INDONESIAN PHYSICIAN FORUM & INDONESIA COLLEGE OF SURGEONS, INDONESIA
Bali Medical Journal
ISSN: 2089-1180, 2302-2914

Denpasar, 16 December 2022

To whom it may concern,

I, as the Editor in Chief of **Bali Medical Journal (BaliMedicalJournal.org) (Indexed by Scopus Elsevier and Web of Science, Clarivate Analytics)**, at this moment declare that:

"Dr. drg. Nanik Zubaidah, M.Kes, Sp.KG(K)"
from Conservative Dentistry Department, Faculty of Dental Medicine,
Universitas Airlangga, Surabaya, Indonesia**.**
Email: (nanik-z@fkg.unair.ac.id**)**
Scopus ID: (https://www.scopus.com/authid/detail.uri?authorId=57200338804)

was indeed a **reviewer** of our Journal with manuscript entitled:
"**Formation of woven bone in orthodontic tooth movement tension areas after giving Mangostin by expression of Runx-2 and IL-10**"

Dr. drg. Nanik Zubaidah, M.Kes, Sp.KG(K) has served her term and still active until **today,** with a degree of thoroughness, and conscientious attention to details. She maintained a willingness to try and held a high drive to learn and be an above average reviewer of the research and special case report in dentistry. She gets along well with other editorial and reviewer board member due to her humble yet broad-minded personality, and she would not hesitate to engage in discussion with other staffs. During her service, she showed an excellent work ethic, able to provide a satisfaction of the articles assigned to her.

Agreed by/Menyetujui:

Menyetujui,
Bali Medical Journal
Prof. Dr. dr. Sri Maliawan, SpBS (K)
Editor in Chief

Menyetujui,
Bali Medical Journal
Prof. Dr. Ir. Ida Bagus Putra Manuaba, MPhil
Associate Editor

Editor Bali Medical Journal

Inbox - Nanik-fkg 08.33

Acknowledgement of Review (#BaliMedJ-3971)

To: nanik-z@fkg.unair.ac.id

Manuscript ID: 3971

Manuscript Title: **Formation of woven bone in orthodontic tooth movement tension areas after giving Mangostin by expression of Runx-2 and IL-10**

Dear Dr. drg. Nanik Zubaidah, M.Kes, Sp.KG(K)

Thank you for reviewing the above-mentioned manuscript for the "**Bali Medical Journal**".

Your contribution is greatly appreciated by the Journal's editorial board and I hope to have your contribution in future as well.

Thank you again.

Editorial Board Member

--

Bali Medical Journal (BaliMedJ)
P-ISSN: 2089-1180
E-ISSN 2302-2914
Indexed at:
Web of Science (WOS) Clarivate Analytics
SCOPUS Elsevier
All Indexing Organisation

ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2022, Volume 11, Number 3: 1956-1962
P-ISSN.2089-1180, E-ISSN: 2302-2914

Formation of woven bone in orthodontic tooth movement tension areas after giving Mangostin by expression of Runx-2 and IL-10

Ida Ayu Arnawati[1*], I Ketut Sudiana[2]

[1]Faculty of Medicine, Universitas Mataram, Mataram, Indonesia
[2]Department of Pathology Anatomy, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

*Corresponding to:
Ida Ayu Arnawati; Faculty of Medicine, Universitas Mataram, Mataram, Indonesia;
arnawati_ia@yahoo.com

Received: 2022-09-08
Accepted: 2022-11-26
Published: 2022-12-20

ABSTRACT

Background: Alveolar bone remodeling is very helpful in orthodontic treatment to prevent relapse after treatment is completed with new bone formation. Using natural materials that have a mechanism of action on the periodontal ligament and alveolar bone as a relapse prevention triggers osteogenesis with the formation of new bone in the tension area so that orthodontic treatment can be achieved maximally. This study aims to determine the formation of woven bone in the area attraction of orthodontic tooth movement after administration of Mangostin

Methods: A total of 30 male Wistar rats were divided into 3 groups, namely a negative control group (K1) without treatment, K2 and K3 a positive control group K(+), K2 a positive control group K(+), which was given a mechanical stressor without Mangostin administration and observed for 7 days, K3 positive control group K(+) which was given a mechanical stressor without Mangostin administration and observed for 14 days, K4 and K5 treatment group (P), K4 treatment group (P) where the group was given a mechanical stressor and Mangostin which was observed for 7 days, K5 the treatment group (P) where the group was given a mechanical stressor and Mangostin which was observed for 14 days. Dara was analyzed using SPSS version 23 for Windows.

Results: It was seen that the administration of Mangostin was very effective in increasing the expression of Runx-2, IL-10 and the formation of woven bone in the area of higher tension than without the administration of Mangostin significantly ($p<0.05$). There was a significant increase ($p<0.05$) of Runx-2 and IL-10 in the treated group compared to the control group on day 7 and day 14, respectively.

Conclusion: The administration of Mangostin effectively prevented orthodontic relapse by increasing the expression of Runx-2 and Il-10 and accelerating the formation of woven bone in the tension area of orthodontic movement.

