RESEARCH PAPER

Comparative Modulation of Systemic Inflammatory and Oxidative Stress Biomarkers by Green-Synthesized SiO_2 Nanoparticles and Rhus coriaria in a Sheep Tibial Defect Model

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ABSTRACT

For dental implantation as well as for guided bone regeneration, the process of bone regeneration is of utmost importance. In the past, various bioactive nanomaterials as well as plant derived bioactive molecules have been explored to create a more conducive healing environment for bone regeneration. The purpose of this study was to investigate the effect of locally applied Rhus coriaria extract and bio-synthesised silicon dioxide nanoparticles (SiO_2 NPs) on bone regeneration in a tibial bone defect created in a sheep. To test the effects of Rhus coriaria extract and bio-synthesised silicon dioxide nanoparticles (SiO_2 NPs) on bone regeneration, three groups of sheep tibial defects were established and analyzed after different healing times. In addition to serum parameters of inflammation (IL-6 and TNF-α) and of oxidative stress (MDA, SOD and T-AOC), also the radiographic densitometric measurements of the bone defects were recorded. The results indicated that the healing process in the two treated groups were significantly higher than that of the untreated control group. Bio-synthesised SiO2 nanoparticles provided the most positive results for the healing process as they possessed the lowest values of IL-6, TNF-α and MDA whereas the highest values of SOD and T-AOC were recorded. The radiographic mineral density of the treated bone continued to increase throughout the study period with the late-stage values indicating the highest degree of mineralization and maturity in the bone of SiO2 nanoparticles treated group. The bio-synthetic SiO2 NPs have higher regenerative potential than Rhus coriaria extract alone. The NPs decrease inflammation and oxidative stress and induce better radiographic bone mineralization than Rhus coriaria extract. Findings of this study could be useful for future preclinical studies aimed at bone regeneration around implant.

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INTRODUCTION

Bone regeneration is one of the biggest challenges in today's implant dentistry, in oral and maxillofacial surgery as well as in periodontal reconstruction. In order to achieve a sufficient osseointegration of dental implants and a long-lasting stability of implants, sufficient bone with the correct density is needed in order to guarantee an adequate oral function. Due to accidents (trauma), to the loss of teeth by extraction as well as to periodontal diseases, congenital malformations and surgical errors, the alveolar

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bone is often insufficient in terms of quantity and quality and thus has to be increased by so-called bone regenerating procedures [1,2].

Bone healing is a highly complex process which is divided into four stages of healing: (1) the inflammatory process with replication of cells and tissue, (2) the hard and soft tissue remodeling, and (3) the vascularization and mineralization. Inflammatory responses play an important initial role in bone healing by attracting both immune cells and osteogenic cells to a bone fracture. The level and duration of the inflammatory response is critical to the healing process. Excessive or prolonged levels of inflammation can impede the process of differentiating osteoblasts and also may stimulate osteoclasts that are involved in resorbing bone thereby interfering with bone maturation. Two of the major inflammatory cytokines, IL-6 and TNF-α, are crucial in the bone healing process; however, at high levels and/or of a protracted duration, these cytokines can interfere with bone formation and osseointegration [3,4].

In addition to the inflammatory processes, also the oxidative stress can affect the bone healing process and the general process of bone regeneration to be used for dental implantation. The excessive production of reactive oxygen species (ROS) by different cell types can cause severe damage to cells. In fact, it has been shown that the process of bone formation by osteoblasts as well as the degradation of the extracellular matrix by the peroxidation of lipids can be impaired by ROS. The degree of lipid peroxidation is measured by malondialdehyde (MDA), while the systems of scavengers for ROS as well as the endogenous antioxidant capacity of tissues (T-AOC, total antioxidant capacity) are defensive systems that protect cells from damage by ROS and allow to maintain the redox balance, which is required for the bone repair processes [5,6]. Therefore, for the induce of bone regeneration in the dental implant field, it would be very useful to develop strategies to suppress also the inflammatory and the oxidative stress processes.

