Original Article

Innovative evaluation of local injective gel of curcumin on the orthodontic tooth movement in rats

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ABSTRACT

Background: Curcumin is the most active compound in turmeric. It can suppress the nuclear factor kappa-light-chain-enhancer of activated B cells pathway and prevent the osteoclastogenesis procedure. This study aimed to be the first to evaluate the effect of curcumin on the rate of orthodontic tooth movement (OTM).

Materials and Methods: Forty rats were used as follows in each group: (1) negative control: Did not receive any appliance or injection; (2) positive control: received 0.03 cc normal saline and appliance; (3) gelatin plus curcumin (G): Received 0.03 cc hydrogel and appliance; and (4) chitosan plus curcumin (Ch): Received 0.03 cc hydrogel and appliance. They were anesthetized and closed nickel-titanium coil springs were installed between the first molars and central incisors unilaterally as the orthodontic appliance. After 21 days, the rats were decapitated, and the distance between the first and second molars was measured by a leaf gauge. Howship's lacunae, blood vessels, osteoclast-like cells, and root resorption lacunae were evaluated in the histological analysis. Data were analyzed by one-way ANOVA, Tukey's test, and t-test ($P < 0.05$ consider significant).

Results: No significant difference was found in OTM between groups delivered orthodontic forces. Curcumin inhibited root and bone resorption, osteoclastic recruitment, and angiogenesis significantly.

Conclusion: Curcumin had no significant inhibitory effect on OTM. While it had a significant role on decreasing bone or root resorption ($P > 0.05$).

Key Words: Bone resorption, curcumin, rat, root resorption, tooth movement

INTRODUCTION

Orthodontic tooth movement (OTM) is characterized by simultaneous modeling and remodeling processes in the periodontal apparatus. Coupled collaboration of osteoclasts and osteoblasts is the main feature here. The remodeling process involves cutting or filling cones. Previous bone was resorbed by osteoclasts activity and osteoblasts substitute these areas by forming new bone. The rate of bone remodeling can be controlled by local or systemic conditions. Endocrine regulation can control it systematically; however, inflammatory cytokines or local regulatory systems have a more site-specific role. The receptor-activator system of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) ligand has a significant

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regulatory effect on the bone remodeling procedure through the interaction of receptor activator of nuclear factor-kappaB ligand (RANKL)/RANK/ and osteoprotegerin.[1,2]

Fixed orthodontic treatment is a time-consuming procedure that may lead to bad cooperation from the patient, higher caries occurrence, root resorption, and undesired tooth movement like anchorage loss. Several modalities can be used to decrease treatment time and accelerate tooth movement. These include low-level laser therapy, electrical currents, pulsed electromagnetic fields, distraction osteogenesis, corticotomy, mechanical vibration, and using drugs, synthetic cytokines, or growth factors.[3-10] These modalities influence tooth movement by controlling bone remodeling.

Curcumin is a novel therapeutic ingredient. It is the most active compound in turmeric, which is a herbal rhizome of the Zingier family and is also known as Curcuma longa. Turmeric is used as a spice and medicine in India and China.[11,12] "Nutraceuticals" are foods or their derivatives that have preventive or therapeutic effects safely and without any side effects.[13] These foods have been used for a long time in daily human life; therefore, there is no controversy in terms of the cultural or religious issues of people. Bharti *et al*.[14] showed that curcumin can suppress the NF-κB pathway and prevent the osteoclastogenesis procedure. It seems that curcumin may play a significant role in controlling bone remodeling.

This study aims to be the first to evaluate local administration of curcumin on the OTM rate. Biocompatible hydrogels (4% w/v chitosan and 10% w/v gelatin) were used as the local drug-delivery system to provide sustained release of curcumin, with a hydrophobic feature, in the rat's physiologic environment.

MATERIALS AND METHODS

Chitosan (medium molecular weight, degrees of deacetylation: 75%–85%) was purchased from Sigma-Aldrich Chemie GmbH, gelatin from Sigma-Aldrich (FLUKA), twin 80 from Sigma-Aldrich (Germany), curcumin (99% pure) from SBU Medical Drugs Institute, and acetic acid and methanol from Merck (Germany). Citric acid, high-pressure liquid chromatography-grade acetonitrile, sodium hydroxide, and methanol were purchased from Merck (Germany).

