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Acceleration of Ulcer Healing by Local Application of Myrrh Oil: An Experimental Study

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ABSTRACT

Background: Oral mucosa refers to the mucous membrane that lines the tissues within the oral cavity. Wound healing is an essential physiological process that involves the collaboration of numerous cell strains and their products to restore damage caused by a local aggressor. This process begins very early in the inflammatory phase and finishes with tissue repair. Myrrh oil has an anti-inflammatory effect on wound contraction, re-epithelization, early neovascularization, and increased collagen density.
Objectives: To evaluate the effectiveness of myrrh oil in rats oral mucosal ulcer healing.
Materials and methods: 36 adult male albino rats (Rattus norvegicus) of about 250–300 g of weight and an age of about 2–3 months were used in this experimental study. The practical part of this study lasted two months (June–July 2022) in the private animals' house of Al-Dhyaa in Baghdad City, Iraq. The traumatic ulcer, with an 8 mm diameter and 1 mm depth was made on the right cheek mucosa by using a round diamond bur. The ulcer was treated once daily with a single topical dosage of 10 L of sterile distilled water (control Group). While in the myrrh oil Group, the ulcer was managed once a day with a micropipette dose of 10 ml of 1 mg/ml of myrrh oil. Animals were sacrificed after ulceration with general anesthesia over healing periods 1, 3, and 7 days. Histological analysis was performed by calculating the average wound contraction size, inflammatory cells and epithelial cells, and blood vessels. On days 1, 3, and 7 of the healing process, Van Gieson stain and Periodic Acid-Schiff stain were used to organise collagen fibre deposition and extracellular matrix production in all of the groups that were looked at.
Results: Histological findings of an induced oral ulcer treated with daily application of myrrh oil showed more epithelization, reduced inflammation, increased angiogenesis, and decreased healing time in comparison to the control Group. The histochemical findings showed a significant difference in collagen fibers synthesis and extracellular matrix formation in myrrh oil in comparison to the control Group.
Conclusion: Myrrh oil is more effective in promoting the healing of ulcers than the control Group.
Keywords: Wound healing; Myrrh oil; Histological evaluation; Periodic Acid-Schiff stain; Van Gieson stain.

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INTRODUCTION

There are three distinct forms of oral mucosa, each distinguished from the others by their histology, clinical presentation, and functional characteristics. Lining, also known as movable mucosa, masticatory mucosa, and specialized mucosa, can all be either keratinized or non-keratinized, depending on the type of mucosa they are [1]. Histologically, the oral mucosa is composed of three layers: the oral epithelium, which is a stratified squamous type and can be either keratinized or non-keratinized. Keratinized oral epithelium includes the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum, while non-keratinized oral epithelium contains Merkel cells, Langerhans cells, and lymphocytes. The connective tissue that lies beneath the oral epithelium is called the lamina propria. It

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is composed of two layers: the papillary layer, which is made up of loose connective tissue, and the deeper layer, which is made up of dense, irregular connective tissue (reticular layer). The submucosa is made up of dense connective tissue that has an uneven pattern. This layer is not present in certain areas, in this case, the mucosa will be attached to either bone or muscle by the lamina propria [2].

The wound healing process is a straightforward linear mechanism. Growth factors stimulate cell proliferation, which then leads to an integration of dynamic changes involving soluble mediators, blood cells, the creation of an extracellular matrix, and the proliferation of parenchymal cells [3]. The steps that biochemical processes go through in the healing process of wounds are as follows: Hemostasis, inflammatory response, cell proliferation, and remodeling, which are the processes that create the materials that make up the extracellular matrix, are all processes that take place throughout the healing process [4].

It is common practice in Saudi Arabia to treat minor ailments at home with myrrh, which is a well-known medicinal plant [5]. It is known as "mur" in Arabic, which translates as "bitter." Oleoresin is the name given to the gum that comes from the myrrh tree, and its gum is known as myrrh gum. It is known to have originated in Mecca, which is why it is referred to as "Mur Makki" [6]. The use of myrrh in the treatment of wounds has been a topic of discussion in previous research. Myrrh has been shown to hasten the healing process of wounds by promoting faster wound contraction, re-epithelization, early neovascularization, and higher collagen density. Additionally, myrrh has shown an anti-inflammatory effect and anti-bacterial activity [7, 8].

