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Mangosteen Peel Extract Increases Transforming Growth Factor-Beta in the Wound Healing Process

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ABSTRACT

Transforming growth factor-beta, obtained from mangosteen peel extract, is one of the natural ingredients that can aid in wound healing. It contains antibacterial and anti-inflammatory properties that help accelerate the inflammatory phase so that the proliferative phase can begin immediately. The anti-inflammatory properties in mangosteen peel can bind to factor-κB receptor activator ligands, which can induce osteoclast formation and bone resorption. This study determined the effect of mangosteen peel extract on transforming growth factor-beta expression after tooth extractions of Wistar rats. Six healthy male Wistar rats weighing 150–200 gm were used in this study. The animals were divided into a control group and a treatment group. Both groups had their teeth extracted, but only the treatment group was given mangosteen peel extract at a dose of 300 mg per-oral, three times a day. Following this, the animals were sacrificed, and a specimen of their mandibles was taken to make immunohistochemical staining using the Novocastra detection system and chromogenic detection. Transforming growth factor-beta expression was calculated by selecting the majority of positive visual fields and observation with the OLYMPUS BX 41 series, DP-70 digital camera, and OLYSIA software. Transforming growth factor-beta expression increased after oral administration of mangosteen peel extract on the extraction wounds of Wistar rats in the treatment group. The results indicate that administration of mangosteen peel extract on the extracted teeth of Wistar rats can increase the expression of transforming growth factor-beta on the third day after extraction.

***Keywords*:** *Mangosteen peel extract, Medicine, Wound healing, TGF-β, Tooth extraction.*

Introduction

In dentistry, tooth extraction is a commonly performed procedure that can cause complications.[1] Complications are influenced by various factors, both local and systemic. Local factors can include careless actions, excessive trauma, and patients disobeying instructions. Systemic factors may include patients with hemorrhagic disorders and patients consuming drugs such as anticoagulants or non-steroidal agents. Extraction wounds can also exacerbate bleeding. The extraction wound will go through four overlapping phases.[2] The first is the hemostasis phase, which occurs minutes to hours after the injury. The inflammatory phase is the second stage, which occurs 1–3 days post-injury. The proliferation phase then occurs between days 4–21, and the remodeling phase between days 21–365.[3,4] TGF-*β* has multiple functions in the process of wound healing, including modulating wound contraction, synthesizing collagen contained in fibroblasts, angiogenesis, and influencing fibroblast proliferation. In addition, TGF-*β* can also produce granulation tissue in wounds, leukocyte chemotaxis, and play a role in the differentiation of fibroblasts into myofibroblasts.[5] Socket preservation is important for aesthetics and to ensure the correct placement of teeth; this aims not to interfere with the treatment of dentures or implants.[6] The preservation of the socket itself aims to maintain soft and hard tissue from the socket after tooth extraction.[7]

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Natural ingredients, such as mangosteen, are necessary to help wound healing. Mangosteen possesses antibacterial and anti-inflammatory properties to help accelerate the time of the inflammatory phase so that the proliferative phase can occur immediately.[8] This anti-inflammatory agent interacts with the factor-kB activator receptor, which can promote the formation of osteoclasts and bone resorption.[9] This beta-factor (TGF-*β*) can stimulate matrix protein synthesis, which plays a role in bone remodeling, cell differentiation, embryonic development, immune function, and hormone secretion.[10] Due to the vital role TGF-*β* plays in wound healing, a study was conducted to determine the expression of TGF-*β* in the wound healing process after Wistar rats were given oral mangosteen peel extract following tooth extraction.