Keywords: Mangostana, Woven Bone, Runx-2, IL-10, Relapse.
Cite This Article: Arnawati, I.A., Sudiana, I.K. 2022. Formation of woven bone in orthodontic tooth movement tension areas after giving Mangostin by expression of Runx-2 and IL-10. *Bali Medical Journal* 11(3): 1956-1962. DOI: 10.15562/bmj.v11i3.3971

INTRODUCTION

Runt-Related Transcription Factor-2 (Runx-2) or Cbfa can be considered the central control of the osteoblast phenotypic gene. Runx-2 is a marker expressed by osteoblast precursors. Physical and functional interactions between Runx-2 as an osteogenic factor and HIF-1α as an angiogenic factor stimulate VEGF expression in mesenchymal cells.[1]

Alkaline phosphatase released by osteoblasts will increase the apposition process.[2] The vascular changes that occur cause the migration of leukocytes out of the capillaries resulting in an increase in VEGF followed by an acceleration of the average area of woven bone. The increase in VEGF is caused by Hypoxya-Inducible Factor-1g (HIF-1g) which synergizes with Runx-2.[3]

TGF-b1 together with BMP-2 via the Smad pathway, regulates Runx-2. Runx-2 will stimulate Mesenchymal Stem Cells to alter osteoblast progenitors. Runx-2 induces TGF-b1 to stimulate the differentiation and proliferation of osteoblast progenitors to become active osteoblasts and then bone apposition occurs.[4] Runx-2 can also be called an important transcription factor in osteogenic differentiation, which is shown by stimulating the formation of transcriptional genes in osteoblasts, such as osteocalcin.[5]

Orthodontic treatment aims to straighten the arrangement of teeth into the correct position, improve chewing function, facial harmony, aesthetics, oral tissue health, tooth position stability, and move teeth by minimizing adverse effects.[6] Applying orthodontic mechanical force will cause the area around the tooth to be divided into two areas, namely the pressure area and the tension area. In the pressure area, mechanical forces will stimulate osteoclasts to resorption of alveolar bone. After the resorption process is complete, the osteoclasts will undergo apoptosis so that the resorption process stops.[7,8]

In the tension area, osteoblasts are activated to carry out new bone formation (apposition) activities. If the orthodontic mechanical movement is adequate, the resorption and apposition of the alveolar bone are in balance.[9] New bone is formed in the tension area due to forces applied to

orthodontic tooth movement. Osteoblasts differentiate from mesenchymal cell precursors and then mature osteoblasts form osteoid followed by mineralization.[10]

In relapse, conditions such as the original malocclusion before orthodontic treatment were found or the formation of a new malocclusion with a different malocclusion from the previous one with different tooth relations.[11] Relapse occurs because the bone density in the tension area is not optimal, so the material is needed to compact the tension area through the process of osteogenesis. The material is applied to the tension area, which is the site of bone apposition. The optimal apposition of the alveolar bone in orthodontic treatment will accelerate the formation of woven bone to prevent relapse.[11] Woven bone is the earliest form of bone in the embryo and during growth, consists of a network of irregularly shaped collagen. After adulthood Woven Bone is replaced by layered bone or Lamella Bone, which consists of cortical and trabecular bone.[11]

The development of treatment using natural ingredients that are effective as anti-inflammatory and antioxidant is mangosteen peel extract (Garcinia mangostana) which contains Mangostin. The results showed that the mangosteen rind is rich in a nutrient called xanthones. The extracted mangosteen rind contained 95% xanthones, isoflavones, tannins, flavonoids, vitamin c, phenols and anthocyanins, which have high antioxidant activity.[12] Xanthones from mangosteen rind in the form of α-Mangostin and γ-Mangostin have been studied to have strong anti-inflammatory and antitumor effects.[13] The α-Mangostin is the main component (78%) used worldwide as a traditional treatment for anti-inflammatory, antibacterial and anti-cancer.[14] The content of xanthones in the form of α Mangostin and γ Mangostin in mangosteen peel stops inflammation or inflammation by inhibiting prostaglandin synthesis through inhibition of the cyclooxygenase enzyme that causes inflammation.[15]

This study aimed to analyze the effect of Mangostin on orthodontic tension areas in the formation of woven bone through the expression of Runx-2 and IL-10 to prevent relapse through bone apposition.

METHODS

This study used male Wistar rats aged 2-3 months with a body weight of about 250-350 grams using consecutive sampling technique. Furthermore, by random allocation, 30 rats were divided into 3 research groups, namely: 1) the negative control group (K1) as an initial control group that was not treated and only given standard food and sterile distilled water, which was sacrificed on day 8; 2) The positive control group K(+) which was divided into 2 groups namely: a) K2 was the group that was given a mechanical stressor and standard food and CMC without giving Mangostin and sacrificed on day 8 and K3 which is the group that was given a mechanical stressor without giving Mangostin and standard food and CMC and sacrificed on day 15; 3) the treatment group (P) which was divided into: a) K4 was the group given the mechanical stressors, Mangostin, and CMC by the oral probe and sacrificed on day 8; b) K5 which is the group that was given a mechanical stressor and Mangostin and CMC by oral sondage and sacrificed on day 15. *Garcinia mangostana* was a standardized one containing 90% mangostin produced by Xi'an Biof Bio-Technology Co., Ltd (Room 1-1111, High-tech Venture P ark, No.69 Jinye Road Gaoxin District of Xi'an, People Republic of China).

