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ORIGINAL ARTICLE

EFFECT OF MONTELUKAST ON HEALING OF INDUCED ORAL ULCER IN RATS

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Summary

Background: Oral ulcers are among the common recurrent oral diseases which seek medical help; the underlying pathology is yet obscure, making medical intervention difficult.
Aims: The purpose of this study was to investigate if montelukast could help mouth ulcer model in Albino rats.
Methods: The rats were divided into two groups of 24, the control group of 12 rats with induced ulcer and no therapy, and the treatment group with induced ulcer and treated orally with Montelukast 20 mg/kg. Each group had six rats sacrificed after 3 and 7 days of treatment. The lingual ulcer was produced with cotton soaked in 70% acetic acid solution and rubbed against the tongue for 2 minutes. Discolouration of tongue tissue has been noticed. Animals in all groups were weighed on days 1, 3, and 7 following mucosal ulcerations were confirmed.
Results: On days 1, 3, and 7, the body weight of the treatment group rats improved as compared to the control group. On days 3 and 7, the tongue histological section of the control group revealed a wide gap of the site of ulcer in the lingual mucosa, inflammatory exudate, and severe infiltration of inflammatory cells (score 3) without re-epithelialization (score 0). Lingual sections of MTK treated group after ulcer induction on day 3 showed the same lesions as the control group whereas after 7 days demonstrated improvement in inflammatory indicators as inflammatory exudate and infiltration of inflammatory cells (score 1), formation of granulation tissue composed of fibrous tissue and angiogenesis and Re-epithelialization (score 1) comparing with the control group.
Conclusion: The present study found Montelukast's anti-inflammatory potential characteristics to treat generated lingual ulcers in rats.

Key words: Montelukast; Healing; Oral Ulcer; Rats

Introduction

Oral ulcers are a type of superficial lesion in which the mucosa breaks down resulting in the loss of epithelial tissue (1). Mouth ulcers can disrupt a patient's everyday activities and quality of life by causing pain during eating, swallowing, and speaking. Additionally, mouth ulcers can affect nutritional intake and oral hygiene, as well as

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cause secondary infection (2). Mechanical, therapeutic, chemical, or thermal stress, as well as infections, medicines, autoimmune illnesses, and other systemic conditions like anaemia, can all produce oral ulcers (3,4). Mouth ulcers have become more common as a result of lifestyle changes, and recurrent outbreaks of mouth ulcers can cause foul breath, chronic pharyngitis, constipation, and even metabolic abnormalities (5).

The pain associated with mouth ulcers is generated by exposing the nerve terminals in the lower region of the mouth, which is accompanied by leukocyte infiltration into the focal lumen of the epithelium and increased generation of inflammatory mediators and free radicals from infiltrating leukocytes (6). The inflammatory reaction includes the lamina propria (7).

Topical corticosteroids, anaesthetics, and analgesics are frequently prescribed, with systemic immunosuppressive medication reserved for the most severe patients (8).

Leukotrienes (LTs), a crucial class of pro-inflammatory lipid mediators, are produced when arachidonic acid undergoes oxidative metabolism through the 5-lipoxygenase (5-LOX) pathway. The produced LTA4, transformed into cysteinyl LTs (CysLTs) by the enzymes LTC4 synthase, glutamyl leukotrienase, and LTD4 dipeptidase. Eosinophils, mast cells, monocytes/macrophages, and myeloid dendritic cells are the main cells of the innate immune system that produce CysLTs, the components of the slow-reacting substance of anaphylaxis. These cells are important in the development of edema, bronchoconstriction, and airway remodeling in asthmatics (9-12). These CysLT binds to CysLT receptors expressed on the outer membrane of immune/inflammatory cells resulting in initiation or propagation of inflammatory reactions (12).

Human bronchial asthma is therapeutically treated with many CysLTs receptor antagonists. One of these is montelukast, which was approved by FDA in 1998 and is the most often prescribed CysLTR1 antagonist in the United States and Europe. By opposing the proasthmatic, proinflammatory, and priming activities of CysLTs, it is utilized to cure bronchial asthma and reduce the symptoms of seasonal allergies (12-14).