Most previous studies applied myrrh oil to the wound healing of the skin [9]. Hence, this study was conducted to assess the efficacy of myrrh oil in promoting the healing of oral mucosal ulcers in rats.

MATERIALS AND METHODS

The design for this study is experimental. The 36 rats were randomly assigned into two groups; the myrrh oil Group, consisting of 18 animals, and the control Group, consisting of another 18 animals. The rats of 250-300 g of weight and an age of about 2-3 months were matched together among the two groups. Each group was subdivided into three subgroups according to the day of slaughter; the 1^{st}, 3^{rd}, and 7^{th} days of healing intervals (6 rats from each group for each interval). The practical part of this study lasted two months (June–July 2022) in the private animals' house of Al-Dhyaa in Baghdad City, Iraq. A round diamond bur at a speed of 15,000 rounds per minute (rpm) was utilized to induce an 8 mm traumatic ulcer on the right cheek mucosa. An intramuscular (IM) injection of xylazine 2% (0.08 ml/kg body weight) and ketamine 10% (3 mg/kg body weight) was used to provide the general anesthetic solution. Before the surgery, all surgical instruments and towels were sterilized for 30 minutes in an autoclave at 121°C and 15 bar/cm^2 of pressure. Using the digital vernia, the required ulcer size was determined, and a bur stopper was placed on the surgical bur. The ulcer was treated once daily with a single topical dosage of 10 L of sterile distilled water (Control Group). Myrrh Oil Group: The ulcer was managed once a day with a micropipette dose of 10 ml of 1 mg/ml of myrrh oil [10]. At the end of the healing periods 1, 3, and 7 days following ulceration, animals were slaughtered with an overdose of general anesthetic to collect ulcer samples for histological and histochemical investigation. The study was conducted in compliance with the College of Dentistry, University of Baghdad [Reference No. 489] animal experimentation ethical principles. The specimens were fixed in a 10% formalin solution, embedded in paraffin, and sectioned into thin slices for the production of slides. Under a light microscope, hematoxylin and eosin (H& E) staining was performed for histological evaluation. Histological analysis was performed by calculating the average wound contraction size, inflammatory cells and epithelial cells, and blood vessels. Van Gieson stain and Periodic Acid-Schiff stain (PAS) were used for histochemical examination to organize collagen fiber deposition and extracellular matrix production on days 1, 3, and 7 of the healing periods for all groups that were looked at. The slides stained with Van Gieson stain were examined using a light microscope and with the aid of Image J version 1.8 [11] by following the steps:

1. The image was selected to open the tools bar, and then straight tool for measuring length was chosen.
2. Click on Analyze and Analyze Particles.
3. Click on an image-type-RGB color.
4. Click on a set scale, enter the length of the scale bar into the known distance, and change the unit from pixel to micrometer.
5. Finally, click on plugins and select color deconvolution.

Measurements were made at the intensity of blue, which represents the collagen density. Collagen density was measured under the wound area compared to the normal area at 100 magnifications. The mean of the collagen values obtained for the normal lamina propria was accepted as the equivalent of 100. For each group, the mean of the collagen density under the wound area was expressed as a percentage compared to the collagen density of the normal lamina propria during the post-wounding day [12].

Data Management and Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 25 was utilized to generate a comprehensive description of each variable. The obtained data were controlled daily, and the only thing that was connected to the specifics of the participants was their serial numbers. The mean, standard deviation, standard error, 95% confidence interval, and minimum, and maximum values were used to express the data. The Mann-Whitney U test was utilized to analyze the correlation between the non-normally distributed variables that were under investigation. It was determined to have statistical significance if the P-value was 0.05 or lower and the confidence level was 95%.

RESULTS

Wound Contraction Size

Table 1A shows the percentage of recovery in ulcer size at day 1, day 3, and day 7 for the groups that were examined. The myrrh oil Group had the highest mean percentage of recovery ulcer size value at the 7^{th} day of healing intervals 80%. Table 1B displays the average size of the ulcer on days 1, 3, and 7 for both of the groups that were studied. As can be seen from this table, the size of the induced ulcer reduced over time in all of the groups that were studied, and the lowest mean value of 1.6% was observed in the oil Group on the 7^{th} day of the healing period.

