Dental Journal
Majalah Kedokteran Gigi

Dental Journal
(Majalah Kedokteran Gigi)
2024 June; 572): 118–123

Original article

# Increased TGF-β1 level after cocoa administration during orthodontics tooth movement in *Cavia cobaya*

**Annisa Nurul Fikri[1], Cendrawasih Andusyana Farmasyanti[2], Pinandi Sri Pudyani[2]**
[1]Orthodontics Specialist Education Program, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Department of Orthodontics, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Indonesia

## *ABSTRACT*

***Background:*** *Orthodontic tooth movement (OTM) is a process of tooth movement in the alveolar socket through a bone remodeling process. Cocoa contains caffeine as a bioactive component.* ***Purpose:*** *This study aimed to determine the effect of caffeine in cocoa administration on transforming growth factor β1 (TGF-β1) levels in the pressure side during OTM.* ***Methods:*** *Twelve Cavia cobaya were divided into four groups: a control group and treatment groups with 2.3 mg caffeine in cocoa (Group 1), a 3.45 mg dose (Group 2), and a 4.6 mg dose (Group 3) (n = 3). A NiTi open coil spring with light force was applied to two lower incisor of Cavia cobaya. TGF-β1 level in gingival crevicular fluid (GCF) of the pressure side was analyzed using ELISA on days 0, 1, 7, and 14. The data was examined with two-way ANOVA ($p < 0.05$) and the least significant difference (LSD) post-hoc test.* ***Results:*** *The study found that the control group had the smallest increase in TGF-β1 levels, followed by the caffeine group in Groups 1, 2, and 3 cocoa ($p<0.05$).* ***Conclusion:*** *This study confirmed that caffeine in cocoa administration increases TGF-β1 levels during OTM on Cavia cobaya in the pressure side.*

***Keywords:*** *caffeine; cocoa; orthodontics tooth movement; pressure side; TGF-β1*
***Article history:*** *Received 19 December 2022; Revised 27 July 2023; Accepted 31 July 2023; Published 1 June 2024*

Correspondence: Cendrawasih Andusyana Farmasyanti, Department of Orthodontics, Faculty of Dentistry, Universitas Gadjah Mada. Jl. Denta 1, Sekip Utara, Yogyakarta 55281, Indonesia. Email: cendrawasih@ugm.ac.id

## INTRODUCTION

Orthodontic tooth movement (OTM) is a process of tooth movement in the alveolar socket through a bone remodeling process. The mechanical pressure of orthodontic forces causes reversible minor injuries to the periodontal tissues, resulting in physiological adaptation of the alveolar bone.[1] The early response of periodontal tissue to mechanical stress is characterized by metabolic changes that facilitate tooth movement. Minor changes in the periodontal ligament's thickness occur one hour after the administration of orthodontic force, but considerable alterations occur six hours later.[2] Shortly after the applied orthodontic force, teeth position will shift, resulting in the pressure side on one side of the periodontal tissue and the tension side on the opposite side. Blood flow will decrease on the pressure side, while the tension side will remain stable or increase.[1] Orthodontic mechanical forces cause bone resorption in the pressure side and apposition in the tension side. The application of orthodontic mechanical forces to teeth is characterized by an inflammatory process through macrophage activation followed by cytokines and growth factors release. The growth factor includes a receptor activator of nuclear factor κβ ligand (RANKL) and transforming growth factor β1 (TGF-β1).[3]

One of the cytokines in the extracellular matrix that is synthesized by osteoblasts and osteoclasts is TGF-β (TGF-β1, TGF-β2, and TGF-β3). TGF-β1 regulates various cellular responses in mediating the effects of the immune response, angiogenesis, wound healing processes, and regulation of bone formation. It stimulates bone formation through increased proliferation, osteoblast differentiation, type II collagen level, and proteoglycan synthesis by precursor cells chondrocytes.[4] TGF-β1 also plays a role in bone resorption by stimulating the collection of osteoclast precursors from the bone marrow, maturation, and apoptosis of osteoclasts. TGF-β1 is known to cause osteoclast development based on the results of osteoclast precursor cultures from bone


