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*Original Research Article*

# Therapeutic Impact of *α*-Mangostin and Hyperbaric Oxygen on Alveolar Bone Cell Activity and MMP-8 Expression

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ABSTRACT

Orthodontic treatment often involves tooth retraction involving the alveolar bone. Metalloproteinase-8 (MMP-8) protein, osteoblast cells, and osteoclasts are indicators of bone remodeling. Combining *α*-mangostin and hyperbaric oxygen therapy can improve bone repair after orthodontic retraction. To assess the alveolar cell bone and MMP-8 expression for bone remodeling in endodontic retraction after *α*-mangostin administration and hyperbaric oxygen therapy. A total of 25 model animals were subjected to short (orthodontic) elastomeric chain retraction for 28 days. Then, osteoblast and osteoclast bone cells were treated with H and E staining and MMP-8 protein with immunohistochemistry. The *α*-mangostin therapy or combination with hyperbaric oxygen therapy was a significant increase in the number of osteoblasts (p=0.010) and osteoclasts (p=0.021), as well as MMP-8 expression (p=0.038) in the treatment group. There was a strong and significant positive correlation between the number of osteoblasts and osteoclasts (r=0.803, p= 0.012), osteoclasts and MMP-8 (r=0.973, p=0.021), and osteoblasts and MMP-8 (r=0.82, p=0.041). The *α*-mangosteen, hyperbaric oxygen, and combination therapy showed the ability to improve alveolar bone repair initiated by an increase in osteoblast cells and a decrease in osteoclast cells in line with the response of MMP-8 protein.

***Keywords:*** *α*-Mangostin**,** Hyperbaric Oxygen, Metalloproteinase-8, Bone cells, Orthodontic retraction.

## Introduction

In orthodontic practice, tooth retraction is a routine procedure that significantly impacts the structure and health of the alveolar bone. This process moves the teeth to an ideal position and triggers complex biological responses in the alveolar bone, including adaptation and regeneration.[1] The ability of bones to adapt and regenerate is essential for the success of long-term orthodontic treatment. Tooth retraction causes changes in the alveolar bone, with resorption on one side and the formation of new bone on the other, known as bone remodeling.[2] This process relies heavily on balance between the activity of osteoblasts, which form bones, and osteoclasts, which play a role in bone resorption.[3] The MMP-8 protein is essential in remodeling alveolar bone, especially in orthodontic retraction.[4] This process, which involves the mechanical movement of teeth and biological transformation at the microscopic level, relies heavily on the interaction between growth factors, enzymes, and cells that regulate resorption and bone formation.[5]

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Recent research has explored innovative therapies to support alveolar bone regeneration. One interesting approach is using *α*-mangosteen, a bioactive compound from mangosteen, combined with hyperbaric oxygen therapy.[6] This combination shows potential in promoting bone healing and regeneration, likely through modulation of the expression of essential proteins involved in bone formation and remodeling. [7] Hyperbaric oxygen therapy is an essential innovation in orthodontics and tissue regeneration. [8] Applying *α*-Mangostin in oral cavity therapy has been applied to aphthous stomatitis. [9] *α*-Mangostin shows excellent potential in bone healing with its anti-inflammatory and antioxidant properties that reduce oxidative stress and inflammation,[10] as well as stimulating the proliferation and differentiation of osteoblasts and inhibiting osteoclastogenesis.[11] Meanwhile, hyperbaric oxygen therapy (HBOT) increases oxygen supply, promotes angiogenesis, reduces inflammation and edema, and improves bone growth factors.[12] This approach promises to increase the speed of healing and regeneration of alveolar bone after tooth retraction by increasing the expression of proteins involved in bone remodeling and maintaining a balance between osteoblasts and osteoclasts. The synergistic effect of these two therapies provides more advantages than their separate use, opening up opportunities for developing new treatment protocols that can be applied in orthodontic practice and contributing to developing bone and soft tissue regeneration methods. Therefore, this study evaluated the synergistic effects of *α*-mangostin and hyperbaric oxygen therapy in protein regeneration in alveolar bone after orthodontic retraction based on MMP-8 expression and osteoblast and osteoclast cells in animal models.