Montelukast sodium (MTK), also known as Singulair, is an orally active leukotriene receptor antagonist that inhibits cysteine leukotriene receptor 1 (CysLTR1) (15). Montelukast has been shown to have anti-inflammatory activity in the rat paw-inflammation model, potentiating the anti-inflammatory activity of non-steroidal anti-inflammatory drugs and providing protection for gastric mucosa (16). Montelukast has provided Eosinophil-membrane stabilizing activity in cough-variant asthma patients resulting in improving overall cough symptoms (17). In the prostate inflammation rat model, montelukast has improved the inflammatory reaction and reduced the inflammatory markers and histological findings (18).

Montelukast has been used to mitigate indomethacin-induced gastric ulcers in rats. The results have confirmed that montelukast has reduced microscopically gastric lesions to a greater extent than that of lansoprazole, famotidine or ranitidine (19-21). Additionally, montelukast has been shown to decrease the catalase activity induced by indomethacin, proposing their usefulness in ulceration (22). Moreover, montelukast provides mucosal protection via activation of the glutathione enzyme (23-25).

A pilot study conducted on recurrent aphthous stomatitis by Femiano *et al*., 2010 confirmed that montelukast induced comparable improvement compared to prednisolone; provided that montelukast has lower side effects compared to prednisolone (26). Similarly, a case study conducted by Aquino and Jamora, 2020 confirmed that montelukast improved recurrent aphthous stomatitis when patients were transferred to montelukast for 5 months (27). Because there is little research on the role of MTK in mouth ulcer healing, the primary goal of this study is to look into the effect of MTK on oral ulcer healing by looking at the histological parameters of produced oral ulcers in rats.

Materials and Methods

The drug used: Montelukast sodium used from Merck Sharp & Dom, Crammington, Northumberland, UK.

The Animals: The Research Ethics Committee of the University of Mosul's College of Dentistry (UoM.Dent/A.L.11/22) gave their approval to this study. Animal House, College of Veterinary Medicine, University

of Mosul, Mosul, Iraq, provided 24 healthy male albino rats with an average age of 2-3 months and a weight of 250-350 g for this study. All experimental protocols followed the criteria for the care and use of laboratory animals established by the College of Dentistry at the University of Mosul. At ambient temperature (22 °C 2°C), homogenised sawdust was employed as bedding. In a standard illumination setting (12 h light/12 h dark cycle), food and drink were freely available.

Designing an experience: The animals were split into two groups of 24, one with induced stomatitis and no therapy and the other with induced stomatitis and treated orally with 20 mg/kg montelukast per day. From each group, six rats were sacrificed after 3 days. The remaining animals were sacrificed after therapy and 7 days of treatment.

Oral ulcer formation: The animals were sedated with an intraperitoneal (IP) injection of a mixture of xylazine (5 mg/kg) and ketamine hydrochloride (50 mg/kg) before the oral ulcers were generated using a small cotton ball put at one end of the glass tube at a diameter of 3 mm. After that, a cotton ball is immersed in a 70% acetic acid solution and pushed against the tongue's dorsal surface for two minutes. Mucosal discolouration to white was noticed immediately following acetic acid administration, and mucosal ulcerations were confirmed two days later. On days 1, 3, and 7, all animals were weighed.

Histopathological study: Sections from ulcers were identified and fixed in 10% formalin for 24 hours, after which the samples were treated, dehydrated in an alcohol series, dipped in xylol, impregnated with paraffin, and thawed at 60 °C. At room temperature, samples were packed into paraffin-forming blocks. Using a microtome, samples were sliced to a thickness of 5 Mm and prepared for microscopic histological analysis using routine Hematoxylin and Eosin staining.

Inflammation was assigned the following ranking:

- Score 0 (Absent): 0-10% Inflammation.
- Score 1 (Mild): 10-40% Inflammation.
- Score 2 (Moderate): 40-70% Inflammation.
- Score 3 (Intense): 70-100% Inflammation.

Re-epithelial tissue was recorded as follows consequences:

- Score 0: No re-epithelialization present
- Score 1: Re-epithelization of up to one-third.
- Score 2: Re-epithelization of up to two-third
- Score 3: Re-epithelization of more than two-third.
- Score 4: Normal thickness re-epithelization over the entire wound region.

Statistical analysis: Use the statistical analysis program Sigma Plot, one-way analysis of variance (ANOVA) Duncan test.