DOI: 10.20473/j.djmkg.v57.i2.p118–123

marrow supplemented with RANKL and macrophage colony-stimulating factor (M-CSF).[5]

Various approaches have been introduced to increase OTM, including non-invasive methods. Non-invasive methods are more acceptable to patients and are grouped into drugs, mechanical stimulation, and non-surgical treatment approaches.[6] The use of natural products as a non-invasive method has been extensively evaluated. Cocoa is a natural product derived from plants and widely consumed by people. Cocoa contains polyphenol and methylxanthine bioactive components. One type of active compound in methylxanthine is caffeine.[7] Multiple studies have revealed that caffeine affects bone metabolism. It has been observed that caffeine use increases OTM in rats via its effect on alveolar bone remodeling.[8] Caffeine administration increases prostaglandin E2 (PGE2) levels efficiently. PGE2 stimulates the formation of RANKL in osteoblasts, which then increases the number of osteoclasts and OTM.[9] This study aimed to determine the effect of caffeine in cocoa administration on TGF-β1 levels in the pressure side during OTM.

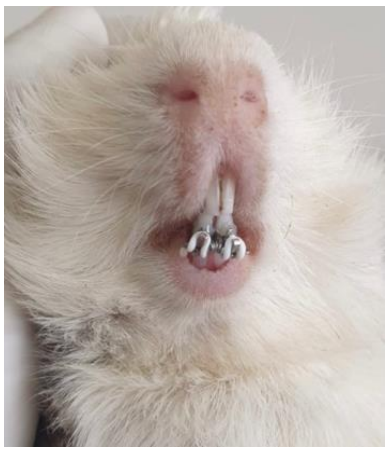

**Figure 1.** Applied orthodontics force to the *Cavia cobaya*.

**Figure 2.** Caffeine administration to *Cavia cobaya.*

## MATERIALS AND METHODS

This experimental laboratory study enrolled 12 male *Cavia cobaya,* aged 2.5–3 months and weighing 300–350 grams. The subjects were divided into four groups: an orthodontic treatment-only control group and orthodontic treatment groups with 2.3 mg caffeine in cocoa (Group 1), a 3.45 mg dose (Group 2), and a 4.6 mg dose (Group 3). Each group consisted of three *Cavia cobaya*. The experimental animal was ethically approved by the Research Ethics Commission, Faculty of Dentistry, Universitas Gadjah Mada, number 00320/KKEP/FKG-UGM/EC/2019. This study is a part of first author's thesis in Faculty of Dentistry, Universitas Gadjah Mada.

This study used the dose of caffeine in chocolate according to FDA recommendations, namely a safe dose of 100–200 mg/day. The human dose (70 kg) conversion to *Cavia cobaya* (400 grams) was 3.1 mg. The weight of *Cavia cobaya* used in this study was 300 grams, the minimum dose conversion used was 2.3 mg, the average dose was 3.45 mg, and the maximum dose was 4.6 mg.

A light orthodontic force was applied at both lower incisor of *Cavia cobaya* (Figure 1). The applied bracket was made of a straight wire slot 0.022" (Marquis™, Ortho Technology®, USA), wire round stainless steel 0.016" (American Orthodontics®, USA), and NiTi open coil springs (American Orthodontics®, USA). The open coil spring length was 1.5 times the distance of the incisor inter bracket with 35 grams of force, measured by a tension gauge dynamometer (Medkraft Orthodontics, USA).

The treatment group was administered 1.37 g, 2.05 g, and 2.74 g cocoa powder (Hershey's natural unsweetened cocoa, USA) dissolved in 3 ml distilled water. Three different caffeine doses were adjusted at 2.3 mg (Group 1), 3.45 mg (Group 2), and 4.6 mg (Group 3). The cocoa was administered orally using a gastric tube two times a day (Figure 2).[9] The cocoa administration, twice a day after 9 AM and 1 PM, was carried out to avoid interactions