Ni-ti coil spring was placed between the maxillary central incisor and the maxillary right maxillary first molar to move the molars medially with a constant force of 10 g/cm^2. The spring was attached to the first molar and the right maxillary incisor using a stainless steel brace. Light-curing bonding was applied to the perforation created with a round bur along the angle of the line on the medio-lingual and disto-lingual sides of the maxillary first molar and distal side of the incisors to increase retention of the coil springs. Intraperitoneal injection of anesthetic ketamine hydrochloride and acepromazine for ni-ti closed coil spring insertion as a mechanical stressor. Afterward, the three groups of male Wistar rats were sacrificed for immunohistochemical observation by being anesthetized using ketamine and acepromazine then, decapitation and maxillary bone tissue were taken and put in a buffered formalin solution.

The total expression of Runx-2 and IL-10 was observed and counted using a light microscope in 10 fields of view with 400 times magnification with two independent observers. Based on the calculation results, Post-Hoc Tests were conducted, followed by the One way ANOVA test to analyze the differences between groups. Data were analyzed using SPSS version 23 for Windows.

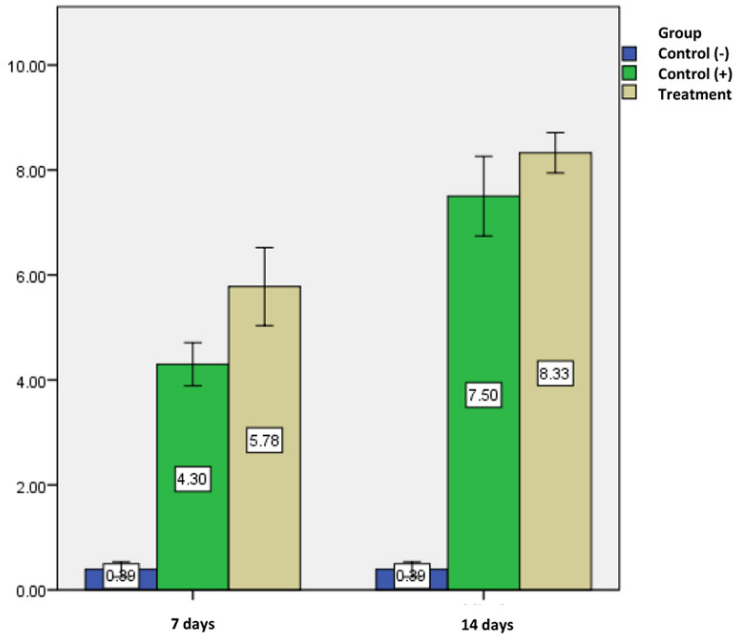

Figure 1. Mean graph and standard deviation of the number of Runx-2 expressions on days 7 and 14

RESULTS

This study showed that the mean total expression of Runx-2 and IL-10 significantly differed between groups. There was a difference in the average number of Runx-2 expressions in the group without Mangostin administration and orthodontic mechanical strength administration with the Mangostin group and orthodontic mechanical strength control group (-) on day 7, control group (+) on day 7 and 14, as well as the treatment group (P) on days 7 and 14. The highest mean amount of Runx-2 expression was found in group P on day 14 (Figure 1).

Figure 1 illustrates that there are differences in the average number of Runx-2 expressions in the group without Mangostin administration and without giving orthodontic mechanical strength with the Mangostin administration group and the orthodontic mechanical strength of the control group (-) on day 7, the control group (+) on the day 7 and 14, control group P on days 7 and 14. The highest number of Runx-2 expressions was found in group P on the 14th day (Figure 1).

Figure 3 illustrates that there are differences in the average number of IL-10 expressions in the group without Mangostin administration and without giving orthodontic mechanical strength with the Mangostin administration group and the orthodontic mechanical strength of the control group (-) on day 7, the control group (+) on the day 7 and 14, control group P on days 7 and 14. The highest number of Runx-2 expressions was found in group P on the 14th day (Figure 3).

Table 1. Mean description, standard intersection (SD), and difference test between groups of Runx-2 expressions in the negative group (K-), positive group (K+), and treatment group (P) with the provision of Mangostin.