Biomaterials in conjunction with nanotechnology have recently seen a marked upsurge in their applications for enhancing bone growth and regeneration. Silicon-containing biomaterials have great potential in skeletal tissue growth of mammals, because of the essential role of silicon in the biosynthesis of collagen, the extracellular matrix and hard tissue mineralization. In recent years, there has been an ever increasing interest in using the silicon dioxide nanoparticles (SiO_2 NPs) for various applications including for making the biomaterials. The wide spread applications of the silica based nanomaterials can be due to their unique physical and chemical properties including their extremely high surface area to volume ratio and bioactivity [7,8]. Different silica based nanomaterials can promote the osteoblast growth and subsequently the formation of the mineralized tissues and thus have the tremendous potential in the applications for the guided bone regeneration and making implant sites. [9].

Nanomaterials have been recently integrated into the field of regenerative medicine by using the green synthesis approach. Green synthesis of nanoparticles involves the bioactive compounds from plants to reduce and stabilize the metal ions. Green synthesized nanoparticles are highly biocompatible and non-toxic and hence environmentally friendly. Importantly, the surface associated phytochemicals with the nanoparticles have antioxidant and anti-inflammatory properties. These additional biological functions are delivered by phytochemicals along with the nanoparticles, which are used as biomaterials for tissue regeneration [10,11].

Rhus coriaria L. (sumac) is one of the most studied medicinal plants and it is rich in a variety of phenolic compounds, such as flavonoids, tannins, and also in anthocyanins and organic acids. All these bioactive compounds of sumac have been reported to possess antioxidant, anti-inflammatory, antimicrobial, and also protective effects against tissue injuries. Several studies have also reported the effects of sumac extracts on reducing oxidative stress, on modulating production of inflammatory cytokines, and also on promoting of healing [12,13]. Sumac thus can create a favorable healing environment for bone regeneration, especially in the initial phase of inflammation and oxidative stress.

The field of regenerative medicine for skeletal defects is using translational research with large animal models to mimic the human skeleton. A tibial defect model in sheep has recently become a commonly used preclinical model for testing novel biomaterials intended for use in bone augmentation in the field of oral and maxillofacial surgery. The model is also suitable for testing biomaterials intended for use in implant dentistry as well as for alveolar bone reconstructions, because of the large size of the bone and its natural remodeling characteristics as well as the relevant biomechanical properties of this model, which are more human like than those of smaller laboratory animals [14].

Although silicon-based nanomaterials and plant-derived bioactive compounds have received increased attention in recent years for their potential biomedical applications, there are some knowledge gaps. In most studies that have already been published on silicon-based nanoparticles and botanical extracts, these two subjects have been studied separately and the effects induced by both have not been compared and contrasted under the same regenerative conditions. Also, most of the studies that have investigated the effects of silicon-based nanoparticles and of botanical extracts on bone have used small animal models and have only assessed some of some of the parameters of interest such as inflammation and oxidative stress, while others such as radiographic mineralization have been only rarely evaluated. Thus, there is a lack of studies that have simultaneously investigated the effects of silicon-based nanoparticles on the three mentioned parameters of interest using large animal models that are relevant for implant dentistry. Also, there is a lack of information on the biological behavior of bio-synthesized SiO_2 nanoparticles, which have been produced using Rhus coriaria extract, especially with regard to their potential to promote bone regeneration and mineralization.

The objective of this work was to evaluate the local application of Rhus coriaria extract and bio-synthesized silicon dioxide nanoparticles as separate treatment modalities in experimentally induced tibial bone defects in sheep. The study assessed bone healing by means of radiographic densitometry and through measurement of the levels of inflammatory (IL-6 and TNF-α) and of oxidative stress parameters (MDA, SOD and T-AOC) parameters. The results of this study shall provide input for the development of a new, biologically active material, to be used in guided bone regeneration and in the preservation of dental implant sites as well as in other bone augmentations to be used in implant dentistry.

MATERIALS AND METHODS

Study Design and Ethical Considerations

This study is a controlled experimental research study for evaluating bone healing in tibial bone defects created in experimental sheep model and treated locally with Rhus coriaria extract and with bio-synthesized silicon dioxide nanoparticles (SiO_2 NPs). The degree of bone healing was evaluated by radiographic densitometry in addition to measurement of serum levels of inflammatory and oxidative stress biomarkers.

All experiments were performed according to the guidelines of the relevant ethical standards for animal experiments. Every effort was made to minimize animals' pain and stress, and also the number of animals used was kept to a minimum in order to avoid their killing. Ethical approval was obtained from the Institutional Animal Care and Use Committee (IACUC), College of Dentistry, University of Mosul (Approval No. 234/2025).