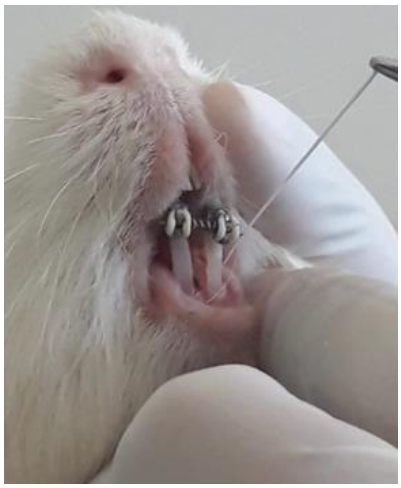

**Figure 3.** Gingival crevicular fluid sampling on *Cavia cobaya* with paper point.


DOI: 10.20473/j.djmkg.v57.i2.p118–123

between caffeine and cortisol during the circadian rhythm, which could affect the research results.[10]

Gingival crevicular fluid (GCF) samples were retrieved using size #15 paper points (Dentsply, Germany) on the pressure side (distal to the incisor ) (Figure 3). GCF retrieval was performed before and on the 1st, 7th, and 14th days after the orthodontics force application. Incisor were wiped with cotton for deposit removal, isolated by a cotton roll, and dried to eliminate residual saliva. Paper points were inserted into the gingival sulcus at 1 mm depth for 30 seconds. The collected samples were stored in Eppendorf tubes containing 350 µL of the saline solution and then centrifuged at 2000 rpm for 25 minutes. The supernatant solution was stored at -80°C until ELISA was performed.

ELISA analysis was carried out in the Pharmacology and Toxicology Laboratory Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta. Measuring the GCF of TGF-β1 from the supernatant solution was conducted using ELISA kit TGF-β1 (Cusabio ®Biotech Co. Ltd., China). Optical density was determined using a microplate reader at 450 nm wavelength.

TGF-β1 levels were tested for normality using the Shapiro–Wilk test and homogeneity using Levene's test. A two-way ANOVA test with a 95% confidence level was carried out to evaluate the data ($p < 0.05$). In addition, the least significant different (LSD) post-hoc test was executed. Statistical analysis was conducted using SPSS Version 26 (IBM, USA).

## RESULTS

TGF-β1 levels varied among groups. Table 1 shows the average and standard deviations of TGF-β1 levels measured using ELISA.

The Shapiro–Wilk normality test and Levene's homogeneity test indicated normally distributed and homogeneous ($p > 0.05$) data. Two-way ANOVA confirmed significant improvement of TGF-β1 levels, with the lowest average in the control group, followed by the groups with the 2.3 mg dose of caffeine in cocoa (Group 1), the 3.45 mg dose (Group 2), and the 4.6 mg dose (Group 3) ($p < 0.05$). The levels of TGF-β1 increased parallel to the administered doses. Increased average of the TGF-β1 level was significant ($p < 0.05$) between the caffeine in cocoa from day 0 to day 1 and day 1 to day 7. However, day 7 to day 14 presented a significant decrease ($p < 0.05$). Interaction between dosage and duration observations also suggested a significant difference in TGF-β1 levels ($p < 0.05$) (Table 1).

Table 1 demonstrates a significantly increasing average of TGF-β1 levels ($p < 0.05$) from day 0 to day 1 in all treatment groups. No significant improvement in the control

**Table 1.** Mean and standard deviation of TGF-β1 level (pg/ml) in all groups at days 0, 1, 7, and 14 on the pressure side of gingival crevicular fluid in *Cavia cobaya*

| Days | Amount of TGF-β1 level | | | |
|---|---|---|---|---|
| | Control group | Group 1 | Group 2 | Group 3 |
| 0 | 106.64 ± 5.55 | 99.61 ± 1.38* | 99.25 ± 0.42* | 90.59 ± 1.39* |
| 1 | 108.57 ± 1.65 | 103.35 ± 2.03* | 117.56 ± 2.05* | 121.90 ± 0.79* |
| 7 | 113.00 ± 1.87 | 114.83 ± 2.03 | 123.84 ± 1.88* | 128.10 ± 2.27* |
| 14 | 93.71 ± 1.35 | 81.56 ± 1.52* | 89.46 ± 1.27* | 102.57 ± 2.69* |