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Table 1. Mean, SD, SE, and 95% confidence interval of the mean, minimum, and maximum levels of recovery ulcer size and final ulcer size in studied groups in all healing periods.

A: Mean percentage of recovery ulcer size in studied groups.								
Day	Group	N	Mean%	SD	SE	95% Confidence interval for the mean	Min.	Max.
Day 1	Myrrh Oil	6	4	1.8	0.8	2 – 5.9	1.3	6.3
	Control	6	4.8	3.8	1.6	0.8 – 8.8	0	11.25
Day 3	Myrrh Oil	6	24	4.4	1.8	19.3 – 28.6	16.3	28.8
	Control	6	12.1	3.7	1.5	8.2 – 15.9	6.3	16.3
Day 7	Myrrh Oil	6	80	10.8	4.4	68.7 – 91.3	71.3	100
	Control	6	62.9	9.1	3.7	53.4 – 72.4	53.8	73.8
B: Mean of final ulcer size in studied groups.								
Day	Group	N	Mean	SD	SE	95% Confidence interval for the mean	Min.	Max.
Day 1	Myrrh Oil	6	7.68	0.1	0.1	7.5 – 7.8	7.5	7.9
	Control	6	7.62	0.3	0.1	7.3 – 7.9	7.1	8
Day 3	Myrrh Oil	6	6.08	0.4	0.1	5.7 –6.5	5.7	6.7
	Control	6	7.03	0.3	0.1	6.7 –7.3	6.7	7.5
Day 7	Myrrh Oil	6	1.6	0.9	0.4	0.7 – 2.5	0	2.3
	Control	6	2.97	0.7	0.3	2.2 – 3.7	2.1	3.7

Table 2. Mean, SD, SE, 95% confidence interval of the mean, minimum, and maximum levels of inflammatory cells, distribution according to score of inflammation, and comparison of the studied groups.

A: Mean, SD, SE, 95% confidence interval of the mean, minimum and maximum levels of inflammatory cells.								
Day	Group	N	Mean	SD	SE	95% Confidence interval for the mean	Min.	Max.
Day 1	Myrrh Oil	6	32.1	8.9	3.6	22.7 – 41.4	23.6	47.5
	Control	6	22.8	1.3	0.5	21.4 – 24.2	21.2	24.6
Day 3	Myrrh Oil	6	22.9	3.2	1.3	19.5 – 26.3	19	27
	Control	6	24.8	1.4	0.6	23.3 – 26.2	23.4	26.6
Day 7	Myrrh Oil	6	19.4	3.4	1.4	15.8 – 23.0	15.2	25.2
	Control	6	26.6	2.1	0.9	24.4 – 28.8	24.4	29.4
B: Distribution according to the score of inflammation.								
Day	Group		Score			Frequency N=6	Percent%	
Day 1	Myrrh Oil		Mild			1	16.7	
			Moderate			5	83.3	
	Control		Mild			6	100	
			Moderate			0	0	
Day 3	Myrrh Oil		Mild			4	66.7	
			Moderate			2	33.3	
	Control		Mild			4	66.7	
			Moderate			2	33.3	
Day 7	Myrrh Oil		Mild			5	83.3	
			Moderate			1	16.7	
	Control		Mild			2	33.3	
			Moderate			4	66.7	
C: Comparison between the studied groups according to inflammation.								
Day	Group		Mean rank			Z	P-value	
Day 1	Myrrh Oil		9.17			2.562	0.010*	
	Control		3.83					
Day 3	Myrrh Oil		5.58			0.882	0.378	
	Control		7.42					
Day 7	Myrrh Oil		3.92			2.486	0.013*	
	Control		9.08					

* Significant result

Inflammatory Cells

Table 2A shows the means of the studied groups at days 1, 3, and 7 of healing intervals. Where the highest mean value was recorded in the myrrh oil Group on the 1st day and the lowest mean value was recorded in the myrrh oil group on the 7th day of healing intervals compared with the control group. Table 2B shows the study groups were also classified according to the score of inflammation in a previous study [13]. The result showed that the inflammatory cells of the in-

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Table 3. Mean, SD, SE, 95% confidence interval of the mean, minimum, and maximum levels of epithelial cells, and comparison of the studied groups according to epithelial cells.