This experimental animal study was conducted using 24 male sheep allocated into three experimental groups. Each group included eight animals, with four animals evaluated at one month and four animals evaluated at two months post-operatively.

Experimental Animals

We used clinically healthy 10–12 month old male sheep of approximately 25–30 kg body weight for the experiment. As a large animal model the sheep is very suitable for making long bone defects and studying the healing process. All animals were clinically examined before surgery and kept in normal housing conditions and had free access to food and water before use and acclimatisation to the surroundings.

Experimental Grouping

In the current study, the experimental study was performed on the animals and the animals were divided into three groups (treatment groups) since local treatments were applied on the tibial defects that were created on the animals in the study.

1. The tibial bone defects of the animals in the negative control group were left open to the surroundings without any further local or systemic treatment.

2. Sumac extract group: tibial defects were locally treated with Rhus coriaria extract.

3. Bio-synthesized SiO_2 nanoparticle group: tibial defects were locally treated with green-synthesized silicon dioxide nanoparticles.

In the treated groups (Sumac extract and Bio-synthesized SiO_2 nanoparticle groups) assessment for bone healing in terms of radiographic signs were made at the end of 1st and 2nd months following surgery. The codes for the radiographic signs for the images were picked from the group sheet (Fig. 1) and the corresponding labels for the control group, sumac-treated group and SiO_2 NP-treated group at 1st and 2nd months post-surgery are shown.

The distribution of the animals in the different treatment groups was done by simple randomization after the acclimatization period. The distribution of the animals in the different treatment groups was done to minimize bias. The base line of the different groups was equalized.

Preparation and Local Application of Treatment Materials

To assess the in vivo bone-healing ability of test samples, Rhus coriaria extract was mixed with a gel formulation, and then the gel test samples were locally applied into bone defects. The concentration of the extract in the test samples was 10 mg/mL and 0.2 mL of the test samples were applied into each of the bone defects, thus a total of 2 mg of the extract was applied into each of the bone defects. In addition, bio-synthesized SiO_2 nanoparticles were also applied into the defect site, at a dose of 5 mg/defect. The test materials were inserted into the defects immediately after they were created, prior to the closure of the wound so that the test materials came into contact with the injured surface of the bone.

Anesthesia and Surgical Procedure

Surgical procedures were conducted under general anesthesia. Animals were intramuscularly injected with a combination of ketamine (10 mg/kg) and xylazine (2 mg/kg) and local infiltration with a mixture of lidocaine containing epinephrine was used to provide additional analgesia and to control hemorrhage.

The left tibia of the animal was first shaved and then cleaned with 10% povidone–iodine solution. A 2 cm longitudinal skin incision was made to expose the bone. By lifting the periosteum the 8 mm in diameter and 5 mm in depth defect was created in the tibia by means of a surgical bur. The created defect of the tibial bone was either left to heal up naturally or filled with sumac extract or bio-synthesized SiO_2 nanoparticles, which had been allocated to the animals according to the groups. The returned to place the periosteum and the soft tissues were closed in layers by means of non-absorbable suture material.

Postoperative Management

After surgery the wound was disinfected and covered with a dressing. The corner of the lip where the operation was performed was treated with oxytetracycline spray and the animal received