Chitosan hydrogel preparation

pH-sensitive and mucoadhesive chitosan directly undergo gelation in physiological pH (7.4), but it has poor water solubility. To prepare an *in situ* injectable hydrogel, acetic acid in a double-distilled water solution (1% v/v) was prepared, its pH adjusted to 6.8 with 1N NaOH. The chitosan powder was then added gradually to the solution –0.1 mg every 5 min – using ultrasonic (CENTIC, China CT-4653) to achieve a homogeneous chitosan solution. After reaching the desired chitosan percentage, the process was stopped. According to the procedure, six chitosan solutions (2%, 3%, 4%, and 6% w/v) were prepared. Increasing the pH in each solution to 7.4 led them to undergo gelation.

Gelatin hydrogel preparation

Gelatin solutions of 4% and 10% w/v were also prepared using double-distilled water. Subsequently, already prepared 1% w/v chitosan solution was added to each to increase the mechanical properties of gelatin hydrogels. According to the previously reported method,[15] thermosensitive gelatin hydrogels were prepared to undergo gelation in a physiological temperature.

Curcumin nanoparticle and emulsion preparation and loading

To obtain higher bioavailability and water solubility, curcumin was fully dissolved in methanol (96%) using a magnetic stirrer (Eppendorf, Germany). It was then left to evaporate the whole methanol in an oven (Heraeus, UK). The process was triplicated to achieve nanocurcumin particles. Curcumin powder was then added to twin 80, and this was sonicated for 2 h.

Afterward, a curcumin emulsion containing the desired curcumin concentration was prepared. The same concentration of each gel was loaded during sonication over 24 times for 30 min, over a period of 12 h.[16,17]

In vitro tests

Curcumin release

To use optimized-releasing hydrogel, *in vitro* curcumin release studies were carried out using a dialysis method for six randomly selected hydrogels. In the next step, 1 ml of each gel was placed in a dialysis bag (D9527, Sigma), and then in 100 ml of a mixed methanol, double-distilled water solution (50:50 v/v).[18] The pH (7.4), temperature (37°C), and other conditions were kept steady over 21 days. Release test samples

were taken and analyzed over 24, 48, and 72 h, and at 7, 14, and 21 days using a UV-vis Multi-Spec 1501 (Shimadzu, Japan) device that was calibrated using a mixture of methanol and water first. The curcumin detection limit wavelength was specified at 450-340 nm for a standard curcumin solution of 5% w/v.

Swelling ratio and water uptake

The hydrogel swelling ratio was calculated using standard methods.[19] The ratios were in the range of 1.16–1.34 for chitosan hydrogels and 2.31 for gelatins. Besides, chitosan hydrogels were saturated over 3 h while the saturation time for gelatin hydrogels was 15 min.

Hydrogels were successfully prepared at room temperature, using both physical and chemical cross-linking procedures. To make a systematic comparison in the release profile for the releasing potential of hydrogels, optimization was done using different ingredient-material percentages. Afterward, *in vitro* and *in vivo* release profiles were recorded. Subsequently, two optimized hydrogels were prepared for injection.

In vitro curcumin release

The release profiles of six randomly selected hydrogels are recorded in Figure 1. The release percentage of curcumin for each hydrogel shows its ability to release curcumin particles in a more sustained manner.[20] In this regard, 2%, 3%, 4% chitosan and 4% gelatin hydrogels have higher initial bursts. Meanwhile, for 4% gelatin hydrogel, the initial burst and overall release rate is the highest. About 2% and 3% chitosan hydrogels do not meet release expectations since they reach the maximum 50% of drug release. 6% chitosan
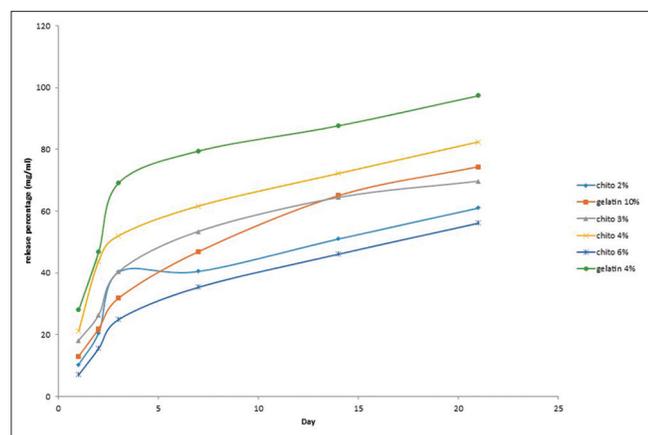
Figure 1: Release percentage (mg/ml) diagrams of each prepared hydrogel in *in vitro* analysis.

