Glenn M, Gomer RH. Trypsin potentiates human fibrocyte differentiation. *PLoS One*. 2013 Aug 7;8(8):e70795.
- Govindaraju L, Gurunathan D. Effectiveness of Chewable Tooth Brush in Children-A Prospective Clinical Study. *J Clin Diagn Res*. 2017 Mar;11(3):ZC31-ZC34. Pubmed PMID: 28511505.
- Christabel A, Anantanarayanan P, Subash P, Soh CL, Ramanathan M, Muthusekhar MR, et al. Comparison of pterygomaxillary dysjunction with tuberosity separation in isolated Le Fort I osteotomies: a prospective, multi-centre, triple-blind, randomized controlled trial. *Int J Oral Maxillofac Surg*. 2016 Feb;45(2):180-5. Pubmed PMID: 26338075.
- Soh CL, Narayanan V. Quality of life assessment in patients with dentofacial deformity undergoing orthognathic surgery--a systematic review. *Int J Oral Maxillofac Surg*. 2013 Aug;42(8):974-80. Pubmed PMID: 23702370.
- Mehta D, Deeksha, Tewari D, Gupta A, Awasthi R, Singh H, et al. Inflammoleptide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases. *Chem Biol Interact*. 2019 Aug 1;308:206-215. Pubmed PMID: 31136735.
- Ezhilarasan D, Apoorva VS, Ashok Vardhan N. Syzygium cumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. *J Oral Pathol Med*. 2019 Feb;48(2):115-21.
- Campeau PM, Kasperaviciute D, Lu JT, Burrage LC, Kim C, Hori M, et al. The genetic basis of DOORS syndrome: an exome-sequencing study. *Lancet*

- Neurol. 2014 Jan;13(1):44-58.Pubmed PMID: 24291220.
- [11]. Sneha S. Knowledge and awareness regarding antibiotic prophylaxis for infective endocarditis among undergraduate dental students. *Asian J Pharm Clin Res.* 2016 Oct 1:154-9.
- [12]. Christabel SL, Gurunathan D. Prevalence of type of frenal attachment and morphology of frenum in children, Chennai, Tamil Nadu. *World J Dent.* 2015 Oct;6(4):203-7.
- [13]. Kumar S, Rahman RE. Knowledge, awareness, and practices regarding biomedical waste management among undergraduate dental students. *Asian J Pharm Clin Res.* 2017;10(8):341.
- [14]. Sridharan G, Ramani P, Patankar S. Serum metabolomics in oral leukoplakia and oral squamous cell carcinoma. *J Cancer Res Ther.* 2017 Jul 1;13(3):556-61.
- [15]. Ramesh A, Varghese SS, Doraiswamy JN, Malaiappan S. Herbs as an antioxidant arsenal for periodontal diseases. *J IntercultEthnopharmacol.* 2016 Jan 27;5(1):92-6.Pubmed PMID: 27069730.
- [16]. Thamaraiselvan M, Elavarasu S, Thangakumaran S, Gadagi JS, Arthie T. Comparative clinical evaluation of coronally advanced flap with or without platelet rich fibrin membrane in the treatment of isolated gingival recession. *J Indian SocPeriodontol.* 2015 Jan;19(1):66-71.
- [17]. Thangaraj SV, Shyamsundar V, Krishnamurthy A, Ramani P, Ganesan K, Muthuswami M, et al. Molecular Portrait of Oral Tongue Squamous Cell Carcinoma Shown by Integrative Meta-Analysis of Expression Profiles with Validations. *PLoS One.* 2016 Jun 9;11(6):e0156582.Pubmed PMID: 27280700.
- [18]. Ponnulakshmi R, Shyamaladevi B, Vijayalakshmi P, Selvaraj J. In silico and in vivo analysis to identify the antidiabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2 diabetic experimental rats. *ToxicolMech Methods.* 2019 May;29(4):276-290.Pubmed PMID: 30461321.