A: Mean of the epithelial cells.								
Day	Group	N	Mean	SD	SE	95% Confidence interval for the mean	Min.	Max.
Day 1	Myrrh Oil	6	190.8	21.3	8.7	168.5 – 213.2	159.23	221.06
	Control	6	194.5	40.8	16.7	151.7 – 237.3	127.16	233.26
Day 3	Myrrh Oil	6	214.2	19.4	7.9	193.9 – 234.6	187.36	233.27
	Control	6	218.7	22.5	9.2	195.0 – 242.3	187.23	247.08
Day 7	Myrrh Oil	6	301.6	46.3	18.9	253.0 – 350.2	235.27	360.05
	Control	6	252.6	46.7	19.1	203.5 – 301.6	197.06	312.23

B: Comparison of the studied groups according to epithelial cells.				
Day	Group	Mean rank	Z	P-value
Day 1	Myrrh Oil	5.67	0.801	0.423
	Control	7.33		
Day 3	Myrrh Oil	6	0.480	0.631
	Control	7		
Day 7	Myrrh Oil	8.17	1.601	0.109
	Control	4.83		

Table 4. Mean, SD, SE, 95% confidence interval of the mean, minimum, and maximum levels of collagen fiber, Comparison of the studied groups according to collagen density and mean of the blood cells.

A: Mean, SD, SE, 95% confidence interval of the mean, minimum and maximum levels of collagen density.								
Day	Group	N	Mean	SD	SE	95% Confidence interval for the mean	Min.	Max.
Day 3	Myrrh Oil	6	37.1	15.9	6.5	20.4 – 53.8	21.6	61.3
	Control	6	28.7	6.8	2.8	21.6 – 35.9	21.3	37.2
Day 7	Myrrh Oil	6	64.4	24.7	10.1	38.5 – 90.3	16.2	83.3
	Control	6	51.5	9.3	3.8	41.7 – 61.2	35.3	62.2

B: Comparison of the studied groups according to collagen density.				
Day	Group	Mean rank	Z	P-value
Day 3	Myrrh Oil	7.33	0.801	0.423
	Control	5.67		
Day 7	Myrrh Oil	8.5	1.922	0.055
	Control	4.5		

C: Mean, SD, SE, 95% confidence interval of the mean, minimum and maximum levels of blood cells.								
Day	Group	N	Mean	SD	SE	95% Confidence interval for the mean	Min.	Max.
Day 1	Myrrh Oil	6	7.4	0.8	0.3	6.5 – 8.3	6.3	8.3
	Control	6	7	2	0.8	4.9 – 9.1	5	10
Day 3	Myrrh Oil	6	11.7	2.4	1	9.2 – 14.2	9	15.3
	Control	6	9.5	3.9	1.6	5.4 – 13.6	6	17
Day 7	Myrrh Oil	6	12.7	2.1	0.9	10.5 – 14.8	10	15.6
	Control	6	11.3	3.1	1.2	8.1 – 14.5	7	16

cluded animals lied within the mild and moderate scores, and no one across the groups during the study period lay within the severe score. Table 2C shows a significant difference was obtained on the 1st day (P-value = 0.010) between the studied groups, in favor of the oil group. On the 3rd day, no significant difference was obtained (P-value = 0.378) between the studied groups. On the 7th day, a significant difference was obtained (P-value = 0.013) between the myrrh oil and control groups in favor of the control Group.

Epithelial thickness

Table 3A illustrates an increase in the mean value of epithelial thickness in both groups with time, but the highest mean value was recorded in the Myrrh oil Group on the 7th day in comparison with the control Group. Table 3B shows no significant difference between the studied groups during all healing periods, where the P-value was 0.423 for the 1st day, 0.631 for the 3rd day, and 0.109 for the 7th day.