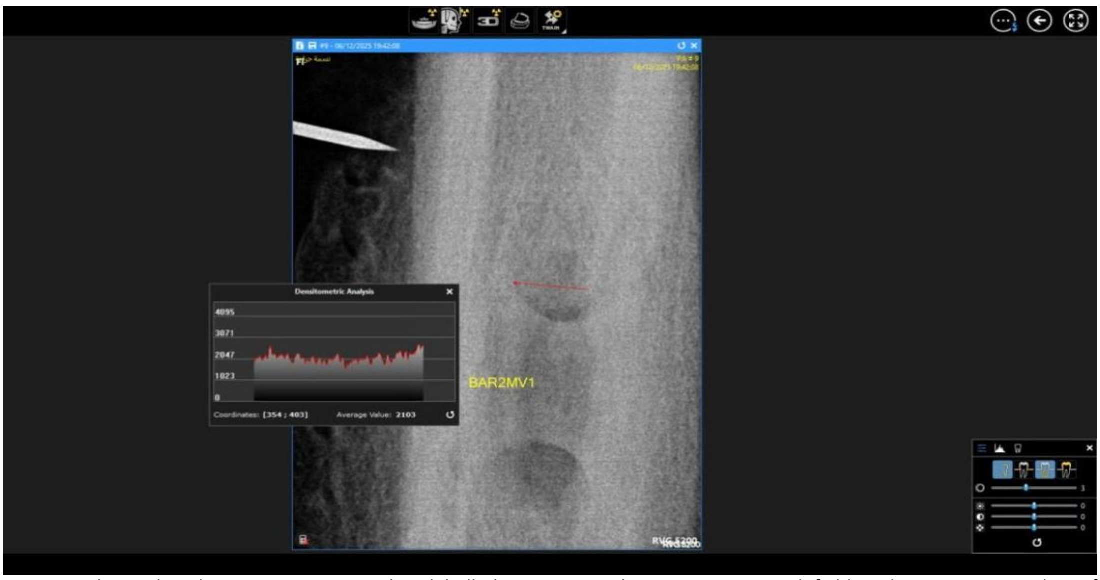

Fig. 1. Radiographic densitometric screenshot labelled BAR2MV1, showing a measured field with an average value of approximately 2103.

a systemic antibiotic to prevent infection. The animals were monitored on a daily basis for signs of healing, of infection, of inflammation, of dehiscence of the wound or of other postoperative complications. After 7 days the sutures were removed, when sufficient healing of the wound had taken place.

Blood Sampling and Serum Preparation

After specific time points blood was collected from veins in tubes. After coagulation at room temperature blood was centrifuged and serum was stored at -20°C for biochemical assays.

Biochemical and Oxidative-Stress Analysis

Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured as inflammatory parameters. Malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (T-AOC) were measured to assess oxidative stress and the relevant antioxidant capability. Assays were carried out using kits from Elabscience Biotechnology Co., Ltd. (Wuhan, China) as instructed by the manual of the assay kits. The results were expressed in appropriate units.

Radiographic Densitometric Assessment

Post- radiographs of the tibial defects were assessed using CS Imaging software. The visible intra-image codes on the screenshots were then matched to the corresponding animal's group in the handwritten group list on the back of the screenshots. Gray-value readings of software-set boundaries within a ROI in the vicinity of the defects were then recorded and summarised in a Table 1 in a manner which grouped the data by time-point and by treatment group.

Radiographic grey-value measurements were extracted and summarized according to treatment group and healing interval to provide a comparative description of mineral-density trends among the experimental groups. That is, average grey levels for the controls at 1 and 2 months post-wounding, for the sumac treated animals with tibial defects at 1 and 2 months post-wounding, and for the bio-synthesized SiO_2 NP treated animals with tibial defects at 1 and 2 months post-wounding were summarized in Table 1. The mean grey levels for radiographs from individual animals within a group and time point were all standardized to a region of interest (ROI) near the tibial defect of that animal. Radiographic densitometric values were summarized according to treatment group and healing interval and were used for descriptive comparison of mineral-density trends among the experimental groups.

Statistical Analysis

Biochemical data points were averaged and expressed as mean ± SD. Comparison between groups were made using one-way ANOVA followed by Tukey's post-hoc test where appropriate. Differences were considered to be statistically significant at p-value ≤ 0.05. Since radiographic images were evaluated by observers blinded to group allocation, only a descriptive comparison of radiographic densitometric values among experimental groups and healing intervals was performed. Care was taken to minimize observer bias during radiographic assessment.

RESULTS AND DISCUSSION

Serum Inflammatory Biomarkers

The serum inflammatory biomarkers demonstrated significant variations among the experimental groups. The untreated control group exhibited the highest concentrations of both IL-6 and TNF-α, recording 181.9 ± 43.5 ng/L and 357.5 ±

Table 1. Serum inflammatory biomarkers across experimental groups.

Experimental group	IL-6 (ng/L)	TNF-α (ng/L)
Negative control	181.9 ± 43.5^a	357.5 ± 35.0^a
Sumac extract, 1 month	112.5 ± 10.6^b	323.0 ± 32.5^b
Sumac extract, 2 months	90.0 ± 19.8^c	265.3 ± 20.9^c
SiO_2 NPs, 1 month	98.0 ± 42.4^c	220.0 ± 35.4^d
SiO_2 NPs, 2 months	75.0 ± 15.0^d	160.0 ± 18.0^e
p-value	<0.001	<0.001

Different superscript letters within the same column indicate significant differences according to Tukey's post-hoc test (p ≤ 0.05).