## Materials and Methods

The research was approved by the Ethics Commission of Universitas Padjajaran, Bandung, Indonesia, reference number 317/UN6.KEP/EC/2023. A total of 25 mice were subjected to orthodontic retraction. They were divided into five groups and were treated with hyperbaric oxygen therapy or α-mangostin as follows; Positive Control Group (C+): retraction was carried out, elastomeric chain, short was applied for 28 days), Negative Control Group (C-): no treatment/normal), Group 1: orthodontic retraction during 28 days, then administered α-mangostin, Group 2: orthodontic retraction was carried out for 28 days, on days 19-28 hyperbaric oxygen therapy was given, and Group 3: retraction was carried out for 28 days, on day 1-28 α-mangostin and on days 19-28, hyperbaric oxygen therapy was administered.

*Orthodontic animal models*

The animal model was acclimatized for 14 days before starting preparation for orthodontic treatment. The animals were anesthetized intramuscularly using ketamine at a dose of 50 mg/kg BW, then weighed to ensure an ideal weight of between 250-300 g. Thereafter, the orthodontic device was installed with an elastomeric chain short that provides a 10 g/mm² pressure. Furthermore, hydrogel *α*-mangostin 2% (from the Sumatra Biota Laboratory, Andalas University, Padang, West Sumatra, Indonesia) was applied to the alveolar bone resorption area of Wistar rats. The 0.1 mL gel applied to the alveolar cavity and bone is expected to trigger the proliferation and differentiation of bone cells. After using the *α*-mangosteen hydrogel, the area was left for 30-60 seconds to ensure gel absorption. Thereafter, hyperbaric oxygen therapy was administered at a pressure of 2.4 ATA for 3x30 min per session with a water rest period of 5 min, performed in a hyperbaric chamber for ten days. The selection of oxygen pressure was carried out at 2.4 ATA.[13]

*Histopathological assessment*

Mice that had undergone therapy for 28 days were euthanized with an overdose of 0.8 mL of 10% Ketamine and 0.2 mL of Xylazine injected intramuscularly into the right thigh. The mandibular incisors were extracted, cleaned with 0.9% NaCl, and fixed in a buffered solution of 10% formalin and 10% EDTA (Sigma-Aldrich Merck, Darmstadt, Germany). This solution was changed daily for approximately two months until the specimen was soft enough to be cut. Then, it was put in liquid paraffin at a temperature of 48°C to form a paraffin block. Sections, cut mesiodistally parallel to the long axis of the tooth with a thickness of 4–6 μm using a microtome, were stained with Hematoxylin Eosin (Sigma-Aldrich Merck, Darmstadt, Germany) and mounted on slides. The stained sections were observed under a light microscope at 400x magnification to count osteoblasts and osteoclasts with the average number of cells per square millimeter.[14]

*Immunohistochemical staining*

On the 28th day after the release of the orthodontic device, the euthanized rats was given a lethal dose combination of ketamine and acepromazine 1:1 (0.05 mg/kg BW). This euthanasia process was followed by the decapitation of the head of the upper jaw, including its teeth. To produce cell slides and study the expression of MMP-8, a transverse dorso-ventral cross-section was cut in the middle of the pull-side alveolar bone (mesial). The maxillary alveolar bone specimen was fixed with a 10% formalin buffer solution. Decalcification dissolves calcium in the alveolar bone to cut the tissue properly. This process lasted for 30 days with EDTA at room temperature, and the solution was changed daily until the tissue becomes soft. The was followed by histological preparations by cutting with a microtomes and immunohistochemistry (IHC) staining was done to measure MMP-8 expression.[15] In examining the expression of MMP-8, an immunohistochemical method with monoclonal antibodies (Abcam, Abcam Limited**,** Cambridge, UK ) was used. Each part of the preparation is then observed and evaluated for size. The photo-making of the preparation was carried out and replicated three times in the viewing area with a 400x magnifying light microscope (Olympus, Industrial Technology Co., Ltd, Guangzhou, China).[16]

*Statistical analyses*

Data from MMP-8 expression of alveolar bones was analysed by Kruskal Wallis Test and the Spearman rho correlation test. While data from osteoblast and osteoclast cell were analysed using One-way ANOVA with Pearson correlation. The value of $p<0.05$ was regarded as significant, while a strong correlation was set at coeffecient limit of $r=1$.