*: compared to control group ($p < 0.05$)

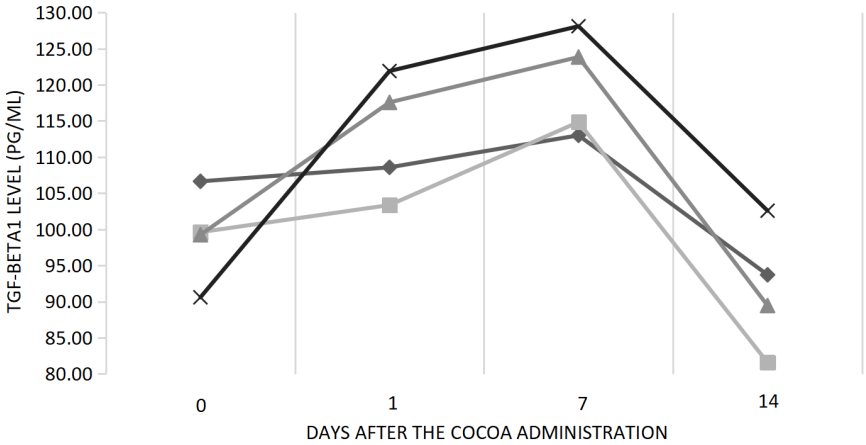


**Figure 4.** The TGF-β1 levels on the pressure side *Cavia cobaya* gingival crevicular fluid after cocoa administration. The control group (diamond) was not administered caffeine in cocoa. Three different caffeine doses were adjusted in treatment groups for Group 1 (square), Group 2 (triangle), and Group 3 (cross). The TGF-β1 levels were significantly higher in the Group 3 than the other groups; higher in Group 2 than Group 1 and the control group; and higher in Group 1 than the control group.


DOI: 10.20473/j.djmkg.v57.i2.p118–123

group was observed from this study ($p > 0.05$). Day 1 marked a significant mean difference ($p < 0.05$) ascending from Group 3, Group 2, Group 1, and the control group. It significantly increased the mean ($p < 0.05$) of day 1 to day 7 reported from all groups. Day 7 denoted a significant mean difference ($p < 0.05$) from the highest average of Group 3, Group 2, Group 1, and the control group. A significant decreasing average occurred from day 7 to day 14 in all groups.

## DISCUSSION

Administration of caffeine in cocoa could increase the average amount of TGF-β1 levels in the treatment group compared to the control group. A significantly increased average of TGF-β1 levels was observed between the control group and treatment groups with 2.3 mg (Group 1), 3.45 mg (Group 2), and 4.6 mg (Group 3) caffeine in cocoa (Figure 4). Additional caffeine doses affect the levels of TGF-β1. Different doses administered between groups increased TGF-β1 levels. According to Rapuri et al.,[11] influencing factors for caffeine in bone metabolic processes include dosage, route of administration, and experimental animal age. In addition, the effect of caffeine is also proportional to the subject's body weight and height; hence, the amount of caffeine must be raised as the subject's body weight increases.[12] The TGF-β1 levels of Group 3, which was given 4.6 mg doses of caffeine on day 0, were lower compared to Group 2 (3.45 mg), Group 1 (2.3 mg), and the control group, but were higher compared to the other groups on days 1, 7, and 14. Group 2 had higher TGF-β1 levels compared to Group 1. The difference in the average levels of TGF-β1 between the groups on day 0 was possibly due to genetic variations between the experimental animals, meaning their responses to the application of orthodontic strength were different. The study findings are in accordance with the report by Golshah et al.,[13] who used the injection of caffeine in doses of 25, 50, and 75 mg/kg and reported that the number of osteoclasts, blood vessels, and Howship's lacunae significantly increased in rats under caffeine therapy during OTM.