Runx-2 Expression (Mean±SD)		p
K1 (0.4±0.1)	K2 (4.3±0.4)	0.000*
	K3 (7.5±0.9)	0.000*
	K4 (5.8±0.8)	0.000*
	K5 (8.3±0.4)	0.000*
K2 (4.3± 0.4)	K3 (7.5±0.9)	0.000*
	K4 (5.8±0.8)	0.000*
	K5 (8.3±0.4)	0.000*
K3 (7.5±0.9)	K4 (5.8±0.8)	0.000*
	K5 (8.3±0.4)	0.018*
K4 (5.8±0.8)	K5 (8.3±0.4)	0.000*

SD: Standard Deviation; *Statistically significant if p-value less than 0.05

DISCUSSION

Mangosteen rind exudes a yellow resin rich in xanthones.[16] Xanthones are polyphenolic compounds with a chemical structure containing an aromatic tricyclic ring. This structure has biological activities such as antioxidant, anti-inflammatory, antibacterial, and anti-cancer.[17] The extracted mangosteen rind contains 95% xanthones, isoflavones, tannins, flavonoids, vitamin c, phenols, and anthocyanins, which have high antioxidant activity.[12] The a-Mangostin is the main xanthone found

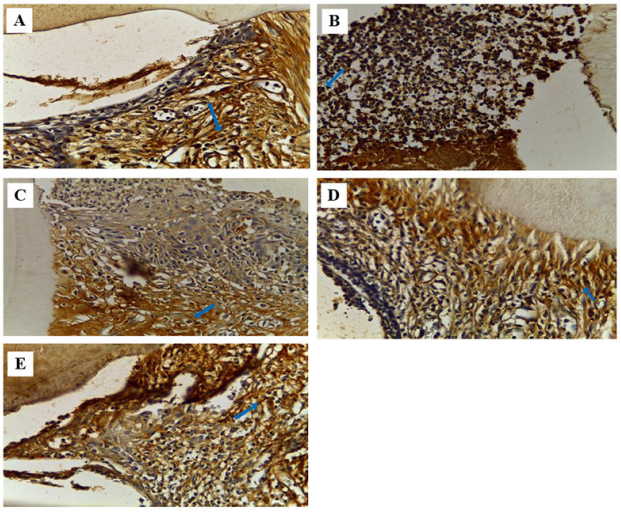

Figure 2. Expression of Runx-2 in alveolar bone osteoblasts (brownish) marked with a blue arrow. A) Negative control group (K-); B) Positive control group (K+); C) Treatment group (P) with Mangostin administration on day 7; D) Positive control group (K+); E) Treatment control group (P) with the provision of Mangostin on day 14 with 400 times magnification.

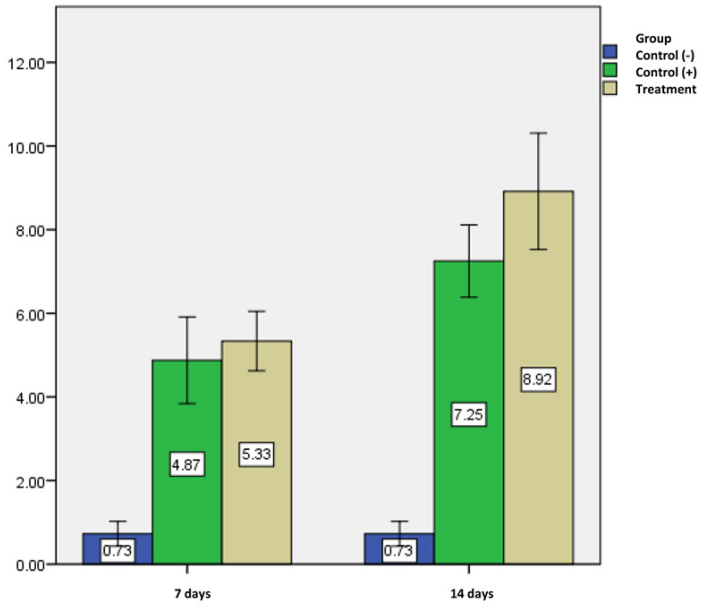

Figure 3. The mean number of IL-10 expressions on days 7 and 14, respectively.

in Mangosteen peel (level 78%) and is used worldwide for traditional medicine as an anti-inflammatory, antibacterial and anti-cancer.[14]

The study group given Mangostin had a significant difference where the highest Runx-2 expression was seen on day 14 compared to the control group (negative control) and the group not given Mangostin (positive control group). This is because mangosteen rind extract (*Garcinia mangostana*) is rich in xanthones, especially a-Mangostin and γ -Mangostin, as an anti-inflammatory that plays a role in inhibiting the production of Cyclooxygenase (COX) enzymes which are the cause of inflammation.[18] Research on rat glioma cells on the in vitro anti-inflammatory activity of γ-Mangostin against the synthesis of Prostaglandin-Estradiol-2 (PGE2) and Cyclooxygenase (COX), which are mediators of inflammation. In in vitro enzymatic experiments, this compound inhibited the activity of COX-1 and COX-2. Wherein γ -Mangostin inhibited lipopolysaccharide-induced COX-2 protein and mRNA expression.[15] Increased COX-2 will increase the synthesis of PGE2. Increased synthesis of PGE2 will increase vasodilation and permeability of the endothelium, increasing inflammatory cell infiltration. In the group given Mangostin, COX-2 decreased, reducing the inflammatory process because γ-Mangostin inhibited the expression of MAPK, NF-Kb and AP-1 in macrophages. COX-2 inhibition can decrease proinflammatory cytokines (IL-1 and TNF-a).[18,19] By decreasing levels of IL-1 and TNF-a, the inflammatory process and cellular responses involved in inflammation and immune regulation can be inhibited so that the process of endothelial dysfunction can be prevented where IL-1 and TNF-a are stimuli for NF-Kb activation, which further inhibits the formation of NF-Kb osteoclasts through RANK, which leads to inhibition of osteoclast formation through RANKL so that there is no differentiation and formation of osteoclasts and decreases the process of osteocalcin which results in increased osteoblast formation. Likewise, the content of a-Mangostin reduces the induction of lipopolysaccharide (LPS) on the synthesis of proinflammatory cytokines TNF-a and IL-4 by inhibiting the expression of the oncostatin M gene in the MAPK pathway in U937 cell culture.[19] Mangostin contained in mangosteen peel extract will activate osteoprogenitor