hydrogel is also discarded. Among the remaining 3%, 4% chitosan and 10% gelatin hydrogels, 4% chitosan hydrogel does have the medium initial burst and expected release after 21 days *in vitro*. Similarly, 10% gelatin hydrogel has a smooth release gradient and an expected initial burst. Hence, these were selected for the final injection process. Therefore, 4% w/v chitosan and 10% w/v gelatin hydrogels were selected for the *in vivo* experimental injection.

In vivo studies and orthodontic tooth movement

This study was designed as a single-blind, split-mouth experiment on 40 male Wistar rats (SCL, Shizuoka, Japan). Based on conservative estimation from previous studies,[21] the sample size was calculated by considering a 0.5 mm standard deviation and a 0.8 mm effect size of OTM. The power was considered to be 80 with the alpha at 5%. The mean age and weight of the animals were 3 months and 270 ± 30 g, respectively. All of the experimental procedures were performed according to the approved protocol of the Institutional Animal Care and Usage Committee (ARRIVE guideline)[22] and confirmed by the Ethical Committee of the shahid beheshti University of Medical Sciences. Samples were selected by nonrandomized sampling, according to aforementioned criteria. The animals were acclimatized to the animal room during 2 weeks before the beginning of the study under similar light and nutritional conditions. They were then randomly divided into four groups of 10 each, wherein every group dyed and were kept in separate cages.

The first group was the negative control (NC) group. It did not receive any orthodontic appliances or gels. These animals were just anesthetized during the study. The positive control (PC) group received 0.01 cc phosphate-buffered saline and an orthodontic appliance. The group that received gelatin plus curcumin (group G) received a 0.03 cc gelatin base gel containing a 50% weight of curcumin, and the fourth group (Ch) received a 0.03 cc chitosan base gel containing 50% of the weight of curcumin. 50% w/v curcumin was loaded onto selected, optimized chitosan (4% w/v), and gelatin (10% w/v). Hydrogels prepared for the injection were filtered before gelation and the loading process (Millex-GV, Millipore, USA).

At first, each rat was weighed by a digital scale (Shimadzu, Kyoto, Japan, 61189). They were anesthetized intraperitoneally using 20 mg/kg of 10% ketamine hydrochloride (Alfasan,

Woerden, Holland) and 2 mg/kg of 2% xylazine (Alfasan, Woerden, Holland) injection through an insulin syringe. After anesthesia, the rats were monitored for their vital signs. In addition, to prevent pulmonary edema, they were rotated from side to side every few minutes. The room temperature was also controlled adequately. Nickel-titanium (NiTi) closed coil springs (American Orthodontics NiTi closed coil, 010 × 030 inch, 9 mm/Eyelet) were used as the orthodontic appliance for tooth movement. They were ligated between the first molars and central incisors using a stainless steel ligature wire (0.01 inch, 3M, Unitek, Monrovia, CA, USA) and fixed by a light-cured flowable composite (DenFil Flow, Vericom co., Korea) [Figure 2]. The force inserted by the coil springs was 30 g. This was measured by a force meter. This force level was desirable for tipping tooth movement. After appliance installation, injection of each prescribed material for each specific group was performed by using an insulin syringe. The material was injected into the buccal vestibular mucosa next to the mesial root of the first molar. Each rat was fed a soft diet during the study to prevent detaching orthodontic appliances and ease swallowing. After 21 days, all the rats were weighed and then sacrificed by inhalation chloroform in a saturated desiccator. They were then decapitated, and the distance between the first and second molars was measured thrice with the use of a leaf gauge with 0.05 mm accuracy (precision stainless steel feeler gauge, FENGHGO) by an operator who was blind to each group. The mean of the three measurements was reported as the final value.