- [19]. Ramakrishnan M, Bhurki M. Fluoride, Fluoridated Toothpaste Efficacy And Its Safety In Children-Review. *Int J Pharm Res.* 2018 Oct 1;10(04):109-14.
- [20]. Christabel A, Anantanarayanan P, Subash P, Soh CL, Ramanathan M, Muthusekhar MR, et al. Comparison of pterygomaxillarydysjunction with tuberosity separation in isolated Le Fort I osteotomies: a prospective, multi-centre, triple-blind, randomized controlled trial. *Int J Oral Maxillofac Surg.* 2016 Feb;45(2):180-5.Pubmed PMID: 26338075.
- [21]. Soh CL, Narayanan V. Quality of life assessment in patients with dentofacial deformity undergoing orthognathic surgery--a systematic review. *Int J Oral Maxillofac Surg.* 2013 Aug;42(8):974-80.Pubmed PMID: 23702370.
- [22]. Mehta M, Deeksha, Tewari D, Gupta G, Awasthi R, Singh H, et al. Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases. *ChemBiol Interact.* 2019 Aug 1;308:206-215.Pubmed PMID: 31136735.
- [23]. Ezhilarasan D, Apoorva VS, Ashok Vardhan N. Syzygiumcumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. *J. Oral Pathol. Med.* 2019 Feb;48(2):115-21.
- [24]. Campeau PM, Kasperaviciute D, Lu JT, Burrage LC, Kim C, Hori M, et al. The genetic basis of DOORS syndrome: an exome-sequencing study. *Lancet Neurol.* 2014 Jan;13(1):44-58.Pubmed PMID: 24291220.
- [25]. Sneha S. Knowledge and awareness regarding antibiotic prophylaxis for infective endocarditis among undergraduate dental students. *Asian J Pharm Clin Res.* 2016 Oct 1:154-9.
- [26]. Christabel SL, Gurunathan D. Prevalence of type of frenal attachment and morphology of frenum in children, Chennai, Tamil Nadu. *World J Dent.* 2015 Oct;6(4):203-7.
- [27]. Kumar S, Rahman RE. Knowledge, awareness, and practices regarding biomedical waste management among undergraduate dental students. *Asian J Pharm Clin Res.* 2017;10(8):341.
- [28]. Sridharan G, Ramani P, Patankar S. Serum metabolomics in oral leukoplakia and oral squamous cell carcinoma. *J Cancer Res Ther.* 2017 Jul 1;13(3):556-61.
- [29]. Ramesh A, Varghese SS, Doraiswamy JN, Malaiappan S. Herbs as an antioxidant arsenal for periodontal diseases. *J IntercultEthnopharmacol.* 2016 Jan 27;5(1):92-6.Pubmed PMID: 27069730.
- [30]. Thamaraiselvan M, Elavarasu S, Thangakumaran S, Gadagi JS, Arthie T. Comparative clinical evaluation of coronally advanced flap with or without platelet rich fibrin membrane in the treatment of isolated gingival recession. *J Indian SocPeriodontol.* 2015 Jan;19(1):66-71.
- [31]. Thangaraj SV, Shyamsundar V, Krishnamurthy A, Ramani P, Ganesan K, Muthuswami M, et al. Molecular Portrait of Oral Tongue Squamous Cell Carcinoma Shown by Integrative Meta-Analysis of Expression Profiles with Validations. *PLoS One.* 2016 Jun 9;11(6):e0156582.Pubmed PMID: 27280700.
- [32]. Ponnulakshmi R, Shyamaladevi B, Vijayalakshmi P, Selvaraj J. In silico and in vivo analysis to identify the antidiabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2 diabetic experimental rats. *ToxicolMech Methods.* 2019 May;29(4):276-290.Pubmed PMID: 30461321.
- [33]. Ramakrishnan M, Bhurki M. Fluoride, Fluoridated Toothpaste Efficacy And Its Safety In Children-Review. *Int J Pharm Res.* 2018 Oct 1;10(04):109-14.