Table 2. The difference test between groups of IL-10 expressions in the negative group (K-), positive group (K +), and treatment group (P) with the administration of Mangostin.

IL-10 Expression (Mean±SD)		P
K1 (0.7±0.3)	K2 (4.9±1.1)	0.000*
	K3 (7.2±0.9)	0.000*
	K4 (5.3±0.8)	0.000*
	K5 (8.9±1.3)	0.000*
	K3 (7.2±0.9)	0.000*
K2 (4.9±1.1)	K4 (5.3±0.8)	0.003*
	K5 (8.9±1.3)	0.000*
K3 (7.2±0.9)	K4 (5.3±0.8)	0.000*
	K5 (8.9±1.3)	0.004*
K4 (5.3±0.8)	K5 (8.9±1.3)	0.000*

SD: Standard Deviation; *Statistically significant if p-value less than 0.05

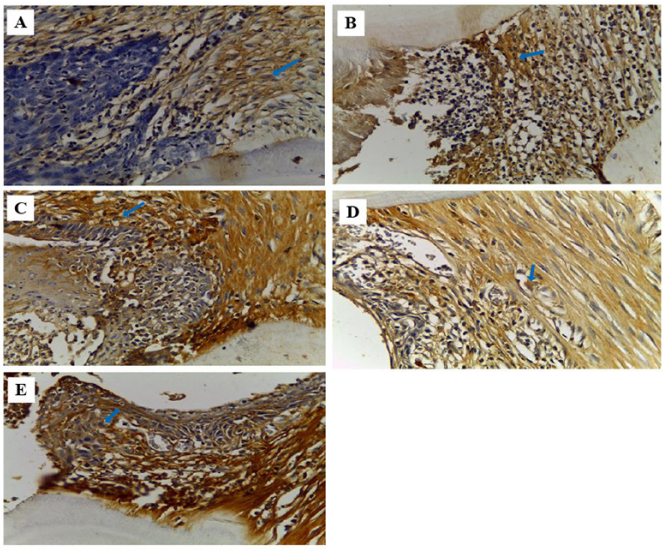

Figure 4. IL-10 expression in alveolar bone osteoblasts (brownish) marked with blue arrows. A) Negative control group (K); B) Positive control group (K +); C) Treatment group (P) with Mangostin administration on day 7; D) Positive control group (K +); E) Treatment control group (P) with the provision of Mangostin on day 14 with 400 times magnification.

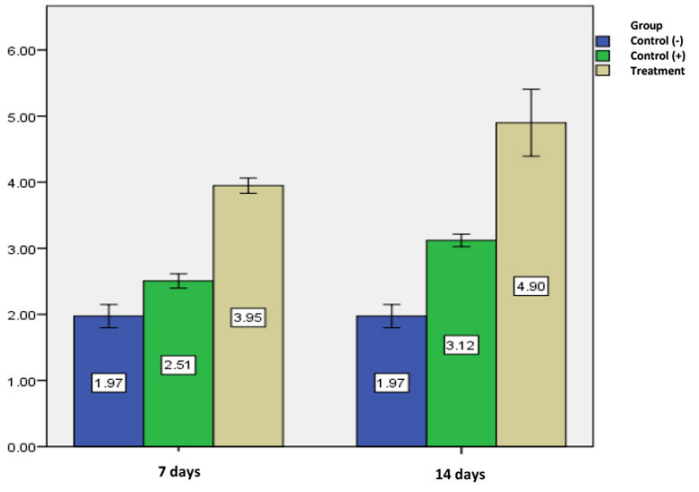

Figure 5. The number of Woven bone expressions between K (-), K (+), and treatment group (P) with the administration of Mangostin on day 7 and day 14.

cells from osteoblast cells to become osteochondral progenitors, which convert Runx-2 and Osterix and catenin into pre-osteoblasts which then form ALP and Collagen type 1. Runx-2 here is an important transcription factor in bone formation.[18,19]

The administration of Mangostin on day 14 in the treatment group increased IL-10 expression in osteoblasts in the tension area. Giving orthodontic mechanical movement in the area of tension will increase Osteoprogesterin (OPG). In addition, the administration of Mangostin in orthodontic tension areas increases IL-10 expression by inhibiting proinflammatory mediators from macrophages, thereby inhibiting the secretion of proinflammatory cytokines, where Mangostin, which contains xanthone compounds as an anti-inflammatory, inhibits Nitric Oxide (NO), Prostaglandin E (PGE) production, and suppresses COX-2 thereby suppressing TNF-a, and IL-1b.[20,21]

Table 3. The difference of woven bone expressions in the negative group (K-), positive group (K+), and treatment group (P) with the provision of Mangostin.