The maxilla was removed and sent for histological evaluations. They were fixed in 10% formalin for 10 days and then decalcified in 10% formic acid for 15 days. The specimens were exposed to an incremental concentration of alcohol and methyl

Figure 2: Closed nickel-titanium coil was installed between incisors and first molars to provide tipping movement.

salicylate. Finally, they were embedded in paraffin blocks. Histological specimens were prepared in the parasagittal direction and cut in 4–6 μm thickness by a microtome (LEICA, Wetzlar, Germany). They were stained by hematoxylin and eosin and inspected with a light microscope (Eclipse E400, Nikon, Japan) by an experienced pathologist blind to each allocated specimen. The amount of Howship's lacunae, blood vessels, osteoblast-like cells, and number and area of root resorption lacunae were assessed. In addition, histomorphometric analyses were performed on the specimens' photographs in 10X and 40X magnifications, which were taken by a camera (E8400, Nikon, Japan). Each specimen was evaluated three times and the mean value was reported as the final measure.

The collected data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) software (version 21, IBM, Armonk, New York, USA). One-way ANOVA, Tukey's tests, and t-tests were used in this regard.

In vivo releasing rate evaluation
After 21 days, three rats were selected randomly from each group that was administered curcumin to evaluate the systemic release rate. They were anesthetized by inhalation of chloroform and their thoraxes were excised by a surgical blade and a pair of scissors. Blood samples were collected by a 5 cc sterile syringe from the apex of the left ventricle even though the rats were alive. The blood samples were then centrifuged, and their plasma was kept in Safe-Lock Microcentrifuge tubes (Eppendorf, Hamburg, Germany) at −80°C for 24 h in a deep freezer (New Brunswick scientific, U570-86, UK).

High-pressure liquid chromatography assay and quantification of curcumin in plasma
Curcumin extraction and sample preparation were performed as previously reported.

Curcumin quantitation was achieved without any internal standard and using (L-7420 UV-VIS Detector, Hitachi, Tokyo, Japan) a C25 column, citric acid buffer adjusted to pH: 3 (35%) and acetonitrile (65%) prepared as a mobile phase, while the flow rate was 0.6 ml/min.[23] The detection wavelength for curcumin was 428 nm. Blank plasma and curcumin spike blank plasma were used to determine the exact curcumin chromatogram. The calibration curve for various curcumin solutions was also prepared to quantify the curcumin content of samples (1 mg/ml, 100 μg/ml, 10 μg/ml, 1 μg/ml, 100 ng/ml, and 10 ng/ml).

RESULTS

In vivo study

Orthodontic tooth movement

Figure 3 shows the mean weight of the experimental groups before and after the study.

Table 1 shows the mean OTM in each group. There were no significant differences between the PC group and the G or Ch groups ($P > 0.05$). The PC group had the highest tooth movement (0.34 mm). The Ch and G groups had the same amount of tooth movement (0.26 mm). The NC group had the least amount of tooth movement (0.01 mm). Consider that the NC group had no orthodontic appliances for active tooth movement.

Histological analysis

Table 2 and Figure 4 show results of histologic analysis
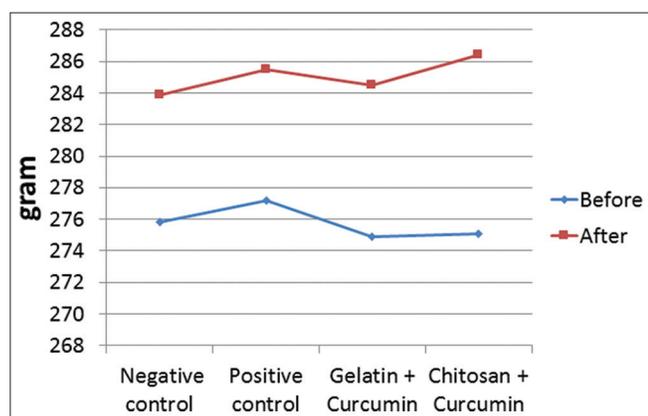
Howship's lacunae

After 21 days, the NC group did not show any Howship's lacunae. However, there were moderate to severe lacunae in the PC group with an active orthodontic force. In contrast, the G and Ch groups had significantly lower Howship's lacunae compared to the PC group. ($P < 0.05$).