## Results and Discussion

This study explores the therapeutic impact of *α*-mangostin and hyperbaric oxygen therapy on bone cell activity and MMP-8 expression during orthodontic retraction. The results showed that these two interventions contributed significantly to the remodeling of alveolar bones. *α*-Mangostin, as a bioactive compound, plays a role in reducing inflammation and increasing osteoblast activity.[17] Hyperbaric oxygen therapy increases tissue oxygenation, accelerates healing, and supports the balance between osteoblasts and osteoblasts.[18] The combination of *α*-mangostin and hyperbaric oxygen therapy synergizes, enhancing bone remodeling and promoting alveolar tissue regeneration. *α*-Mangostin, a compound from mangosteen peel, has anti-inflammatory and antioxidant properties that positively influence bone remodeling,[19] such as hexanoic acid, which also acts as an antioxidant.[20] Hyperbaric oxygen therapy increases tissue oxygenation and accelerates healing. Together, they enhance osteoblast activity, reduce osteoclast activity, and decrease MMP-8 levels, reducing extracellular matrix degradation and contributing to tissue stability during tooth movement. In remodeling alveolar bones, especially during orthodontic retraction, MMP-8 is crucial.[21] This process involves more than just shifting gears; a biological transformation at the microscopic level relies on complex interactions between growth factors, enzymes, and cells that regulate resorption and bone formation.[22] MMP-8 is involved in bone resorption that outlines the extracellular matrix, essential for bone remodeling per changes in tooth position.[23]

*Measured cell bone response*

Table 1 presents the variations in osteoblast numbers across different treatment groups. The positive control group (C+) undergoing 28 days of orthodontic retraction had an average osteoblast count of 35.96 mm², higher than the negative control group (C-) with 32.22 mm², suggesting increased osteoblast activity due to retraction. Group G1, given *α*-mangostin after retraction, showed a mild inhibitory effect with 30.36 mm², still lower than the positive control but higher than the negative control. Group G2, receiving hyperbaric oxygen therapy from days 19 to 28, had the highest osteoblast count at 43.82 mm², indicating a significant increase in osteoblast activity. Group G3, with combined *α*-mangostin and hyperbaric oxygen therapy, had 30.08 mm², showing no significant synergistic effect over hyperbaric oxygen therapy alone.

**Table 1:** Profile of osteoblast cells of alveolar bone *Rattus novergicus* undergoing orthodontic retraction with short elastomeric chain

| Treatment Group | N | Osteoblast (mm²) | | | *p-value** |
|---|---|---|---|---|---|
| | | Mean | SD | Frequency | |
| C+ | 5 | 35.96 | 2.42 | 21% | |
| C- | 5 | 32.22 | 4.36 | 19% | |
| G1 | 5 | 30.36 | 1.20 | 18% | 0.010 |
| G2 | 5 | 43.82 | 2.59 | 25% | |
| G3 | 5 | 30.08 | 1.28 | 17% | |

* One-way ANOVA

One Way ANOVA confirmed substantial differences (p-value < 0.05) among the groups, highlighting the potential of hyperbaric oxygen therapy in enhancing osteoblast activity during orthodontic treatment. The quantity of osteoblast cells in the positive control is higher than in the negative (normal) control group. These findings are consistent with previous research that suggests that mechanical stress during orthodontic tooth movement stimulates osteoblastic activity and contributes to bone remodeling.[24] In the G1 group, which was given *α*-mangostin despite a mild inhibitory effect compared to the positive control, this result was still higher than the negative control, suggesting that *α*-mangostin may have an anti-inflammatory effect that moderately limits osteoblastic activity.[25] In contrast, the G2 group, which underwent retraction and was given hyperbaric oxygen therapy, showed the highest increase in osteoblasts. This supports previous research showing that hyperbaric oxygen can improve bone healing by increasing osteoblast proliferation and angiogenesis.[26] The G3 group, which received a combination of *α*-mangostin and hyperbaric oxygen therapy over the same period, was slightly lower than G1. These results suggest that the combination of therapies does not have a more significant synergistic effect than hyperbaric oxygen therapy alone, possibly because the interaction between the two therapies does not fully support increased osteoblastic activity. These findings confirm that hyperbaric oxygen therapy has significant potential in supporting orthodontic care through increased osteoblastic activity, which is important for effective bone remodeling during orthodontic retraction, supported by previous literature.[27] Table 2 presents the profile of osteoclast cells in the alveolar bone of Rattus norvegicus undergoing orthodontic retraction with a short elastomeric chain. The positive control group (C+) experienced a significant increase in osteoclast activity with an average count of 41.38 mm², while the negative control group (C-) showed normal conditions with an average of 27.58 mm². Group G1, which received *α*-mangostin after 28 days of retraction, had a reduced osteoclast activity average of 30.30 mm². Group G2, given hyperbaric oxygen therapy from days 19 to 28, had an average count of 40.08 mm², indicating a slight reduction in osteoclast activity compared to C+. Group G3, receiving both *α*-mangostin and hyperbaric oxygen therapy, showed a further decrease with an average of 30.08 mm². Statistical analysis using One-way ANOVA confirmed significant differences in osteoclast activity across treatment groups. This highlights that *α*-mangostin and hyperbaric oxygen therapy effectively lower bone resorption during orthodontic treatment.