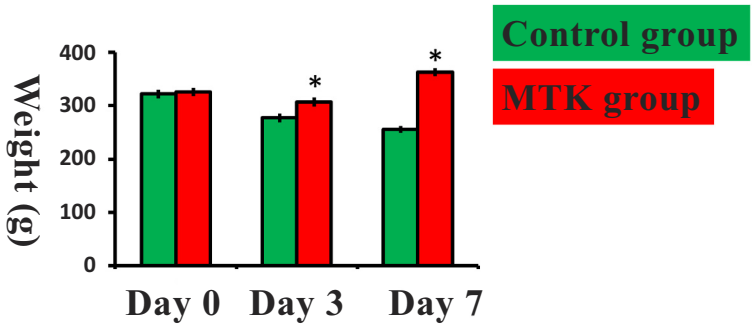

Figure 1. Weight of rats in control group and MTK group at day 0, 3, 7 following injury. Data expressed as mean±SD. *p<0.05 as compared to control group.

Result

The weight of the studied sample of rats has been measured and plotted against each other. MTK-treated groups showed significantly ($p<0.05$) higher level of weight gain over the tested time points (day 3 and day 7) compared to treatment-free groups. The initial weights of rats at day 0 were similar with no significant difference exists between them (Figure 1).

Tongue histological section from the rat of the control group after 3 days of ulcer induction (did not receive any therapy after ulcer induction) revealed a wide gap of the site of ulcer in the lingual mucosa, inflammatory exudate, severe infiltration of inflammatory cells (score 3) and fibrinous exudate in the site of ulcer without re-epithelialization (score 0) (Figure 2 α), while the tongue of the same group after 7 days of ulcer induction showed the same lesions as inflammatory exudate with infiltration of inflammatory cells (score 3), formation of granulation tissue composed of fibrous tissue and new blood vessels and congestion of blood vessel without re-epithelialization (score 0) (Figure 2 β) (Table 1 and 2).