Woven Bone Expression (Mean±SD)		p
K1 (2.0±0.2)	K2 (2.6±1,1)	0.000*
	K3 (3.1±0,1)	0.000*
	K4 (4.0±0,1)	0.000*
	K5 (4.9±0.5)	0.000*
K2 (4.9±11)	K3 (3.1±0.1)	0.000*
	K4 (4.0±0.1)	0.003*
	K5 (4.9±0.5)	0.000*
K3 (3.1±0.1)	K4 (4.0±0.1)	0.000*
	K5 (4.9±0.5)	0.004*
K4 (4.0±0.1)	K5 (4.9±0.5)	0.000*

SD: Standard Deviation; *Statistically significant if p-value less than 0.05

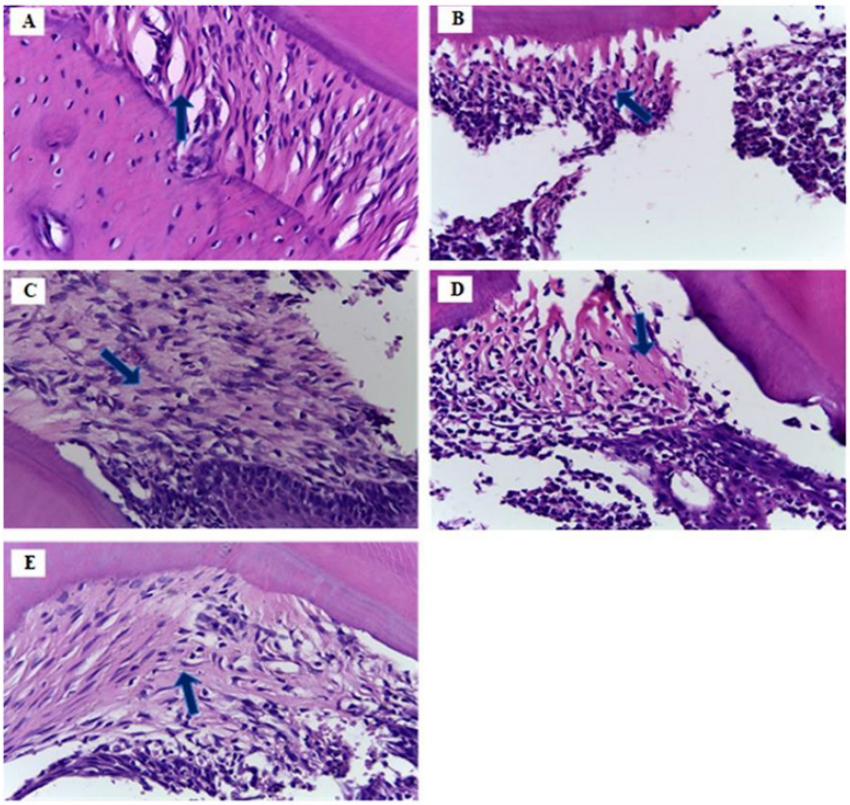

Figure 6. The HE examination results show the woven bone area in each hematoxylin group. A) Negative control group (K-); B) Positive control group (K+) 7 days; C) Positive control group (K+) 14 days; D) Treatment group (P) given mangostana extract on day 7; E) The treatment group (P) was given mangostana extract on day 14, as shown in the picture that presents woven bone on day 7 and day 14 osteoblasts marked with blue arrows.

The content of Mangostin, especially γ-Mangostin found in mangosteen peel extract as an anti-inflammatory in cyclooxygenase activity, can inhibit the convention of aradiconic acid to PGE2 thereby inhibiting IKB kinase inhibitor activity and activate NF-Kb thereby reducing the activity of inflammatory cells increase type 1 collagen as an osteoblast forming so that it can accelerate bone formation.[15]

Various studies indicate Osterix (Osx) triggers Runx-2 precursors to become osteoblasts by expressing the osteoblast gene.[22] Bone formation in orthodontic tooth movement results from osteoblast differentiation controlled by Core Binding Factor Alpha-1 (Cbfa-1) and Osterix genes.[22,23] Cbfa-1, known as Runx-2, is the earliest expressed marker by osteoblasts and is associated with bone formation. Osterix is an advanced transcription factor that induces osteoblasts to produce osteocalcin genes that control osteoblast differentiation through an inhibitory effect.[23] It can be concluded that the administration of Mangostin on the movement of orthodontic teeth in the tension area can increase the formation of osteoblasts, thereby reducing the formation of osteoclasts. This study showed that Runx-2 is the main transcription factor in osteogenesis.