Blood vessels

The PC group exhibited more blood vessels in the field compared to the NC group. Statistical analysis revealed that the G and Ch groups had significantly lower vessel counts than the PC group ($P < 0.05$).

Osteoclast-like cells

The NC group showed almost no osteoclast increment. However, a mild-to-moderate increase was observed in the PC group. In groups that were administered curcumin, there was a mild increase in the number of osteoclast-like cells. The number of osteoclasts was in agreement with Howship's lacunae. The more the number of osteoclasts there were, the more Howship's lacunae were observed. The PC group had a significant difference compared to the G and Ch groups ($P < 0.05$).

Root resorption

There was almost no root resorption in the NC group. Mild-to-moderate root resorption was seen in the PC group, along with active orthodontic force application. In the G and Ch groups, there was significantly lower root resorption compared to the PC group ($P < 0.05$).

The extent of the area of root resorption was nearly similar between the groups that were administered curcumin and the PC group.

High-pressure liquid chromatography results

In vivo curcumin release

To quantify the curcumin remaining in rat blood, blank plasma, and curcumin spike blank plasma were prepared for testing at the beginning. As shown in Figure 5a, no pikes belonging to any additional matter was detected during 20 min. Hence, the chromatogram was considered as the baseline for upcoming curcumin chromatograms.

The curcumin spike blank plasma was also tested to ensure the exact curcumin pike in chromatography of the rat samples [Figure 5b]. According to Figure 5b, curcumin retention time is five to 8 min.

Test samples chromatograms recorded as Figure 5c to h. According to the calibration curve, curcumin content of samples was specified.

As can be seen in the C–E chitosan group samples, curcumin was detected and quantified in the range of 100 µg to 1 mg/ml (closer to 100 µg). In the F, G, H samples that pertained to the gelatin group, curcumin was detected in 100 µg/ml, ≤… ~100 µg/ml, and <100 µg/ml, respectively.

DISCUSSION

The bone remodeling process is the coupled procedure between bone resorption by osteoclasts and bone

**Figure 3:** Diagram of weight change of each group during the study.

Table 1: The tooth movement measurements (mm) in each group between maxillary first and second molars which measured by a leaf gauge (0.05 mm accuracy)

Group	*n*	Mean	Maximum	Minimum	SD
Negative control	10	0.015	0.024	0.00	0.0
Positive control	10	0.34	0.65	0.20	0.14
Gelatin + curcumin	10	0.26	0.45	0.0	0.16
Chitosan + curcumin	10	0.26	0.45	0.05	0.12

SD: Standard deviation

Table 2: The mean and standard deviation of each histologic variable in the experimental groups