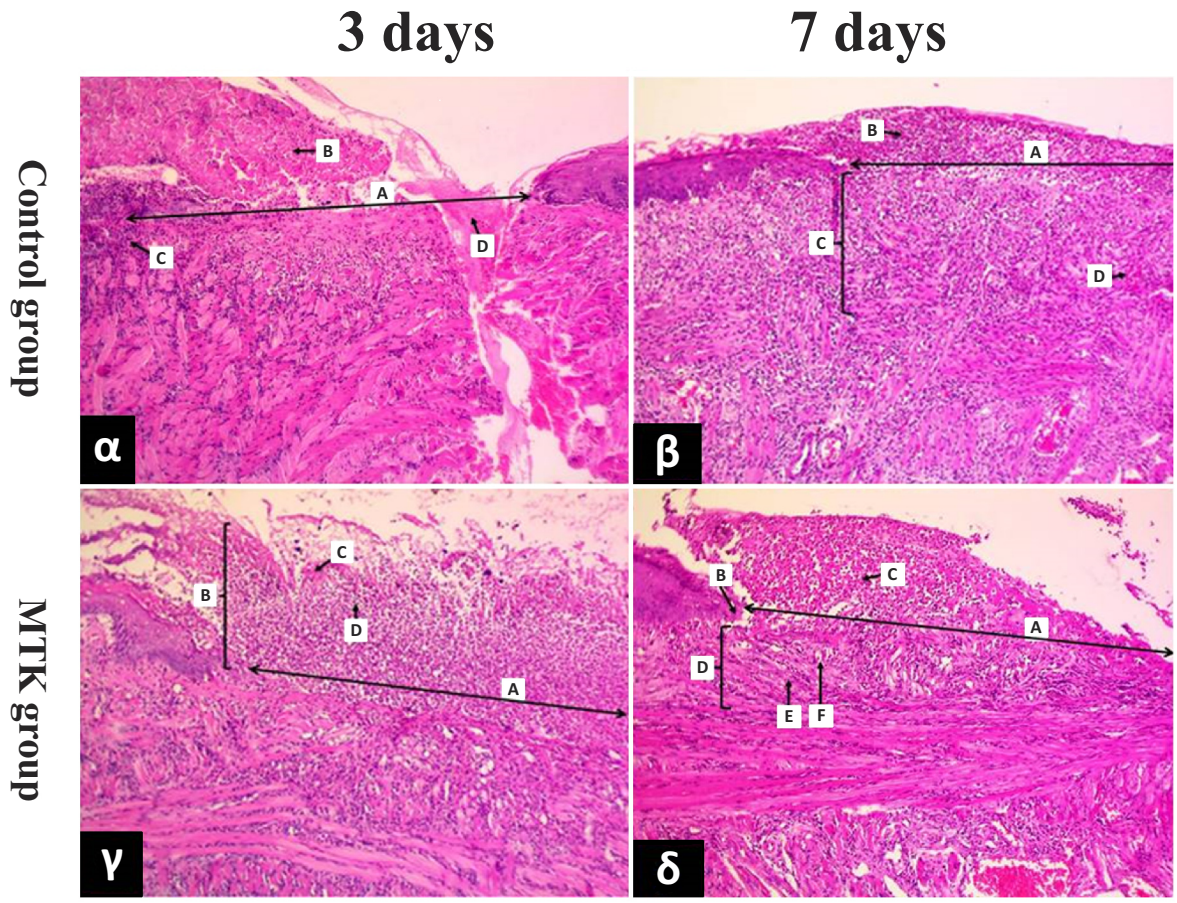

Figure 2. α is a photomicrograph of a tongue from a rat of the control group (3 days) shows the site of ulcer in the lingual mucosa (A), inflammatory exudate (B), severe infiltration of inflammatory cells (score 3) (C) and fibrinous exudate in the site of ulcer (D) without re-epithelialization (score 0). β is a section of the tongue from the rat of the control group (7 days) that shows the site of ulcer in the mucosa (A), inflammatory exudate with infiltration of inflammatory cells (score 3) (B) and formation of granulation tissue composed of fibrous tissue and new blood vessels (C) and congestion of blood vessel (D) without re-epithelialization (score 0). γ is a photomicrograph of a tongue from the rat MTK group (3 days) that shows the site of ulcer in the mucosa (A), inflammation (score 2) (B) composed of fibrinous exudate (C) and moderate infiltration of inflammatory cells (D) without re-epithelialization (score 0). δ is a photomicrograph of a tongue from the rat of the MTK group (7 days) that shows the site of ulcer in the mucosa with sloughing of the epithelium (A), re-epithelialization (score 1) (B), inflammatory exudate with infiltration of inflammatory cells (score 1) (C), formation of granulation tissue (D) composed of fibrous tissue (E) and angiogenesis (F). H&E stain, 100X.

Table 1. The scores of inflammation between the two groups on days 3 and 7.

	Control group (mean±SD)	MTK group (mean±SD)
Day 3	2.83 ± 0.37	2.83 ± 0.37
Day 7	2.67 ± 0.47*	1.33 ± 0.47

*P≤ 0.05 significantly higher as compared to MTK-treated group

Table 2. The scores of re-epithelialization between the two groups on days 3 and 7.

	Control group (mean±SD)	MTK group (mean±SD)
Day 3	0 ± 0.0	0 ± 0.0
Day 7	0 ± 0.0	1.33 ± 0.47*

*P≤ 0.05 significantly higher as compared to MTK-treated group

On the other hand, the tongue histological sections from rats of MTK treated group after 3 days of ulcer induction revealed the site of ulcer in the mucosa with inflammation (score 2) composed of fibrinous exudate and moderate infiltration of inflammatory cells compared with the control group without re-epithelialization (score 0). (Figure2 γ), Whereas after 7 days of ulcer induction the tongue sections demonstrated improvement in inflammatory indicators as inflammatory exudate with infiltration of inflammatory cells (score 1), formation of granulation tissue composed of fibrous tissue and angiogenesis and Re-epithelialization (score 1) compared with the control group (Figure2 δ) (Table 1, 2 and 3).

Table 3. The scores of inflammation and re-epithelialization in MTK-treated group.