The results showed that Runx-2 in the pulling area of orthodontic tooth movement on the 7th day with Mangostin administration would increase Runx-2. In contrast, on the 14th day, there was no significant increase or difference in Runx-2. On day 14, Runx-2 will stop differentiating while Osterix will increase to become

osteocytes. The decrease in Runx-2 on day 14 was due to Runx-2 being the earliest expressed transcription factor associated with bone formation.[24] In this study, on day 14, Osterix showed an increase, but there was no significant difference. This is because the administration of Mangostin can increase the formation of type 1 collagen as an osteoblast, so Osterix also increases and accelerates bone formation.

The results showed that on the 7th day of administration of Mangostin in the orthodontic tooth pull area, there was an increase in Il-10, but the increase in IL-10 did not increase Woven bone. On the 7th day of periodontal tissue given, Mangostin also induces an increase in IL-10, but the increase in IL-10 has not been able to induce or suppress inflammation, so the Woven bone has not experienced repair or growth of Woven bone. On the 14th day of administration of Mangostin, there will be an increase in IL-10, which induces an increase in Runx-2 and Osterix. Improved Runx-2 and Osterix will increase Woven bone formation. If the remodeling time is longer, it is possible to increase osterix and decrease Runx-2 so that the woven bone is mature and osteocytes are formed.

IL-10 is a cytokine produced by activating macrophages and helper T cells.[25] IL-10 is a potent anti-inflammatory cytokine, suppressing the expression of inflammatory cytokines such as TNF-a, IL-6, and IL-1 by activating macrophages.[25] IL-10 inhibits the proliferation and synthesis of CD4+ T cells, including the production of IL-2 and IFN-g by Th1 and IL-4 and IL-5 by Th2. IL-10, together with Transforming Growth Factor-b (TGF-b), acts as a cytokine synthesis inhibitory factor and as a major immunoregulator capable of limiting excessive inflammation, increasing the adaptive immune response that increases the number of CD4+ T cells expressing IL-10 and TGF-b. IL-10 inhibits the release of proinflammatory mediators from monocytes/macrophages, inhibiting the LPS and IFN-g induced secretion of TNF-a, IL-6, IL-1, IL-8, G-CSF and GM-CSF.[25]

The results of the analysis showed that administration of mangostana extract in orthodontic tension areas increased IL-10 expression by inhibiting proinflammatory mediators from macrophages, thereby inhibiting the secretion of proinflammatory cytokines where mangostana extract containing xanthones as anti-inflammatory compounds inhibited nitric oxide (NO), prostaglandin E (PGE) production, and suppress COX-2 expression thereby suppressing TNF-a and IL-1b.[20]

The results showed that the administration of Mangostin on day 14 in the formation of Woven bone in the treatment group was greater than the negative control group and the positive control group. In the positive control group, the formation of Woven bone was greater than in the negative control group. This shows that Mangostin, which contains xanthones, can reduce TNF-a, IL-1b, IL-6, IL-8, MCP, and TLR. The γ-mangostin will inhibit proinflammatory cytokines and PGE2, which will inhibit the formation of osteoclasts through RANKL and increase OPG in the orthodontic tooth pull area so that there is no differentiation of osteoclasts.[26] OPG is here as a RANKL receptor that competes with RANK to bind and avoid interaction with RANK, resulting in the inhibition of the osteoclastogenesis process, thereby increasing the formation of osteoblasts and stimulating the process of osteogenesis.[26] Increased woven bone formation on mangostin administration was indicated by inhibiting proinflammatory cytokines and osteogenic potential in osteoblasts characterized by increased mineralization and bone formation.

CONCLUSION

The administration of Mangostin was very effective in preventing orthodontic relapse by increasing the expression of Runx-2 and Il-10 and accelerating the formation of woven bone in the tension area of orthodontic movement.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICS

Ethics approval was obtained from the Ethics Committee, Faculty of Medicine, Universitas Mataram, Mataram, Indonesia, before the study was conducted.

FUNDING

The authors are responsible for the study's funding without the involvement of grants, scholarships, sponsorships, or any other funding sources.

AUTHOR CONTRIBUTION

All authors equally contribute to the study from the conceptual framework, data acquisition, data analysis, until reporting the results of study through publication.