Variables	Group			
	Negative control	Positive control	Gelatin + curcumin	Chitosan + curcumin
Number of how ship lacunae	0±0.009	4±0.040	2±0.064	2±0.069
Number of blood vessels	4±0.063	8±0.000	7±0.062	7±0.061
Number of osteoclasts	0±0.005	6±0.079	4±0.096	4±0.000
Number of root resorptive lacunae	0±0.002	4±0.055	2±0.048	2±0.074
Area of root resorptive lacunae	$0.003×10^{-3}±0.000$	$0.270×10^{-3}±0.013$	$0.273×10^{-3}±0.010$	$0.281×10^{-3}±0.007$
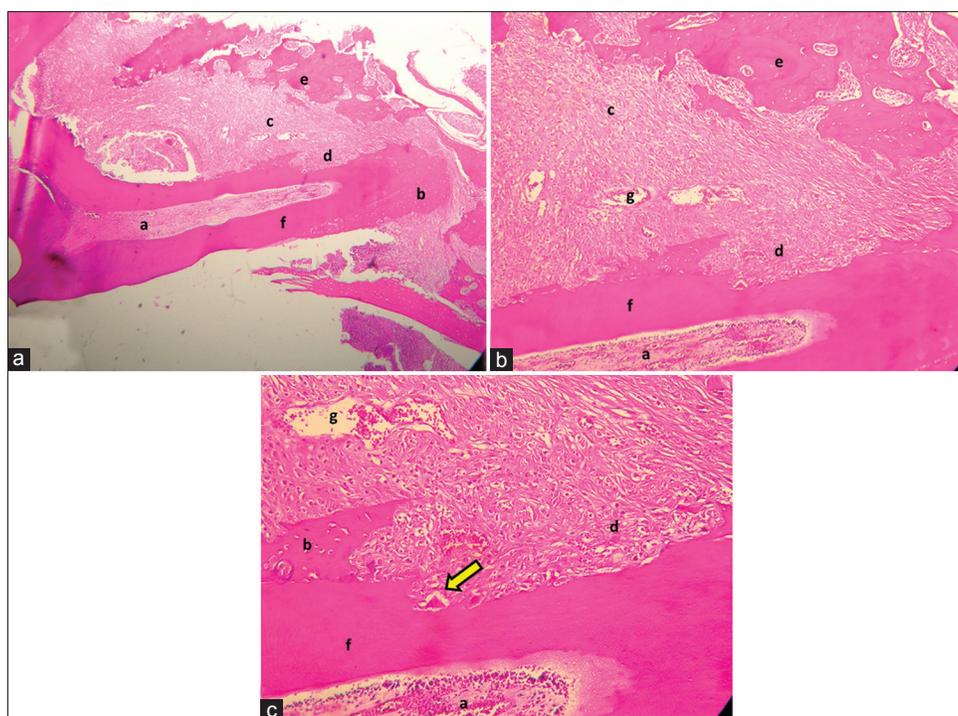
Figure 4: Histologic micrographs. (a) There is sagittal segment of molar root with root resorption (×10). (b) There is magnified zone of root resorption in cellular cementum and root dentin also Howship lacunae can be seen (×40). (c) There is a multinucleated cell (shown by arrow) in the root resorption lacunae (×100). a - dental pulp, b - cellular cementum, c - periodontal ligament with fibrous Sharpey's fibers, d - root resorption lacuna, e - alveolar bone, f - dentine, g - blood vessel.

formation through osteoblasts.[24] Osteoclasts have the RANK receptors that recruit them from blood vessels by T-lymphocyte stimulation through RANKL production.[1] Ozaki revealed that NF-kβ plays a major role in osteoclastogenesis and bone resorption.[25]

OTM depends on bone remodeling, which is time-consuming. It is important to consider probable side effects like anchorage loss or an uncooperative patient. Anchorage control is the more important concern given the increasing number of adult orthodontic patients in recent decades.[26] In adult patients, there are insufficient teeth in a mutilated dentition. Moreover, they do not use extraoral appliances because of social and peer group pressures. Intraoral anchorage devices lean against soft tissue like palatal mucosa or other anchor teeth, but they do not provide absolute anchorage and may lead to soft tissue irritation by palatal anchorage devices. Recent temporary anchorage devices can provide better anchorage control but have a more invasive procedure and may come loose during treatment. Sometimes, there is a limitation for the placement area because of anatomical consideration, insufficient bone density, or root proximity. Therefore, anchorage control by the localized drug is ideal for optimizing the treatment outcome and decreasing the treatment time.

Figure 3 shows that drug administration did not influence the normal development of animals.