MTK group (mean±SD)	Inflammation	Re-epithelialization
Day 3	2.83 ± 0.37*	0 ± 0.0
Day 7	1.33 ± 0.47	1.33 ± 0.47*

*P≤ 0.05 as compared between day 3 versus day 7

Discussion

Oral ulcers are a frequent oral mucosa condition that involves recurring and excruciating symptoms. Wound healing is a complex biological process that occurs naturally in the human body. Inflammation, cell proliferation, wound contraction, angiogenesis, matrix remodelling, and re-epithelialization are all finely regulated processes (28). Anti-LTs have been shown to have good therapeutic potential in many inflammatory clinical diseases linked with a decrease in pleomorphic leukocyte infiltration since leukotrienes (LTs) are one of the primary mediators of inflammation and are mostly produced by neutrophils (18). We examined the anti-ulcerative impact of MTK on produced oral ulcers in rats under the microscope, which could be related to its anti-inflammatory, antioxidant, and anti-apoptotic properties. These findings were compared to body weight changes as a clinical indicator of oral ulcer healing. This study discovered that MTK has an anti-inflammatory effect, which was demonstrated by a reduction in the degree of inflammation in the treated group.

These findings are consistent with those of Abdelhady *et al*. (2021), who found that taking 20 mg/kg of MTK orally with one of the NSAIDs (particularly Celecoxib) can improve the anti-inflammatory effect and provide significant stomach protection in mice (16). Furthermore, the findings of the present study are in agreement with Pu, *et al*., (2019), who discovered that MTK protects mice against acetaminophen-induced liver injury by suppressing oxidative stress and reducing inflammation (28).

MTK can boost the antioxidant defense against acute lung injury in dogs, according to Soltanieh *et al* (29). El-Rashidy (2021) also showed that MTK has a better urinary protective effect against cyclophosphamide-induced hemorrhagic cystitis in mice by suppressing apoptotic signalling, inhibiting mast cell infiltration, and stimulating autophagy (30). All of these findings could explain why the treatment group's epithelial remodelling improved on the seventh day, whereas the control group had no epithelial remodelling on any of the study's days.

There were no clinical trials previous to the current investigation that sought to test the anticarcinogenic impact of MTK on oral ulcers, so we used bodyweight observations as a clinical criterion to measure oral ulcer healing in addition to the above histological findings. Mouth ulcers can lead to weight loss, which exacerbates the pain and causes dysphagia, and this malnutrition can lead to delayed healing and additional weight loss (31).

This study discovered that weight loss improved after the fourth day of treatment, whereas the control group significantly ($p<0.05$, at day 3 and 7) lost weight continuously. These similarities between ulcer repair and weight gain are consistent with the findings of a study conducted by Wafaa *et al.*, 2021(32). MTK was discovered to have analgesic activity in addition to its anti-inflammatory effect by Kolhe and Kalem (2017), therefore the improvement in weight loss reported in the treatment group in this study could be largely related to this analgesic effect, which requires more research (33). The limitations of the present study include the short duration of therapy and using one drug therapy. The future direction will focus on a combination therapy of montelukast with antibiotics to identify their combined effects.

Conclusion

Finally, MTK promotes the healing of produced lingual ulcers in male rats while also lowering the impact of induced ulcers on body weight. This could come in handy in clinical practice.

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Conflict of Interest

The authors declare that no conflict of interest exists for this research.

Adherence to Ethical Standards

The study was approved by the Research Ethical Committee and Scientific Committee in the Department of Dental Basic Science of College of Dentistry/University of Mosul with approval number (UoM.Dent/A.L.11/22).

References

1. Rezazadeh F, Nazhvani AD, Abolmaali SS, et al. Efficacy of silver nanoparticle gel on healing of traumatic oral ulcers compared with triamcinolone oral paste: An experimental study on rats. Dental research journal. 2021;18.
2. Wu W, Ruan J, Li D, et al. Effect of dexamethasone on levels of inflammatory factors and EGF mRNA in rabbits suffering from oral ulcers. Tropical Journal of Pharmaceutical Research. 2021;20(2):351-357. https://doi.org/10.4314/tjpr.v20i2.19
3. Idrus E, Hartanti PD, Suniarti DF, et al. An experimental model of chemically-induced ulceration of the buccal mucosa of Mus musculus. Makara Journal of Health Research. 2019;23(3):10. https://doi.org/10.7454/msk.v23i3.1158
4. Al-Abdaly YZ, Saeed MG, Al-Hashemi HM. Effect of methotrexate and aspirin interaction and its relationship to oxidative stress in rats. Iraqi J Vet Sci. 2021;35(1):151-156. https://doi.org/10.33899/ijvs.2020.126490.1335