The effect of caffeine in OTM has been reported in various studies. Caffeine, an adenosine antagonist, can increase calcium excretion in urine by enhancing prostaglandins (PGE) synthesis.[14] Liu et al.[15] proved that low-concentration caffeine administration could increase the cyclooxygenase-2 (COX-2) levels. During the application of orthodontic force on the pressure side, various inflammatory mediators are released, one of which is a PGE. Increased COX-2 levels will increase PGE production, which plays an essential role in bone resorption.[16] PGE activates osteoblasts for producing RANKL, colony stimulating factor-1 (CSF), and TGF-β1, which play a significant role in osteoclast formation.[17] Caffeine influences tooth movement through changes in RANKL, osteoprotegerin (OPG), and TGF-β1 levels.[3,18]

The average of TGF-β1 levels increased from day 0 to day 1 and day 1 to day 7, but there was a decrease from day 7 to day 14. The results of this study are in accordance with the research of Alhasyimi and Rosyida:[18] that administration of a dose of 2.7 mg of caffeine can increase OTM through the mechanism of increasing RANKL starting on days 0, 1, and 7. There is a difference in the average levels of TGF-β1 between the control group and treatment groups on day 0. It might be associated with genetic variation between experimental animals that affects their responses to applied orthodontics force. In addition, only the caffeine in cocoa treatment group experienced significantly increasing average TGF-β1 levels for 24 hours. The substantially increased average TGF-β1 levels are consistent with additional administered caffeine doses. The findings are in line with the studies done by Kikuta et al.[19], which indicate that increasing TGF-β1 levels on the pressure side could be observed in the first 24 hours after applying optimal orthodontics strength. Applied mechanical orthodontics force to teeth triggers the macrophages-mediated inflammatory process, then, cytokines and growth factors are released. One type of cytokine in the extracellular matrix synthesized by osteoblasts and osteoclasts is TGF-β1. Administering caffeine could increase levels of TGF-β1.[3,4] Caffeine doses of 2.3 mg, 3.45mg, and 4.6 mg were effective in increasing TGF-β1 levels from day 0 to day 1, with the most effective dose being 4.6 mg.

The increased average TGF-β1 levels continued from day 1 to day 7. The study result regarding the involvement of TGF-β1 in bone remodeling in OTM using optimal orthodontic force (10 g), showing that TGF-β1 protein is expressed in the periodontal tissue on the pressure side on day 7, aligns with the results found by Kikuta et al.[19] TGF-β1 produced by tooth movement stimulates bone resorption on the pressure side through osteoclastogenesis activation. TGF-β1 increases receptor activator of nuclear factor kappa B (RANK) level to stimulate osteoclasts differentiation. An enhanced number of osteoclasts are also found on the bone surface after 7 days. The role of TGF-β1 in bone resorption is to stimulate the recruitment of osteoclast precursors from the bone marrow, maturation, and apoptosis of osteoclasts. The results of osteoclast precursor cultures from the bone marrow with the addition of RANKL, M-CSF, and TGF-β1 are known to induce osteoclast differentiation.[5] The more significant increase in the average TGF-β1 levels leads to more osteoclast formation, affecting faster bone resorption and increased OTM.

Several studies have shown that TGF-β1 has biphasic effects on osteoclast maturation. At the initial phase of the osteoclast maturation process, TGF-β1 induces osteoclastogenesis from hematopoietic precursors by activating nuclear factor kappa B (NF-κB) levels and RANK in osteoclast precursors. The RANKL-RANK interaction is important for the survival and differentiation of osteoclast precursors into osteoclasts. At the end stage of osteoclast maturation, high concentrations of TGF-β1


DOI: 10.20473/j.djmkg.v57.i2.p118–123

promote osteoblast OPG levels and decrease RANKL levels. OPG inhibits the RANKL-RANK interaction, causing osteoclast differentiation into active-inhibited osteoclasts.[20]

OTM depends on the rate of bone remodeling. The increase in TGF-β1 occurs in both the pressure side and the tension side. The increase in TGF-β1 levels during tooth movement was significantly greater on the tension side rather than on the pressure side. TGF-β1 levels have an important role in OTM, as they can promote bone formation and resorption.[21] TGF-β1 stimulates bone formation in the tension side through increased proliferation and osteoblast differentiation.[4] TGF-β1 also plays a role in the process of bone resorption in the pressure side by stimulating the collection of osteoclast precursors from the bone marrow, maturation, and osteoclast differentiation.[5] The study result aligns with those of Herniyati et al.:[3] that administration of caffeine can increase the levels of TGF-β1 on the pressure side and tension side, with the level of TGF-β1 on the tension side significantly greater than that on the pressure side.