In this study, we found no significant difference between OTM of the PC and drug-administered
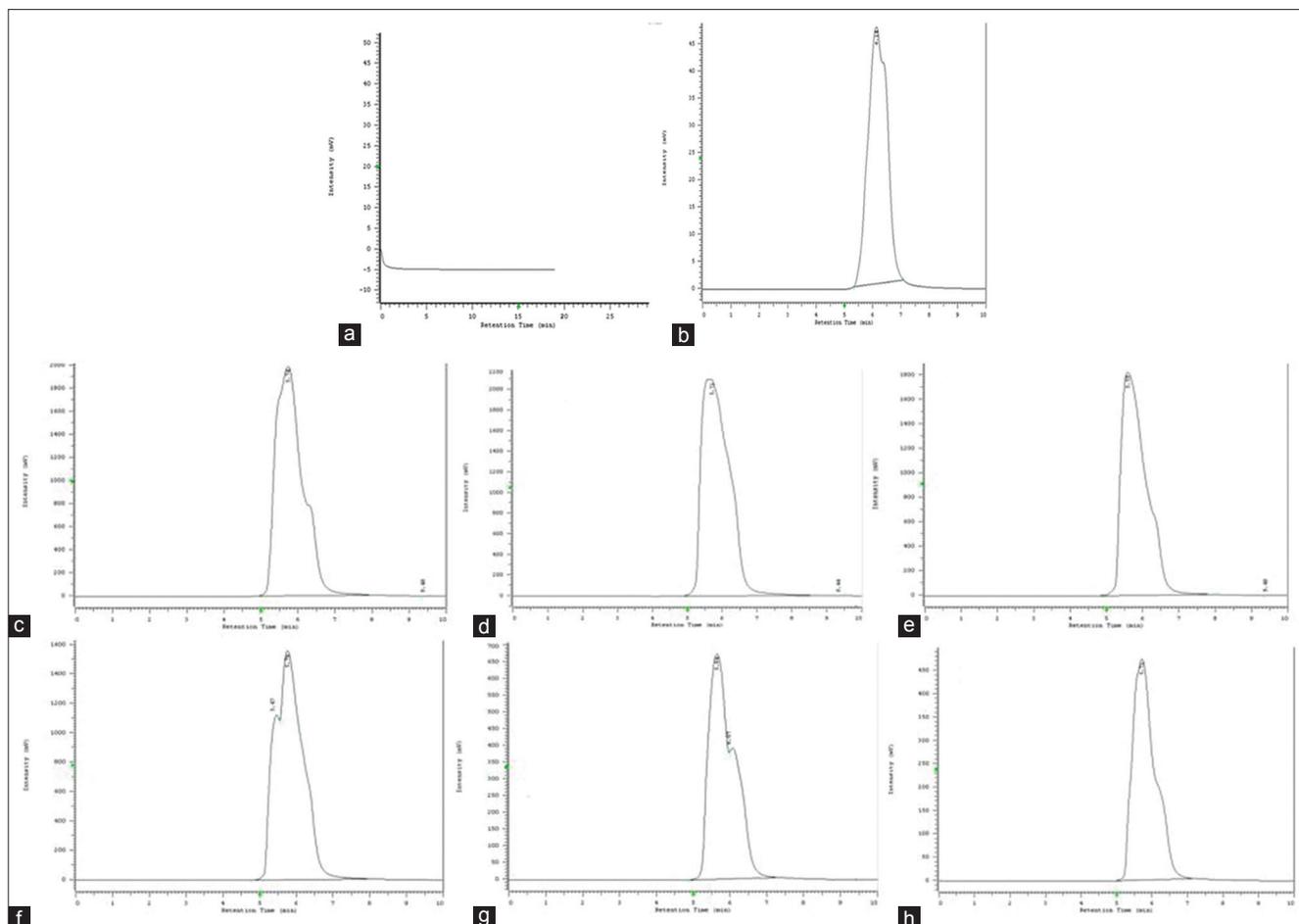
Figure 5: High-performance liquid chromatography analysis of curcumin (μg/ml) in rat plasma: (a) Blank plasma, (b) Curcumin spike blank plasma, (c-e) Chitosan group samples, (f-h) gelatin group samples.

groups. In evaluating the effect of curcumin on the OTM, the PubMed, Google Scholar, and Science Direct databases were searched and no related article found in this regard. Therefore, it should be considered that the explanation of the results is based on the curcumin effect on bone remodeling.

Ozaki *et al.* explained that curcumin has a dose- and time-dependent influence on the osteoclast apoptosis, which lead to significant bone resorption inhibition.[27] Bharti *et al.* confirmed the suppressive effect of curcumin on RANKL signaling and the osteoclastogenesis procedure. Curcumin had a regulatory effect on the NF-kβ pathway.[14] It was shown that curcumin can suppress the expression of inflammatory mediators like cyclooxygenase-2, vascular endothelial growth factor, interleukins (IL-1 β, IL-6 and IL-8), nitric oxide (NO), and prostaglandin E2.[13] The authors believe that since these mediators have a critical role in OTM, suppression of these elements may play a crucial role in controlling tooth movement.

Other studies indicated a bone preservative effect of curcumin in an osteoporotic condition, such as during menstruation or after ovarectomy.[28,29] It also has a synergic effect on the bisphosphonates (alendronate) to decrease bone resorption.[30] Therefore, it seems logical that curcumin has a regulatory effect on the bone remodeling process and can be used as an anchorage-controlling or anti-relapse drug during OTM. However, this was not observed in our study.