**Table 2:** Cell profile of Osteoclast alveolar bone *of Rattus novergicus* undergoing orthodontic retraction with short elastomeric chain

| Treatment Group | N | Osteoclast (mm²) | | | *p-value** |
|---|---|---|---|---|---|
| | | Mean | SD | Frequency | |
| C+ | 5 | 41.38 | 2.73 | 24% | |
| C- | 5 | 27.58 | 2.72 | 16% | |
| G1 | 5 | 30.30 | 1.17 | 18% | 0.021 |
| G2 | 5 | 40.08 | 1.42 | 24% | |
| G3 | 5 | 30.08 | 0.70 | 18% | |

* One-way ANOVA

The results showed that the positive control group significantly increased osteoclast activity due to retraction over 28 days. This is in line with previous research that showed that mechanical stress during orthodontic retraction increases the activity of osteoclasts, which play a role in bone resorption.[28] In contrast, the negative control group (C-) had lower osteoclast activity compared to the other treatment group, which indicated normal conditions without the influence of retraction. Under normal conditions, osteoclast activity was relatively stable. [26] Meanwhile, the group given *α*-mangostin showed osteoclasts. This effect suggests that *α*-mangostin may reduce osteoclast activity. The anti-inflammatory effects and inhibition of bone resorption by *α*-mangostin.[29] The group was given hyperbaric oxygen therapy, although osteoclast activity was slightly lower than the C+ group. These results indicate that hyperbaric oxygen therapy may help reduce osteoclast activity, whereas enhanced oxygenation may inhibit osteoclastogenesis activity.[30] The group that received the combination of *α*-mangostin and hyperbaric oxygen therapy showed that both therapies appeared effective in decreasing osteoclast activity, similar to the effects observed in the G1. Combining antioxidant agents and oxygen therapy can improve the effectiveness of bone resorption reduction. [31] Meanwhile, the group receiving *α*-mangostin and oxygen therapy showed a significant decrease in osteoclast activity, supporting the potential use of these two therapies in lowering bone resorption during orthodontic treatment.

*Expression of MMP-8*

Table 3 presents the expression levels of MMP-8 protein in the alveolar bone of *Rattus norvegicus* undergoing orthodontic retraction with a short elastomeric chain. The positive control group (C+) exhibited increased MMP-8 expression with an average of 32.28 μm, while the negative control group (C-) showed a normal average of 26.72 μm. Group G1, treated with *α*-mangostin after 28 days of retraction, had reduced MMP-8 expression averaging 26.33 μm. Group G2, which received hyperbaric oxygen therapy from days 19 to 28, showed a high MMP-8 expression similar to the positive control, averaging 32.36 μm. Group G3, receiving *α*-mangostin and hyperbaric oxygen therapy, exhibited decreased MMP-8 expression with an average of 25.73 μm. One-way ANOVA statistical analysis confirmed significant differences (p-value < 0.05) in MMP-8 expression among the groups, highlighting that *α*-mangostin can effectively reduce MMP-8 expression, potentially minimizing matrix degradation during orthodontic treatment.

The positive control group showed a significant increase in MMP-8 expression, according to a study by Alhashimi *et al*. (2001), which showed that mechanical stress on the bones increased MMP-8 expression, played a role in the degradation of the bone matrix and the negative control group did not undergo any changes and under normal conditions, the expression of MMP-8 was lower.[32] The group given *α*-mangostin (G1) showed a decrease in MMP-8 expression, indicating the effect of *α*-mangostin in decreasing MMP-8 activity. The *α*-mangostin has anti-inflammatory properties that can reduce the activity of MMPs.[33] In addition, the group with hyperbaric therapy showed a mean expression of MMP-8 similar to that of the positive control group. These results suggest that although oxygen therapy increases tissue oxygenation, MMP-8 expression remains high. While in combination therapy, both showed a decrease in MMP expression similar to that of the *α*-mangostin therapy group and showed that combination therapy could increase the effectiveness of reduced proteolytic activity and matrix degradation.[34] This indicates the potential of *α*-mangostin in reducing matrix degradation during orthodontic treatment, offering a beneficial therapeutic approach to minimize tissue damage during orthodontic retraction.