5. Nazir MA, Almas K. Awareness about the effects of tobacco consumption on oral health and the possibility of smoking behavior among male Saudi schoolchildren. Eur J Dent. 2017;11(1):29-35. https://doi.org/10.4103/ejd.ejd_300_16
6. Mahattanadul S, Mustafa MW, Kuadkaew S, et al. Oral ulcer healing and anti-candida efficacy of an alcohol-free chitosan-curcumin mouthwash. Eur Rev Med Pharmacol Sci. 2018 Oct 1;22(20):7020-7023. https://doi.org/10.26355/eurrev_201810_16173
7. Chen P, Yao H, Su W, et al. Pharmacodynamic and Metabolomics Studies on the Effect of Kouyanqing Granule in the Treatment of Phenol-Induced Oral Ulcer Worsened by Sleep Deprivation. Frontiers in pharmacology. 2020:824. https://doi.org/10.3389/fphar.2020.00824
8. Wen SD, Sans-Serramitjana E, Santander JF, et al. Effects of natural extracts in the treatment of oral ulcers: A systematic review of evidence from experimental studies in animals. Immediate and long-term microshear bond strength of resin-based cements to core build-up materials. J Clin Exp Dent. 2021;13(10):e1038-1048. https://doi.org/10.4317/jced.58567.
9. Abdel-Raheem IT, Khedr NF. Renoprotective effects of montelukast, a cysteinyl leukotriene receptor antagonist, against methotrexate-induced kidney damage in rats. N-S Arch Pharmacol. 2014;387:341–353. https://doi.org/10.1007/s00210-013-0949-x
10. El-Sisi AE, Sokar SS, Salem TA, et al. Role of cysteinyl leukotriene receptor-1 antagonists in treatment of experimentally induced mammary tumor: does montelukast modulate antitumor and immunosuppressant effects of doxorubicin? Toxicol Ind Health. 2015;31:1024–1036. https://doi.org/10.1177/07482337134858
11. Matsuyama M, Hayama T, Funao K, et al. Overexpression of cysteinyl LT1 receptor in prostate cancer and CysLT1R antagonist inhibits prostate cancer cell growth through apoptosis. Oncol Rep. 2007;18:99–104. https://doi.org/10.3892/or.18.1.99
12. Theron AJ, Steel HC, Tintinger GR, et al. (2014) Cysteinyl leukotriene receptor-1 antagonists as modulators of innate immune cell function. J Immunol Res 608930. https://doi.org/10.1155 /2014/608930
13. Kuru S, Kismet K, Barlas AM, et al. The effect of montelukast on liver damage in an experimental obstructive jaundice model. Viszeralmedizin. 2015;31:131– 138. https://doi.org/10.1159/000375434
14. Wu S, Zhu X, Jin Z, et al. The protective role of montelukast against intestinal ischemia-reperfusion injury in rats. 2015;Sci Rep 5:15787. https://doi.org/10.1038 /srep15787
15. Tintinger GR, Feldman C, Theron AJ, et al. Montelukast: more than a cysteinyl leukotriene receptor antagonist?. TheScientificWorldJournal. 2010 Dec 14;10:2403-2413. https://doi.org/10.1100/tsw.2010.229
16. Abdelhady SA, Ali MA, Al-Shafie TA, et al. Montelukast potentiates the antiinflammatory effect of NSAIDs in the rat paw formalin model and simultaneously minimizes the risk of gastric damage. Inflammation Research. 2021 Sep;70(9):981-992. https://doi.org/10.1007/s00011-021-01492-9
17. Takemura M, Niimi A, Matsumoto H, et al. Clinical, physiological and anti-inflammatory effect of montelukast in patients with cough variant asthma. Respiration. 2012;83(4):308-315. https://doi.org/10.1159/000332835
18. Said MM, Bosland MC. The anti-inflammatory effect of montelukast, a cysteinyl leukotriene receptor-1 antagonist, against estradiol-induced nonbacterial inflammation in the rat prostate. Naunyn-Schmiedeberg's archives of pharmacology. 2017 Feb;390(2):197-205. https://doi.org/10.1007/s00210-016-1325-4
19. Halici M, Odabasoglu F, Suleyman H, et al. Effects of water extract of Usnea longissima on antioxidant enzyme activity and mucosal damage caused by indomethacin in rats. Phytomedicine. 2005 Sep 15;12(9):656-662. https://doi.org/10.1016/j.phymed.2004.06.021.
20. Hayes JD, Pulford DJ. The glut athione S-transferase supergene family: regulation of GST and the contribution of the lsoenzymes to cancer chemoprotection and drug resistance part I. Critical reviews in biochemistry and molecular biology. 1995 Jan 1;30(6):445-520. https://doi.org/10.3109/10409239509083491.
21. Idrus E, Pramatama IA, Suniarti DF, et al. Experimental Model of Thermally Induced-Tongue Ulcer in Mice. Journal of International Dental and Medical Research. 2019 Sep 1;12(3):929-934.
22. Kwon YB, Kim HW, Roh DH, et al. Topical application of epidermal growth factor accelerates wound healing by myofibroblast proliferation and collagen synthesis in rat. Journal of veterinary science. 2006 Jun 1;7(2):105-109. https://doi.org/10.4142/jvs.2006.7.2.105.
23. Mammdoh JK, Al-Mashhadanee FA, Al-Moula AD, et al. Effect of Topical Serratiopeptidase on Facial Wound Healing in Rabbit. 2020; 12(6): 284-290
24. Clinical Trial. Effect of taking Montelukast tablets in mouth ulcers. CTRI/2017/11/010522.https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2017/11/010522, 2017 | added to CENTRAL: 31 March 2019 | 2019 Issue 3. 2019;(3).