35.0 ng/L, respectively. In contrast, both treatment modalities resulted in progressive reductions in inflammatory marker levels throughout the healing period.

In the sumac-treated group, IL-6 values were 112.5 ± 10.6 ng/L after one month and further decreased to 90.0 ± 19.8 ng/L after two months. TNF-α values were 323.0 ± 32.5 ng/L after one month and declined to 265.3 ± 20.9 ng/L after two months.

The bio-synthesized SiO_2 nanoparticle group demonstrated the most pronounced anti-inflammatory response. IL-6 values reached 98.0 ± 42.4 ng/L after one month and further decreased to 75.0 ± 15.0 ng/L after two months. Similarly, TNF-α values decreased from 220.0 ± 35.4 ng/L at

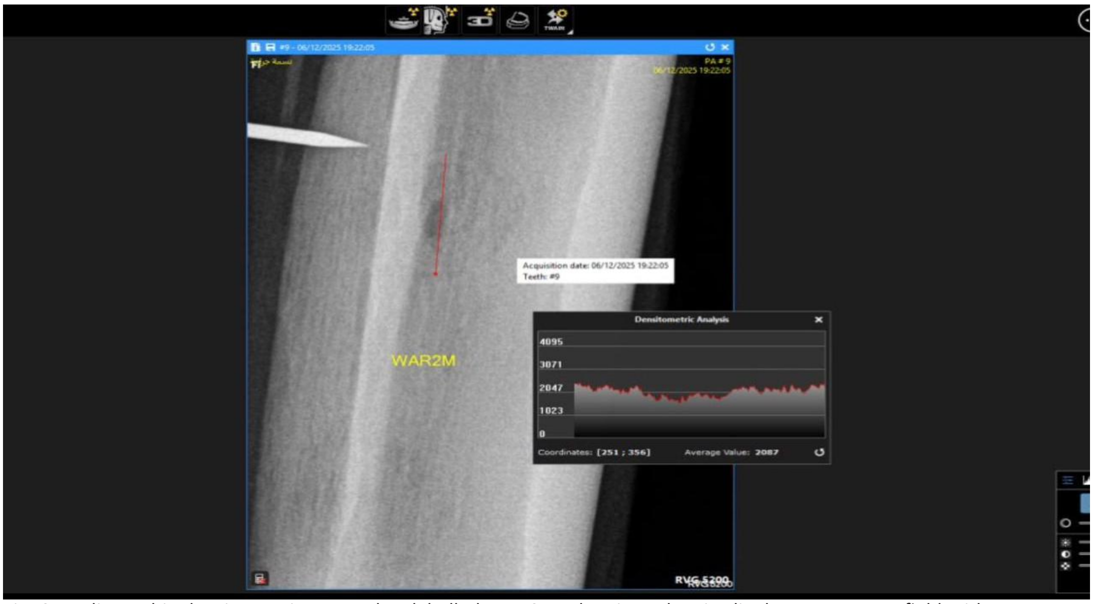

Fig. 2. Radiographic densitometric screenshot labelled WAR2M, showing a longitudinal measurement field with an average value of approximately 2087.