Materials and Methods

Six healthy male Wistar rats aged 2–3 months, weighing between 150–200 gm, were acclimatized for one week. Mangosteen peel extract was obtained in capsule form. Each capsule had a dose of 400 mg/kg BW. The dose for each sample was 300 mg/kg BW dissolved in 10 ml of distilled water and given orally three times a day. Anesthesia was administered with 10% ether by inhalation, and the right lower incisor was extracted using a needle holder and elevator. The extracted wound was left for three days and treated with mangosteen peel extract. On the third day after the tooth extraction of the Wistar rats, specimens in the form of mandibles were taken from the sacrificed Wistar rats. The experimental protocols were approved by the ethics committee, Faculty of Dental Medicine, Universitas Airlangga, with the ethical clearance number 25/KKEPK.FKG/III/2015. These specimens were processed in immunohistochemical preparations. The kit included the Biogear Universal HRP Excell Stain System — Biogear, BDK-HES25, with the Novocastra detection system and chromogenic detection, related to the color that appears when the *slide* reacts with SA-HRP DAB (diaminobenzidine) and H_2O_2. Antibodies used in

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immunohistochemistry were primary antibodies and secondary antibodies labeled with biotin. The procedure to calculate TGF-*β* expression occurred by selecting the majority of positive visual fields. These were then divided into five fields of view in a clockwise direction, and preparations were observed using the OLYMPUS BX 41 series with a DP-70 digital camera and OLYSIA software.

Statistical analysis

Data analysis was conducted using the Kolmogorov-Smirnov test and the test of homogeneity of variances. The Shapiro-Wilk test of normality was 0,240 for the control group and 0,555 for the treatment group, which were both greater than 0.05 ($p > 0.05$). An independent t-test was conducted, which resulted in a significant value of 0.005 ($p < 0.005$). This indicated that there was a significant difference between the control and treatment groups.

Results and Discussions

After the third day of tooth extraction of Wistar rats and treatment with mangosteen peel extract, TGF-β expression in the treatment group increased compared to the control group. This indicates that mangosteen peel extract has the potential to increase TGF-β in wound healing, as shown in Figure 1 and Figure 2. TGF-β is a growth factor that has a role in the wound healing process. TGF-β belongs to the cytokine group, which functions to stimulate the chemotaxis of fibroblasts, inhibit the production of collagen and fibronectin, and inhibit collagen degradation due to an increase or decrease in protease inhibitors. These protease inhibitors are released from the storage sites in the extracellular matrix into the wound microenvironment and secreted by macrophages, fibroblasts, and platelets.[5,11,12]

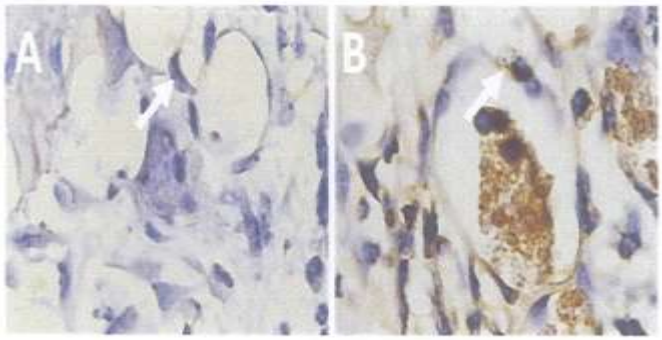

Figure 1: The expression of TGF-β in immunohistochemistry staining (white arrow). A. Control group, B. Treatment Group. Mag. 1000x.

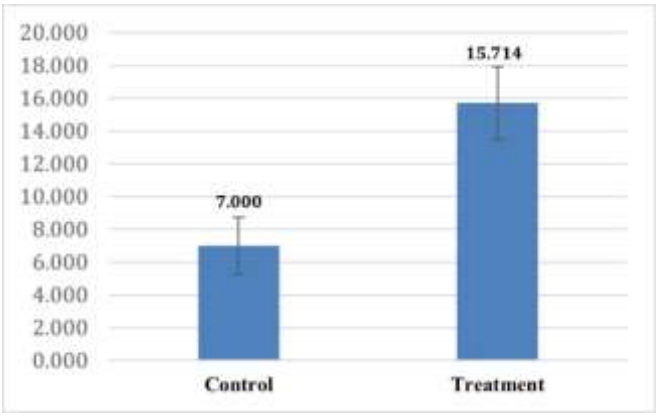

Figure 2: The expression of TGF-*β* in the treatment group after the third day of administration of mangosteen peel extract following the tooth extraction of Wistar rats.