- [34]. Govindaraju L, Gurunathan D. Effectiveness of Chewable Tooth Brush in Children-A Prospective Clinical Study. *J ClinDiagn Res.* 2017 Mar;11(3):ZC31-ZC34.Pubmed PMID: 28511505.
- [35]. Christabel A, Anantanarayanan P, Subash P, Soh CL, Ramanathan M, Muthusekhar MR, et al. Comparison of pterygomaxillarydysjunction with tuberosity separation in isolated Le Fort I osteotomies: a prospective, multi-centre, triple-blind, randomized controlled trial. *Int J Oral Maxillofac Surg.* 2016 Feb;45(2):180-5.Pubmed PMID: 26338075.
- [36]. Soh CL, Narayanan V. Quality of life assessment in patients with dentofacial deformity undergoing orthognathic surgery--a systematic review. *Int J Oral Maxillofac Surg.* 2013 Aug;42(8):974-80.Pubmed PMID: 23702370.
- [37]. Mehta M, Deeksha, Tewari D, Gupta G, Awasthi R, Singh H, et al. Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases. *ChemBiol Interact.* 2019 Aug 1;308:206-215.Pubmed PMID: 31136735.
- [38]. Ezhilarasan D, Apoorva VS, Ashok Vardhan N. Syzygiumcumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. *J Oral Pathol Med.* 2019 Feb;48(2):115-21.
- [39]. Campeau PM, Kasperaviciute D, Lu JT, Burrage LC, Kim C, Hori M, et al. The genetic basis of DOORS syndrome: an exome-sequencing study. *Lancet Neurol.* 2014 Jan;13(1):44-58.Pubmed PMID: 24291220.
- [40]. Sneha S. Knowledge and awareness regarding antibiotic prophylaxis for infective endocarditis among undergraduate dental students. *Asian J. Pharm. Clin. Res.* 2016 Oct 1:154-9.
- [41]. Christabel SL, Gurunathan D. Prevalence of type of frenal attachment and morphology of frenum in children, Chennai, Tamil Nadu. *World J Dent.* 2015 Oct;6(4):203-7.
- [42]. Kumar S, Rahman RE. Knowledge, awareness, and practices regarding biomedical waste management among undergraduate dental students. *Asian J. Pharm. Clin. Res.* 2017;10(8):341.
- [43]. Sridharan G, Ramani P, Patankar S. Serum metabolomics in oral leukoplakia and oral squamous cell carcinoma. *J Cancer Res Ther.* 2017 Jul 1;13(3):556-61.
- [44]. Ramesh A, Varghese SS, Doraiswamy JN, Malaiappan S. Herbs as an antioxidant arsenal for periodontal diseases. *J IntercultEthnopharmacol.* 2016 Jan 27;5(1):92-6.Pubmed PMID: 27069730.
- [45]. Thamaraiselvan M, Elavarasu S, Thangakumaran S, Gadagi JS, Arthie T. Comparative clinical evaluation of coronally advanced flap with or without platelet rich fibrin membrane in the treatment of isolated gingival recession. *J Indian SocPeriodontol.* 2015 Jan;19(1):66-71.
- [46]. Thangaraj SV, Shyamsundar V, Krishnamurthy A, Ramani P, Ganesan K, Muthuswami M, et al. Molecular Portrait of Oral Tongue Squamous Cell Carcinoma Shown by Integrative Meta-Analysis of Expression Profiles with Validations. *PLoS One.* 2016 Jun 9;11(6):e0156582.Pubmed PMID: 27280700.
- [47]. Ponnulakshmi R, Shyamaladevi B, Vijayalakshmi P, Selvaraj J. In silico and in vivo analysis to identify the antidiabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2 diabetic experimental rats. *ToxicolMech Methods.* 2019 May;29(4):276-290.Pubmed PMID: 30461321.