**Table 3:** Expression of MMP-8 protein in the alveolar bone *of Rattus novergicus* undergoing orthodontic retraction with short elastomeric chain

| Treatment Group | N | MMP-8 (μm) | | | *p-value** |
|---|---|---|---|---|---|
| | | Mean | SD | Frequency | |
| C+ | 5 | 32.28 | 1.17 | 23% | |
| C- | 5 | 26.72 | 0.98 | 19% | |
| G1 | 5 | 26.33 | 14.77 | 18% | 0.038 |
| G2 | 5 | 32.36 | 1.75 | 23% | |
| G3 | 5 | 25.73 | 14.41 | 18% | |

* One-way ANOVA

*Correlation between the bone cell and MMP-8*

Table 4 shows the significant association between bone cells (osteoblast and osteoclast) and MMP-8 protein in alveolar bone repair of *Rattus norvegicus* after orthodontic retraction with elastomeric

chain short. There was a strong positive correlation between osteoblast and osteoclast activity, as well as between osteoclast and MMP-8 expression and between osteoblast and MMP-8. These results highlight the critical role of bone cell interaction and MMP-8 in bone repair. The study results show a significant association between bone cells (osteoblast and osteoclast) and MMP-8 protein in the repair of alveolar bone. There was a strong positive correlation between osteoblast and osteoclast activity, as well as between osteoclast and MMP-8 expression and between osteoblast and MMP-8. This positive correlation highlights the important role of the interaction between bone cells and MMP-8 in bone repair. Increased osteoclast activity triggers the expression of MMP-8, which plays a role in matrix degradation and bone remodeling. MMP-8 plays a role in the regulation of osteoclast activity and bone remodeling. [23] In addition, osteoblast activity is also related to MMP-8 expression. The interaction between osteoblasts and matrix proteins, including MMPs, is essential for repairing and forming new bones.[35]This interaction indicates that MMP-8 plays a role in the degradation and stimulation of osteoblastic activity, which is essential in bone repair after orthodontic retraction. These findings emphasize the importance of considering the Role of MMP-8 and bone cell interactions in therapy development to accelerate bone repair during orthodontic treatment.

**Table 4:** Relationship of bone cells (osteoblast and osteoclast) with MMP-8 protein in alveolar bone repair *of Rattus novergicus* undergoing orthodontic retraction

| S/N | Group | Spearman's rho Correlations | | |
|---|---|---|---|---|
| | | N | Correlation Coefficient | Sig. (2-tailed) |
| 1 | Osteoblast-Osteoclast | 25 | 0.803 | 0.012 |
| 2 | Osteoclas-MMP-8 | 25 | 0.973 | 0.021 |
| 3 | Osteoblast-MMP-8 | 25 | 0.82 | 0.041 |

Figure 1 shows an alveolar bone undergoing orthodontic retraction in *Rattus norvegicus*. In the top row, a histological profile of the alveolar bone is seen showing osteoblast cells (blue arrow) and osteoclast cells (yellow arrow), which play a role in bone formation and resorption, respectively, signaling an active remodeling process during orthodontic retraction. In the lower row, the expression of the MMP-8 protein (blue arrow) is visible, indicating its role in the degradation of the extracellular matrix and bone remodeling. Osteoblasts play a role in bone formation, while osteoclasts play a role in resorption, reflecting the dynamic interactions required for bone homeostasis.[36] The expression of MMP-8 protein shows its role in extracellular matrix degradation and bone remodeling, and it plays a role in the regulation of osteoclast activity.[23] Its modulation by $\alpha$-mangostin during orthodontic retraction can balance bone resorption and formation, enhancing bone repair and stability.