During the wound healing process, several mechanisms can activate TGF-*β*, for example, avb6, which activates TGF-*β*1 by interacting between the inactive complex TGF-*β*1 and Latency Associated Protein (LAP). This integrin activates latent TGF-β1 (L-TGF-*β*1) through a conformational change in the L-TGF-β1 complex, which allows active TGF-*β*1 to be released and interact with its receptor. In addition, TGF-β activation can also be carried out through proteases. In this mechanism, L-TGF-*β*1 and proteinases (MMP-2 and MMP-9) are bound by integrins causing active TGF-β to be cleaved from the inactive form.[13] This enables TGF-*β* to appear and help the wound healing process. In the results of this study, an increase in TGF-*β* was identified in the treatment group after the mangosteen peel extract was administered. This is related to the presence of saponins in the mangosteen peel. Saponins are amphipathic glycosides found in various plant species, such as mangosteen peel.[14] Saponins in mangosteen peel extract can activate the function of TGF-*β* and increase the number of macrophages. These macrophages secrete TGF-*β*, increasing TGF-*β*.[5] This occurs when macrophages interact with microbes and ingest them, resulting in the formation of antigens residing on the outer surface of the plasmalemma. These antigens are recognized by helper T cells. This recognition causes T lymphocytes to release cytokines, such as TGF-β.[15] The role of saponins in TGF-*β* begins when saponins activate and stimulate TGF-*β*. After that, saponins will activate and change the TGF-*β* receptor, resulting in an increase in TGF-β.[16] In addition, the tannin and flavonoid content in mangosteen peel extract can increase the expression of TGF-*β* due to the antioxidant properties of tannins. Flavonoids stimulate the release of TGF-*β*, which can cause the proliferation and migration of fibroblasts to the injured area and synthesize the extracellular matrix.[17,18] Research on the flavonoid content in fruit has found that flavonoids can increase the expression of TGF-*β* after oral administration on the third, fifth, and seventh day of tooth extraction sites of Wistar rats. This is due to the presence of macrophages stimulated by flavonoids, resulting in the increased expression of TGF-*β*.[19] The increase in TGF-*β* following mangosteen peel extract treatment found in this study was also identified in a study examining the effect of alpha mangosteen on the quantity of TGF-*β*1 titter in periodontitis. In the study, alpha mangosteen hydrogel was applied to the entire area of the damaged and sutured *Rattus norvegicus* mandibular bone. After seven days, the results showed an increase in TGF*β*1 titter in the mandibular bone of the treatment group, which was given alpha mangosteen. However, the results of these studies contradict the study of alpha mangosteen on cancer cells. Based on the research, alpha mangosteen (depending on the dose), decreased TGF-*β* mRNA and TGF-*β*R mRNA to inhibit hepatic stellate cell activation.[20,21] Increased TGF-*β* will cause signaling cascades in Smad2, Smad3, and Smad4 phosphorylation to be induced due to the binding between TGF-*β* and type I receptors. Smad2/3/4 will be translocated so that activation and deactivation of transcription factors can be modulated. To promote healing, keratinocyte migration will be enhanced by TGF-*β* after the cell surface receptor is bound by the ligand.[22]