25. Şener G, Kapucu C, Cetinel S, et al. Gastroprotective effect of leukotriene receptor blocker montelukast in alendronat-induced lesions of the rat gastric mucosa. Prostaglandins Leukotrienes and Essential Fatty Acids. 2005;72(1):1–11. https://doi.org/10.1016/j.plefa.2004.04.005
26. Femiano F, Buonaiuto C, Gombos F, et al. Pilot study on recurrent aphthous stomatitis (RAS): a randomized placebo-controlled trial for the comparative therapeutic effects of systemic prednisone and systemic montelukast in subjects unresponsive to topical therapy. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2010 Mar 1;109(3):402-407. https://doi.org/10.1016/j.tripleo.2009.10.024
27. Aquino TM, Jamora MJ. Primary Idiopathic Complex Aphthosis: Diagnosis and Successful Treatment with Montelukast in a 44-Year-Old Filipino Female. Case Reports in Dermatology. 2020;12(1):12–18. https://doi.org/10.1159/000505475
28. Pu S, Liu Q, Li Y, et al. Montelukast prevents mice against acetaminophen-induced liver injury. Frontiers in pharmacology. 2019:1070. https://doi.org/10.3389/fphar.2019.01070
29. Soltanieh A, Avizeh R, et al. Antioxidant Effect of Montelukast on Acute Lung Injury Induced by Lipopolysaccharide in Dogs. Journal of Babol University of Medical Sciences. 2021 Mar 10;23(1):229-235.
30. Elrashidy RA, Hasan RA. Modulation of autophagy and transient receptor potential vanilloid 4 channels by montelukast in a rat model of hemorrhagic cystitis. Life Sciences. 2021 Aug 1;278:119507. https://doi.org/10.1016/j.lfs.2021.119507.
31. El-shafaei A, Abdelmaksoud R, Elshorbagy A, et al. Protective effect of melatonin versus montelukast in cisplatin-induced seminiferous tubule damage in rats. Andrologia. 2018 Nov;50(9):e13077. https://doi.org/10.1111/and.13077
32. Wafaa K. Abid, Alyaa I. Naser.The efficacy of a new paste formulation as an alternative therapeutic agent for traumatic ulcers.Journal of Taibah University Medical Sciences. 2021;16(5):724-732. https://doi.org/10.1016/j.jtumed.2021.05.005.
33. Kolhe AM, Kale A. Evaluation of analgesic, anti-inflammatory, and antipyretic activity of leukotriene receptor antagonist-montelukast: An experimental study. National Journal of Physiology, Pharmacy and Pharmacology. 2017;7(1):32. https://doi.org/10.5455/njppp.2016.6.0616811072016.