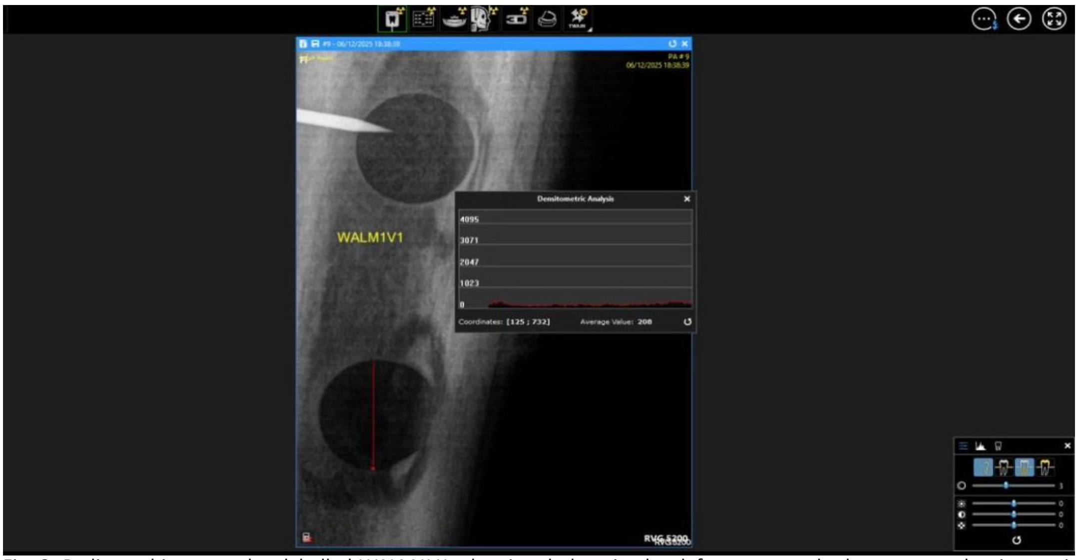

Fig. 3. Radiographic screenshot labelled WALM1V1, showing darker circular defect areas and a low average densitometric value in the selected field.

one month to 160.0 ± 18.0 ng/L at two months.

These findings indicate a marked suppression of inflammatory activity during the healing process, particularly in the SiO_2 nanoparticle-treated defects.

Serum inflammatory biomarkers

Serum IL-6 and TNF-α concentrations were measured using commercially available sheep-specific ELISA kits (Elabscience Biotechnology Co., Ltd., Wuhan, China) according to the manufacturer's instructions. Although IL-6 values in the SiO_2 NP group at one month were numerically lower than those in the sumac group, no significant difference was detected between these groups according to Tukey's test.

Substantial differences were observed in oxidative-stress and antioxidant-defense parameters among the study groups.

The untreated control group showed the highest MDA level (238.8 ± 48.2 ng/mL), indicating increased lipid peroxidation and oxidative injury.

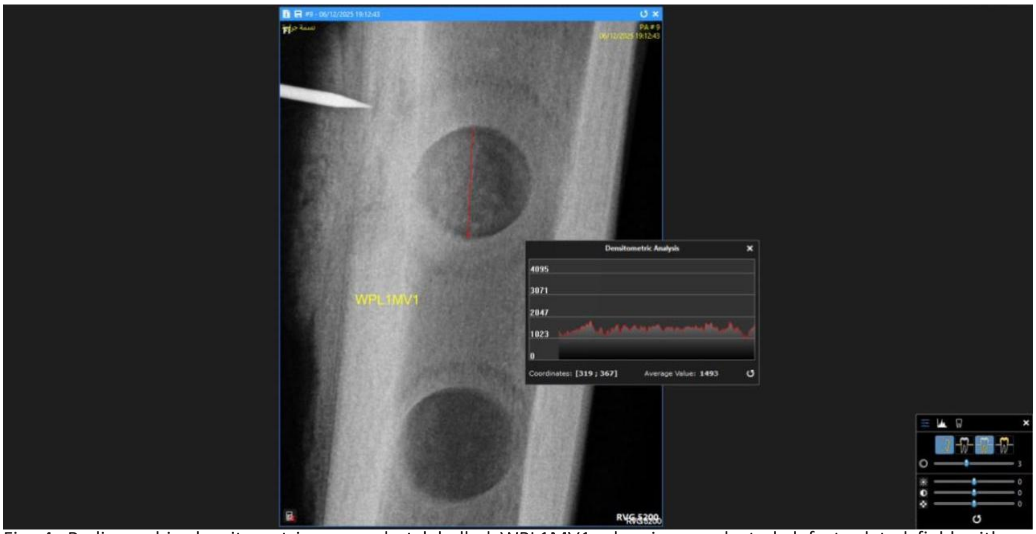

Fig. 4. Radiographic densitometric screenshot labelled WPL1MV1, showing a selected defect-related field with an average value of approximately 1493.