Conclusion

This research concludes that the administration of mangosteen peel extract following tooth extractions of Wistar rats can increase the expression of TGF-*β* on the third day post-extraction.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Rusdy H, Saruksuk ASP, Dalimunte RS, Dohude GA. Effectiveness of betadine (*Jatropha multifida* L.) stem sap on the wound healing after tooth extraction in Sprague-Dawley rats. Padjadjaran J Dentis. 2021; 33(2):145-152.
2. Ellis S, Lin EJ, Tartar D. Immunology of wound healing. Current dermatology reports 2018; 7(4):350-8.
3. Cano SM, Lancel S, Boulanger E, Neviere R. Targeting oxidative stress and mitochondrial dysfunction in the treatment of impaired wound healing: a systematic review. Antioxidants 2018; 7(98):1-14.
4. Yamakawa S and Hayashida K. Advances in surgical applications of growth factors for wound healing. Burns & trauma 2019; 7.
5. Baniasadi B and Evrard L. Alveolar ridge preservation after tooth extraction with DFDBA and platelet concentrates: a radiographic retrospective study. The open dent J. 2017; 11:99.
6. Avila-Ortiz G, Chambrone L, Vignoletti F. Effect of alveolar ridge preservation interventions following tooth extraction: A systematic review and meta-analysis. J Clin Periodontol. 2019; 46:195-223.
7. Putri K, Darsono L, Mandalas H. Anti-inflammatory properties of mangosteen peel extract on the mice gingival inflammation healing process. Padjadjaran Journal of Dentistry 2017; 29(3):190-5.
8. Hong RH, Liang YM, Pan HS, Cheng ZH, Li YH. Alpha-mangostin suppresses receptor activator nuclear factor-κB ligand-induced osteoclast formation and bone resorption in RAW264. 7 cells by inhibiting the extracellular signal-regulated kinase and c-Jun N-terminal kinase signaling. Pharmacogn Mag. 2018; 14(56):390.
9. Kasagi S and Chen W. TGF-beta1 on osteoimmunology and the bone component cells. Cell & Biosci. 2013; 3(1):1-7.
10. Mohamed GA, Al-Abd AM, El-Halawany AM, Abdallah HM, Ibrahim SR. New xanthones and cytotoxic constituents from Garcinia mangostana fruit hulls against human hepatocellular, breast, and colorectal cancer cell lines. J Ethnopharmacol. 2017; 198:302-12.
11. Yuan J, Wu Y, Lu G. α-Mangostin suppresses lipopolysaccharide-induced invasion by inhibiting matrix metalloproteinase-2/9 and increasing E-cadherin expression through extracellular signal-regulated kinase signaling in pancreatic cancer cells. Oncology Letters. 2013; 5(6):1958-64.
12. Pakyari M, Farrokhi A, Maharlooei MK, Ghahary A. Critical role of transforming growth factor beta in different phases of wound healing. Advances in wound care. 2013; 2(5):215-24.
13. Xia J, Chen J, Zhang Z, Song P, Tang W, Kokudo N. A map describing the association between effective components of traditional Chinese medicine and signaling pathways in cancer cells *in vitro* and *in vivo*. Drug discoveries & therapeutics 2014; 8(4):139-53.
14. Arango DG and Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Frontiers in immunol. 2014; 5:491.
15. Chiquet M, Katsaros C, Kletsas D. Multiple functions of gingival and mucoperiosteal fibroblasts in oral wound healing and repair. Periodontol 2000. 2015; 68(1):21-40.
16. Lesmana FL, Rizqiawan A, Mulyawan I, Sumarta NP, Kamadjaja DB, Danudiningrat CP, Kei T, Rurus GD, Sativa NA, Fanddhy RA. The Effect of the Application of (*Garcinia mangostana* L.) towards PDGF-B Expression on Human Gingival Fibroblast Cell Culture After Wound Healing Scratch Test Assay (*In-Vitro* Study). J Inter Dent and Med Res. 2021; 14(4):1413-18.
17. Simandjuntak RM, Soesanto R, Permatasari D. The Effect of Mangosteen Rind on Fibroblasts Proliferation in Wound Healing Process Post Tooth Extraction of Rat. Doctoral dissertation, Repository Unair. 2014.
18. Luthfi M, Yuliati EH, Razak FB, Irmalia WR. The efficacy of okra fruit extract on the expression of transforming growth factor beta 1 in the tooth socket of diabetic Wistar rats. Dental Res J. 2021;18:1-7.
19. Lestari C, Darwin E, Putra DP, Suharti N. The α-mangostin effect on the quantity of TGF-β1 titer relate to the mandibular bone volume of *Rattus novergicus* in the periodontitis model. J Pharmacy & Pharmacog Res. 2021; 9(5):609-18.
20. Rahmaniah R, Yuyuntia Y, Soetikno V, Arozal W, Antarianto RD, Louisa M. Alpha mangostin inhibits hepatic stellate cells activation through TGF-β/Smad and Akt signaling pathways: an in vitro study in LX2. Drug Res. 2018; 68(03):153-8.
21. Hameedaldeen A, Liu J, Batres A, Graves GS, Graves DT. FOXO1, TGF-β regulation and wound healing. International J mol sci. 2014; 15(9):16257-69.

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