Collagen density

Table 4A illustrates an increase in the mean value of collagen fibers in both groups with time, but the highest mean value was recorded in the myrrh oil Group on the 7th day in comparison with the control Group. Table 4B shows no significant difference between the studied groups during all healing periods, where the P-value for the 3rd day = 0.423 and 0.055 for the 7th day. Table 4C shows an increase in the mean value of the blood vessels with time in both studied groups in favor of the myrrh oil Group in all healing intervals.

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Histological and Histochemical Findings

Figure 1 reveals the histological and histochemical findings of the present study. On the 7th day after the ulcer had formed, a histological look at the control group showed that new thin epithelium had grown on the ulcer surface, but there were no rete ridges (Figure 1A). Vangieson stain showed the formation of collagen fibers with granulation tissue, which contains congested blood vessels (Figure 1B). PAS stain showed the control group on the 7th day with a positive reaction of granulation tissue (Figure 1C). The histological view of the ulcer treated with myrrh oil on the 7th day revealed a well-defined keratinized squamous epithelium. Shows that the lamina propria had granulation tissue with signs of collagen fibre remodelling, a lot of blood vessels, and less infiltration of inflammatory cells. (Figure 1D). Vangieson stain showed significant quality of collagen fibers in the positive (Figure 1E). PAS stain showed the myrrh oil group on the 7th day with a positive reaction of granulation tissue (Figure 1F).

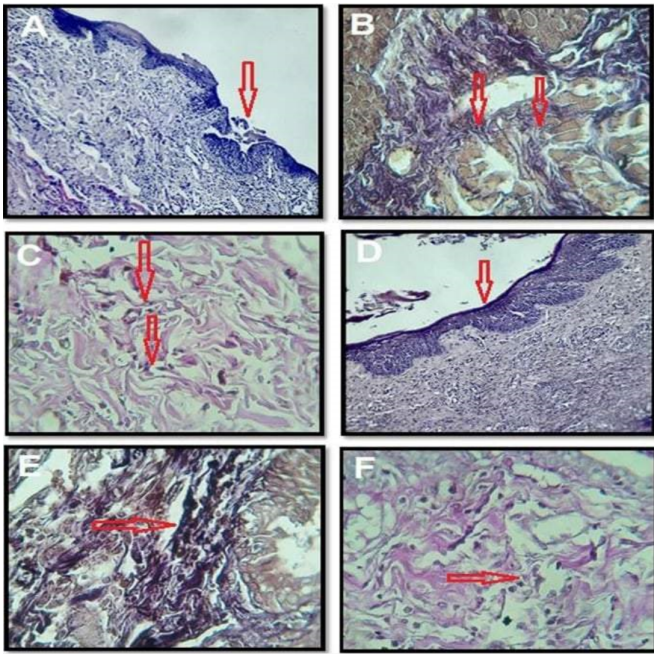

Figure 1. Photomicrograph A shows the induced ulcer on the 7th day of the control Group stained with a thin layer of epithelium (red arrow), H& E stain ×10. Photomicrograph B shows the control Group on the 7th day with collagen fiber (red arrow) in the lamina propria, Van Gieson stain ×40. Photomicrograph C shows the control Group on the 7th day with a positive reaction of granulation tissue (red arrow), PAS stain ×40. Photomicrograph D represents the myrrh oil Group on the 7th day with keratinized squamous epithelium (red arrow), H& E stain ×10. Photomicrograph E shows a myrrh oil Group on the 7th day with collagen fibers (red arrow), Van Gieson stain ×40. Finally, photomicrograph F represents the myrrh oil Group at day 7 with a positive reaction of granulation tissue (red arrow), PAS stain ×40.

DISCUSSION

Traumatic ulcers are damage to the oral mucosa produced by mechanical or physical trauma, such as sharp food, unexpected biting during mastication, biting while speaking, puncturing by sharp objects, or cracked, deformed, or decayed teeth [14].

Myrrh oil can speed up wound healing due to its effect on wound contraction, re-epithelization, early neovascularization, and increased collagen density [7, 10]. In the present study, the mean percentage of recovery ulcer size grew over time in all groups, with the control Group having the lowest mean value compared to the myrrh oil Group. The mean of final ulcer size decreased with time in both of the studied groups, with the least ulcer size recorded in the myrrh oil Group on the 7th day of healing intervals in comparison with the control Group. This may be the result of myrrh oil's antibacterial properties, which minimize the time required for wound contraction and eliminate postoperative bleeding [8] and this is in agreement with previous investigations [13–15].