A probable explanation for this result can be attributed to the controversial effect of curcumin on bone formation. Moran *et al.*[31] revealed that curcumin can inhibit NO synthase (NOS) expression and subsequent NO production, and interfere with the NF-kβ pathway. NO has been supposed to have a regulatory effect on osteoblast proliferation and bone formation. Therefore, it may be suggested that curcumin decreases bone formation in this way. In contrast, Gu *et al.*[32] indicated a stimulatory effect of curcumin on the rats' mesenchymal stem cell differentiation to osteoblast and increasing alkaline

phosphatase activity, mineralized nodule formation, and Runx2 expression. Therefore, we can expect curcumin to have a bone formative effect. As orthodontic movements consist of bone formation and resorption processes, absolute effects of curcumin on tooth movement cannot be determined precisely.

Histological analysis

Howship's lacunae

Note that the NC group had no orthodontic appliances; therefore, they did not show any Howship's lacunae. However, the PC group exhibits higher bone resorption in comparison to the G or Ch groups, which showed mild severity.

It seems that administering curcumin can decrease bone resorption significantly compared to the PC group. Therefore, the bone preservative effect of curcumin can promise effective anchorage control on using this drug as a local regulator in orthodontic treatment. Although there was no significant inhibitory effect on the orthodontic treatment in this study on curcumin, it may be related to properly released drugs in the movement site. This hypothesis should be investigated in future studies.

Blood vessels

The groups that were administered curcumin showed significantly lower blood vessel counts. It confirmed the inhibitory effect of curcumin on angiogenesis.[33-35] Previous studies demonstrated that curcumin can inhibit endothelial proliferation or affect other growth factors like bFGF, which collaborate in angiogenesis. This can support the inhibitory effect of curcumin on tooth movement. OTM depends on bone remodeling, which is a cell-related procedure. Blood supply and nutrition are necessary in this regard. A lack of these crucial elements can delay the remodeling process and indirectly, the OTM.

Osteoclast-like cells

Tartrate-resistance acidic phosphatase staining is the method of interest for evaluating osteoclast cells.[36] Owing to the limited availability and higher cost of this specific staining method, we had to use a traditional morphometric evaluation of osteoclasts based on previous studies.[37,38] Osteoclasts have been identified as multinucleated cells on bone surfaces. Finally, the results of the osteoclast evaluation should be interpreted with caution.

No increase was noted in the osteoclastic number in the NC group. However, the PC group showed

a mild–to-moderate increase. By comparing the osteoclast number between groups, a significant difference was noted between the Ch or G groups and the PC group. In this situation, it is possible to suggest that there was an agreement between the count of Howship's lacunae and the number of osteoclasts. The groups administered curcumin showed a lower count of Howship's lacunae and osteoclasts concomitantly. This confirmed the suppressive effect of curcumin on the recruitment of osteoclasts.

Keles *et al*.[39] indicated an important point about the close relationship between the number and function of osteoclasts in pressure sites and the maintaining of applied force. He revealed that in systems, using mesializing springs, it will be logical for the orthodontic force to decay rapidly during the first 5–7 days. This may be an interfering factor in evaluating the relationship between the number of osteoclasts and clinical OTM. Force maintenance during this period is important for osteoclast recruitment and function.

Root resorption

The NC group did not show any root resorption, but there was a moderate count of resorption lacunae in the PC group. Groups that were administered curcumin showed almost mild root resorption, which was statistically significantly lower than in the PC group.

It may be concluded that curcumin decreases the amount of root resorption. This may be related to the suppression of inflammatory mediators by curcumin, especially IL-1.[13] IL-1 has a significant effect on the orthodontically induced inflammatory root resorption.[40,41]

CONCLUSION

Curcumin did not show any significant inhibitory effect on OTM. However, the practical conclusion of this study was a probable efficacy of curcumin on tooth movement. Curcumin decreased bone and/or root resorption significantly. It also reduced angiogenesis and the number of osteoclasts in the field of OTM. Therefore, it is recommended for a useful local anchorage-controlling method with minimal invasive and side effects. Future studies on this drug are suggested to investigate the effect of curcumin on OTM with a higher dose released in the area of tooth movement.

Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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