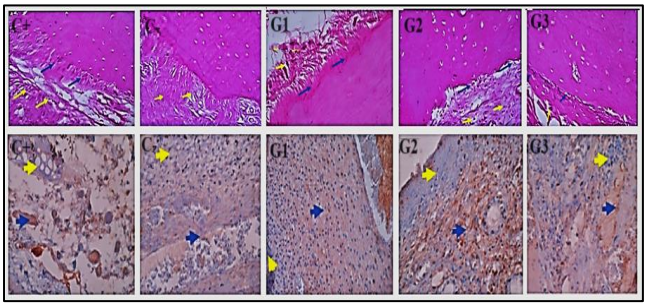


**Figure 1:** Bone cell and MMP-8 expression. (Top) Profile of osteoblast cells (blue arrow) and osteoclast cells (yellow arrow) in the alveolar bone repair of *Rattus novergicus* on orthodontic retraction. (Bottom ) Protein profile of MMP-8, blue arrow (marker of MMP-8 expression), yellow arrow (bone cell). (400X magnification).

Figure 2 illustrates the impact of $\alpha$-mangostin and hyperbaric oxygen therapy on bone cell activity (osteoblasts and osteoclasts) and MMP-8 protein expression during orthodontic retraction. Group G1, which was subjected to 28 days of orthodontic retraction followed by $\alpha$-mangostin administration, exhibited a remarkable response regarding osteoblast activity, osteoclast activity, and MMP-8 expression. Post-retraction administration of $\alpha$-mangostin enhanced osteoblast activity, decreased osteoclast activity and regulated MMP-8 expression, which is crucial for bone repair and regeneration.[37] Group G3, which received $\alpha$-mangostin from days 1 to 28 and hyperbaric oxygen therapy from days 19 to 28, also showed positive outcomes, although slightly less than Group G1. This combination promotes osteoblast activity and reduces osteoclast activity, aiding bone remodeling.[38]

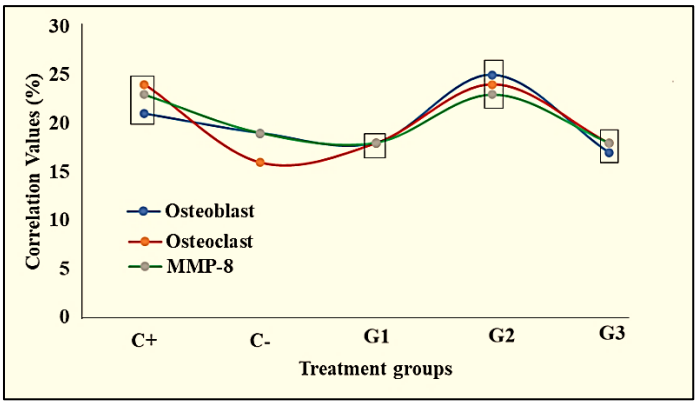


**Figure 2:** The correlation value of the bone cell and MMP-8 in post-treatment bone retraction.

Group G2, which received hyperbaric oxygen therapy from days 19 to 28 after 28 days of orthodontic retraction, demonstrated a significant increase in osteoblast activity, a reduction in osteoclast activity, and an elevation in MMP-8 expression, albeit slightly less than Groups G1 and G3. The study demonstrates that $\alpha$-mangostin effectively enhances osteoblast activity, reduces osteoclast activity, and modulates MMP-8 expression during bone remodeling in orthodontic retraction, suggesting its strong potential as a therapeutic agent. While hyperbaric oxygen therapy (HBOT) is also practical, its combination with $\alpha$-mangostin does not produce a significantly more significant synergistic effect than $\alpha$-mangostin alone. These findings indicate that $\alpha$-mangostin may be sufficient as a standalone treatment for optimizing bone repair in orthodontic procedures, with the role of HBOT potentially requiring further evaluation.[39]

## Conclusion

The $\alpha$-mangostin therapy or combination with hyperbaric oxygen on the use of a short elastomeric chain in orthodontic retraction on *Rattus norvegicus* leads to a significant increase in osteoblasts, osteoclasts, and MMP-8 protein expression in the alveolar bone. Additionally, a strong and significant positive correlation exists between the number of osteoblasts and osteoclasts and between osteoclast and osteoblast activity with MMP-8 expression. This suggests that the increased activity of osteoblasts and osteoclasts plays a crucial role in the alveolar bone repair process through mechanisms involving elevated MMP-8 expression during orthodontic retraction.

## Conflict of interest

The authors declare no conflict of interest.

## Author's 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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