Re-epithelialization is an attempt to repair a wound through the proliferation and migration of basal and suprabasal cells during the healing phase. The present study revealed that re-epithelialization for both the control and experimental groups increased with time, with the myrrh oil Group recording a high mean value on day 7 that was slightly higher than the control group due to increased proliferation and progression of epithelial cells, as well as an increase in neovascularization, fibroblast cells, and collagen fiber. This is in agreement with previous studies [15, 16].

Van Gieson stain can distinguish between fine and coarse collagen fibers, which typically emerge during the phases of proliferation and remodeling [17]. The experimental groups did not differ significantly from the control group in terms of collagen fiber deposition on days 3 and 7, even though the values of both groups rose with time. These deposited collagen fibers provided strength and integrity to the tissue matrix during the wound-healing process. This was a result of the increased number of blood vessels (occurring early in the healing phase) and the appropriate migration of fibroblast to the location of the wound, and this is in agreement with [17, 18].

In this study, PAS was used to investigate the extracellular matrix in both control and treatment groups [19]. PAS stain showed the keratin layer, an apparent degree of re-epithelialization with the restoration of rete ridges, and subepithelial infiltration of mononuclear cells. A considerable increase in the PAS-positive reaction in the myrrh oil Group in the basement membrane, particularly on day 7 of healing intervals, and this is similar to the histochemical findings of a previous study [19] which observed a PAS-positive reaction in the basement membrane of the rat oral mucosa. The present study also indicated a positive PAS reaction in the lamina propria of both examined groups at both healing periods, which disagrees with the findings of a previous study [20] which suggested a negative PAS reaction in the oral buccal mucosa of mice due to a lack of glycogen. This finding disagrees with a prior investigation [19] which reported an intensely positive PAS reaction in the epithelium of the gastric mucosa in the experimental rats. This is due to the presence of mucin in the gastric mucosa and the absence of mucin in the oral epithelium of rats [21]. In the present study, the neovascularization in both the control and experimental groups revealed an increase in angiogenesis with the healing

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time, but the oil Group recorded the highest mean value of blood vessels at the 1st, 3rd, and 7th days of healing intervals as compared to the control Group. The present result is in agreement with [16, 22]. The current study revealed variable degrees of inflammatory reaction between the studied groups at all healing intervals. The intensity of inflammatory cells in the ulcer area was found to be predominant in the experimental Group as compared to the control Group. On the 1st day, and the myrrh oil Group recorded the highest mean value, while on the 7th day, the inflammatory cells of the myrrh oil Group recorded the lowest mean value. This may be due to the anti-inflammatory effects of myrrh oil [7]. This result is in agreement with other studies [23, 24].

The study had many limitations. First, there is difficulty in obtaining the animals, which takes more time and effort. Second, electron microscopy is absent from our college. The use of electron microscopy enhances the accuracy of the results. Third, there are no facilities for obtaining pure essential myrrh oil in our regional area. Lastly, for animal research studies like the present study, it is important to provide a well-developed research center to facilitate the researcher's work. The housing of the animals is also very important to avoid the loss of animals before the end of the study. These limitations may have impacted or influenced the application or interpretation of the study results.

CONCLUSION

The topical application of essential myrrh oil is significantly more beneficial in promoting the healing of oral traumatic ulcers in comparison to the control Group. This study indicated that a myrrh solution with a controlled and low concentration could expedite healing as a supplement or replacement for existing therapies. The global use of plants for medicinal purposes has increased significantly. To determine the various properties, effective doses, and forms of these herbs, as well as their adverse effects and toxicity, additional research is required. Other factors, such as the nature, size, and location of the wound, as well as vascular supply, infection, and other complications that may delay the healing process, must also be considered in future studies.

ETHICAL DECLARATIONS

Acknoweldgements

None.

Ethics Approval and Consent to Participate

The ethical committee had approved the protocol of the study of the Oral Diagnosis Department, College of Dentistry, University of Baghdad [No. 489] of animal experimentation ethical principles.

Consent for Publication

Not applicable.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

Both authors have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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