REFERENCES

1. Lee W, Eo SR, Choi JH, Kim YM, Nam MH, Seo YK. The Osteogenic Differentiation of Human Dental Pulp Stem Cells through G0/G1 Arrest and the p-ERK/Runx-2 Pathway by Sonic Vibration. Int J Mol Sci. 2021;22(18):10167.
2. Andrade Jr I, Taddei SRA, Souza PEA. Inflammation and Tooth Movement: The Role of Cytokines, Chemokines, and Growth Factor. Seminars in Orthodontics. 2012;18(4):257-269.
3. Orth M, Shenar AK, Scheuer C, Braun BJ, Herath SC, Holstein JH, et al. VEGF-loaded mineral-coated microparticles improve bone repair and are associated with increased expression of epo and RUNX-2 in murine non-unions. J Orthop Res. 2019;37(4):821-831.
4. Luo XH, Liao EY, Su X. Progesterone upregulates TGF-b isoforms (b1, b2, and b3) expression in normal human osteoblast-like cells. Calcif Tissue Int. 2002;71(4):329-334.
5. Prall WC, Haasters F, Heggebö J, Polzer H, Schwarz C, Gassner C, et al. Mesenchymal stem cells from osteoporotic patients feature impaired signal transduction but sustained osteoinduction in response to BMP-2 stimulation. Biochem Biophys Res Commun. 2013;440(4):617-622.
6. Sharif MO, Waring DT. Contemporary orthodontics: the micro-screw. Br Dent J. 2013;214(8):403-408.
7. Henneman S, Von den Hoff JW, Maltha JC. Mechanobiology of tooth movement. Eur J Orthod. 2008;30(3):299-306.
8. Park HJ, Baek KH, Lee HL, Kwon A, Hwang HR, Qadir AS, et al. Hypoxia inducible factor-1α directly induces the expression of receptor activator of nuclear factor-κB ligand in periodontal ligament fibroblasts. Mol Cells. 2011;31(6):573-578.
9. Nimeri G, Kau CH, Abou-Kheir NS, Corona R. Acceleration of tooth movement during orthodontic treatment--a frontier in orthodontics. Prog Orthod. 2013;14:42.
10. Sprogar S, Vaupotic T, Cör A, Drevensek M, Drevensek G. The endothelin system mediates bone modeling in the late stage of orthodontic tooth movement in rats. Bone. 2008;43(4):740-747.
11. Lilley J, Walters BG, Heath DA, Drolc Z. In vivo and in vitro precision for bone density measured by dual-energy X-ray absorption. Osteoporos Int. 1991;1(3):141-146.

12. Priya V, Jainu M, Mohan SK, Saraswati P, Gopan CS. Antimicrobial activity of pericarp extract of garcinia mangosatan linn. International Journal of Pharma Sciences and Research. 2010;1(8):278-281.
13. Jiang DJ, Dai Z, Li YJ. Pharmacological effects of xanthones as cardiovascular protective agents. Cardiovasc Drug Rev. 2004;22(2):91-102.
14. Yodhnu S, Sirikatitham A, Wattanapiromsakul C. Validation of LC for the determination of alpha-mangostin in mangosteen peel extract: a tool for quality assessment of Garcinia mangostana L. J Chromatogr Sci. 2009;47(3):185-189.
15. Nakatani K, Atsumi M, Arakawa T, Oosawa K, Shimura S, Nakahata N, et al. Inhibitions of histamine release and prostaglandin E2 synthesis by mangosteen, a Thai medicinal plant. Biol Pharm Bull. 2002;25(9):1137-1141.
16. Akao Y, Nakagawa Y, Nozawa Y. Anti-cancer effects of xanthones from pericarps of mangosteen. Int J Mol Sci. 2008;9(3):355-370.
17. Nakagawa Y, Iinuma M, Naoe T, Nozawa Y, Akao Y. Characterized mechanism of alpha-mangostin-induced cell death: caspase-independent apoptosis with release of endonuclease-G from mitochondria and increased miR-143 expression in human colorectal cancer DLD-1 cells. Bioorg Med Chem. 2007;15(16):5620-5628.
18. Jung HA, Su BN, Keller WJ, Mehta RG, Kinghorn AD. Antioxidant xanthones from the pericarp of Garcinia mangostana (Mangosteen). J Agric Food Chem. 2006;54(6):2077-2082.
19. Liu SH, Lee LT, Hu NY, Huange KK, Shih YC, Munekazu I, et al. Effects of alpha-mangostin on the expression of anti-inflammatory genes in U937 cells. Chin Med. 2012;7(1):19.
20. Lee JW, Juliano R. Mitogenic signal transduction by integrin- and growth factor receptor-mediated pathways. Mol Cells. 2004;17(2):188-202.
21. Indharty S, Japardi I, Siahaan AMP, Tandean S. Mangosteen extract reduce apoptosis via inhibition of oxidative process in rat model of traumatic brain injury. Bali Medical Journal. 2019;8(1):227-232.
22. Nakashima K, Zhou X, Kunkel G, Zhang Z, Deng JM, Behringer RR, et al. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. Cell. 2002;108(1):17-29.
23. Tanaka S, Matsuzaka K, Sato D, Inoue T. Characteristics of newly formed bone during guided bone regeneration: analysis of cbfa-1, osteocalcin, and VEGF expression. J Oral Implantol. 2007;33(6):321-326.
24. Karsenty G. The complexities of skeletal biology. Nature. 2003;423(6937):316-318.
25. Niikura M, Inoue S, Kobayashi F. Role of interleukin-10 in malaria: focusing on coinfection with lethal and nonlethal murine malaria parasites. J Biomed Biotechnol. 2011;2011:383962.
26. Rucci N. Molecular biology of bone remodelling. Clin Cases Miner Bone Metab. 2008;5(1):49-56.