- [48]. Ramakrishnan M, Bhurki M. Fluoride, Fluoridated Toothpaste Efficacy And Its Safety In Children-Review. *Int J Pharm Res.* 2018 Oct 1;10(04):109-14.
- [49]. Website.
- [50]. Lenselink EA. Role of fibronectin in normal wound healing. *Int Wound J.* 2015 Jun;12(3):313-6.
- [51]. Ambrus JL, Lassman HB, De Marchi JJ. Absorption of exogenous and endogenousproteolytic enzymes. *ClinPharmacolTher.* 1967 May;8(3):362-8.
- [52]. RaviKumar T, Ramakrishnan M, Jayaraman V, Babu M. Effect of trypsin-chymotrypsin (Chymoral Forte D.S.) preparation on the modulation of cytokine levels in burn patients. *Burns.* 2001 Nov;27(7):709-16.Pubmed PMID: 11600250.
- [53]. Najafipour F, Najafipour F, Hassan M. The Risk Factors for Ankle Sprain in Cadets at a Male Military School in Iran: A Retrospective Case-control Study. *in depth.* 2017;4(5):20-6.
- [54]. Apsangikar P, Chaudhry S, Naik M, Kozgi P. A phase III, multicentric, parallel, two-arm, parallel group, active-control, randomized, comparative clinical study to evaluate efficacy and safety of RituxiRel (TM) arm (rituximab) with reference arm (rituximab) in patients with non-Hodgkin's lymphoma. *Asian j. oncol.* 2017;3(1):17-22.
- [55]. VijayashreePriyadharsini J. In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens. *J Periodontol.* 2019 Dec;90(12):1441-1448.Pubmed PMID: 31257588.



- [56]. PC J, Marimuthu T, Devadoss P, Kumar SM. Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study. *Clin Implant Dent Relat Res*. 2018 Apr 6;20(4):531-4.
- [57]. Ramesh A, Varghese S, Jayakumar ND, Malaiappan S. Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study. *J Periodontol*. 2018 Oct;89(10):1241-1248. Pubmed PMID: 30044495.
- [58]. Ramadurai N, Gurunathan D, Samuel AV, Subramanian E, Rodrigues SJ. Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial. *Clin Oral Investig*. 2019 Sep;23(9):3543-50.
- [59]. Sridharan G, Ramani P, Patankar S, Vijayaraghavan R. Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma. *J Oral Pathol Med*. 2019 Apr;48(4):299-306.
- [60]. Ezhilarasan D, Apoorva VS, Ashok Vardhan N. Syzygiumcumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. *J Oral Pathol Med*. 2019 Feb;48(2):115-21.
- [61]. Mathew MG, Samuel SR, Soni AJ, Roopa KB. Evaluation of adhesion of *Streptococcus mutans*, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: randomized controlled trial. *Clin Oral Investig*. 2020 Sep;24(9):1-6. Pubmed PMID: 31955271.
- [62]. Samuel SR. Can 5-year-olds sensibly self-report the impact of developmental enamel defects on their quality of life? *Int J Paediatr Dent*. 2021 Mar;31(2):285-286. Pubmed PMID: 32416620.
- [63]. R H, Ramani P, Ramanathan A, R JM, S G, Ramasubramanian A, et al. CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020 Sep;130(3):306-312. Pubmed PMID: 32773350.
- [64]. Chandrasekar R, Chandrasekhar S, Sundari KKS, Ravi P. Development and validation of a formula for objective assessment of cervical vertebral bone age. *ProgOrthod*. 2020 Oct 12;21(1):38. Pubmed PMID: 33043408.
- [65]. VijayashreePriyadharsini J, SmilineGirija AS, Paramasivam A. In silico analysis of virulence genes in an emerging dental pathogen *A. baumannii* and related species. *Arch Oral Biol*. 2018 Oct;94:93-98. Pubmed PMID: 30015217.