Decreased TGF-β1 levels occur from day 7 to day 14 in all groups. The decrease in the average TGF-β1 level is reversely associated with caffeine administered doses, due to the lag phase. The lag phase is characterized by slight or no OTM. During this phase, OTM is suspended for approximately 20-30 days. This phase is distinguished by PDL hyalinization (necrotic tissues) until osteoclasts, macrophages, and foreign body giant cells have removed all of the necrotic tissues.[22] TGF-β1 plays an important role in the initial phase of osteoclast formation by stimulating osteoclast differentiation from monocyte precursors with RANKL induction.[23]

On day 14, bone resorption led to a considerable drop in TGF-β1 levels, indicating an active participation in OPG control via feedback mechanisms.[15] TGF-β1 has a double effect by inhibiting osteoclast differentiation through an OPG enhancement mechanism causing inhibited osteoclastogenesis.[11] Once the initial formation phase has been completed, the TGF-β1 osteoclast amount must be diminished to avoid alteration in osteoclastogenesis. Tsukada et al.'s[24] research reported that a high level of TGF-β1 on the seventh day after a large magnitude of orthodontics force was applied could trigger root resorption through increasing RANKL and interleukin-6 production by the periodontal tissue cells. In contrast to their study, this study applied minimal orthodontics strength, which caused a decline in TGF-β1 levels from day 7 to day 14 as a root resorption prevention mechanism.

According to Uematsu et al.,[25] an increase of TGF-β1 in GCF during OTM was observed 24 hours to 168 hours after application of orthodontic force. Increased levels of TGF-β1 resulted in 1.1 ± 0.1 mm/168 hours tooth movement. Alhasyimi and Rosyida,[18] by measuring OTM rates in guinea pigs that were given cocoa orally, showed significantly greater movement from day 1 to day 7. Comparison of OTM rates on day 7 between the experimental and control groups was 1.317 ± 0.149 mm and 1.127 ± 0.219 mm. Administration of cocoa can improve OTM rates in clinical practice.

This study demonstrated that cocoa administration increases TGF-β1 level during OTM in *Cavia cobaya* on the pressure side. Doses of 2.3 mg, 3.45 mg, and 4.6 mg of caffeine in cocoa increased TGF-β1 levels, with the most effective dose being 4.6 mg.

## REFERENCES


1. Li Y, Jacox LA, Little SH, Ko C-C. Orthodontic tooth movement: The biology and clinical implications. Kaohsiung J Med Sci. 2018; 34(4): 207–14.
2. Herniyati H, Harmono H, Devi LS, Hernawati S. Evaluation of orthodontic tooth movement by 3D micro-computed tomography (μ-CT) following caffeine administration. Dent J. 2019; 52(1): 1–7.
3. Herniyati H, Narmada IB, Soetjipto S. Effects of Robusta coffee (Coffea canephora) brewing on levels of RANKL and TGF- β1 in orthodontic tooth movement. Dent J. 2016; 49(3): 143–7.
4. Alhasyimi AA, Suparwitri S, Christnawati C. Effect of carbonate apatite hydrogel-advanced platelet-rich fibrin injection on osteoblastogenesis during orthodontic relapse in rabbits. Eur J Dent. 2021; 15(3): 412–9.
5. Indriasari V, Suparwitri S, Christnawati C, Alhasyimi AA. Different effects of soybean isoflavone genistein on transforming growth factor levels during orthodontic tooth movement among young and old rabbits. F1000Research. 2019; 8: 2074.
6. Naidu S, Suresh A. The applications of 2 x 4 appliance during mixed dentition treatment. Acta Sci Dent Sci. 2018; 2(11): 49–51.
7. Franco R, Oñatibia-Astibia A, Martínez-Pinilla E. Health benefits of methylxanthines in cacao and chocolate. Nutrients. 2013; 5(10): 4159–73.
8. Alhasyimi AA, Pudyani PS. Effect of cocoa administration during orthodontic tooth movement on RUNX2, calcium levels, and osteoclast bone-resorbing activity in rats. J Pharm Pharmacogn Res. 2022; 10(5): 857–64.
9. Herniyati, Narmada IB, Devi LS. Caffeine increases PGE2 levels at compression and tension areas during orthodontic tooth movement. Int J Chem. 2018; 11(6): 177–82.
10. Lovallo WR, Whitsett TL, Al'Absi M, Sung BH, Vincent AS, Wilson MF. Caffeine stimulation of cortisol secretion across the waking hours in relation to caffeine intake levels. Psychosom Med. 2005; 67(5): 734–9.
11. Rapuri PB, Gallagher JC, Nawaz Z. Caffeine decreases vitamin D receptor protein expression and 1,25(OH)2D3 stimulated alkaline phosphatase activity in human osteoblast cells. J Steroid Biochem Mol Biol. 2007; 103(3–5): 368–71.
12. Arnanda BB, Suparwitri S, Pudyani PS. Effect of caffeine in chocolate (Theobroma cacao) on the alveolar bone mineral density in guinea pigs (Cavia cobaya) with orthodontic tooth movement. Dent J. 2020; 53(3): 164–9.
13. Golshah A, Omidi K, Nikkerdar N, Ghorbani F. Effect of caffeine injection on orthodontic tooth movement in rats: An experimental study on rats. Int J Dent. 2022; 2022: 7204806.
14. Socała K, Szopa A, Serefko A, Poleszak E, Wlaź P. Neuroprotective effects of coffee bioactive compounds: a review. Int J Mol Sci. 2020; 22(1): 107.
15. Liu SH, Chen C, Yang R Sen, Yen YP, Yang YT, Tsai C. Caffeine enhances osteoclast differentiation from bone marrow hematopoietic cells and reduces bone mineral density in growing rats. J Orthop Res. 2011; 29(6): 954–60.
16. Niklas A, Proff P, Gosau M, Römer P. The role of hypoxia in orthodontic tooth movement. Int J Dent. 2013; 2013: 1–7.
17. Jones DH, Kong Y-Y, Penninger JM. Role of RANKL and RANK in bone loss and arthritis. Ann Rheum Dis. 2002; 61 (Suppl 2): ii32-9.



DOI: 10.20473/j.djmkg.v57.i2.p118–123

18. Alhasyimi AA, Rosyida NF. Cocoa administration may accelerate orthodontic tooth movement by inducing osteoclastogenesis in rats. Iran J Basic Med Sci. 2019; 22(2): 206–10.
19. Kikuta J, Tsukada M, Takagi K, Shimizu M, Hikida T, Nakayama E, Kasai K. TGF-β1 stimulates bone resorption during orthodontic tooth movement. Int J Oral-Medical Sci. 2020; 19(3): 193–9.
20. Kasagi S, Chen W. TGF-beta1 on osteoimmunology and the bone component cells. Cell Biosci. 2013; 3(1): 1–7.
21. Wang LL, Zhu H, Liang T. Changes of transforming growth factor beta 1 in rat periodontal tissue during orthodontic tooth movement. Chinese J Dent Res. 2000; 3(1): 19–22.
22. Asiry MA. Biological aspects of orthodontic tooth movement: A review of literature. Saudi J Biol Sci. 2018; 25(6): 1027–32.
23. Fox SW, Lovibond AC. Current insights into the role of transforming growth factor-β in bone resorption. Mol Cell Endocrinol. 2005; 243(1–2): 19–26.
24. Tsukada M, Kikuta J, Shimizu M, Hikida T, Nakayama E, Iwane T, Kasai K. TGF-β1 induces orthodontic root resorption through RANKL and IL-6 production in hPDL cells. Int J Oral-Medical Sci. 2021; 19(4): 278–87.
25. Uematsu S, Mogi M, Deguchi T. Increase of transforming growth factor-β1 in gingival crevicular fluid during human orthodontic tooth movement. Arch Oral Biol. 1996; 41(11): 1091–5.


DOI: 10.20473/j.djmkg.v57.i2.p118–123