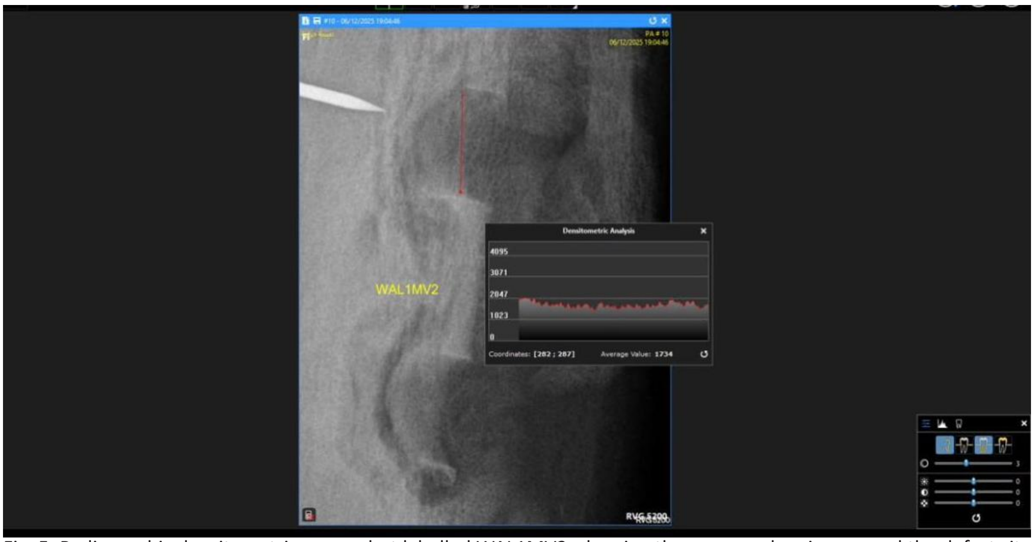

Fig. 5. Radiographic densitometric screenshot labelled WAL1MV2, showing the measured region around the defect site with an average value of approximately 1734.

In contrast, both treatment groups demonstrated lower MDA concentrations, with the lowest value observed in the bio-synthesized SiO_2 nanoparticle group at two months (97.0 ± 20.0 ng/mL).

Regarding antioxidant defense, SOD activity and T-AOC values were markedly elevated in the treated groups compared with controls. The highest SOD activity was recorded in the SiO_2 nanoparticle group after two months (2925 ± 120 U/mL), whereas the untreated control group exhibited the lowest activity (1035 ± 458 U/mL).

Similarly, T-AOC increased progressively throughout the healing period, reaching 1.971 ± 0.050 µmol/mL in the SiO_2 nanoparticle group after two months compared with only 0.576 ± 0.058 µmol/mL in the untreated controls.

Overall, these results demonstrate enhanced antioxidant defense and reduced oxidative stress in treated defects, with the strongest response observed in the SiO_2 nanoparticle-treated animals.

Radiographic Densitometric Evaluation

Radiographic examination of the tibial defects revealed noticeable differences in mineral density among the experimental groups during the healing period. Densitometric analysis performed using CS Imaging software provided grey-value measurements that reflected variations in mineral deposition within the defect sites.

At the one-month evaluation period, the sumac-treated defects exhibited the highest radiographic density value (2248 grey units), followed by the untreated control group (2087 grey units), whereas the bio-synthesized SiO_2 nanoparticle group showed a lower density value (1494 grey units).

At two months post-operation, the radiographic pattern changed substantially. The bio-synthesized SiO_2 nanoparticle group demonstrated the highest densitometric value (2103 grey units), which may reflect increased mineral deposition and progressive maturation of newly formed bone tissue. The sumac-treated group exhibited an intermediate value (1734 grey units), whereas the untreated control group showed the lowest density value (1493 grey units).

The radiographic observations suggest that bone mineralization continued to progress over time in the treated groups, particularly in the SiO_2 nanoparticle group, which displayed the greatest increase in radiographic density during the late healing phase.

The radiographic series provides a descriptive visual counterpart to the biochemical findings. Fields with higher grey values may indicate greater relative mineral density or less radiolucency within the selected region, whereas darker fields suggest incomplete mineral filling or low-density defect content. Nevertheless, because exposure, contrast, field placement, and screenshot-based extraction can affect grey values, these images should be used as supportive documentation unless the original calibrated radiographic files are analyzed using a standardized region-of-interest protocol.

Overall Comparative Assessment

The results of the assessment of parameters of inflammation, oxidative stress and radiographic assessment revealed progressive healing of all

Table 2. Oxidative-stress and antioxidant defense markers across experimental groups.

Experimental group	MDA (ng/mL)	SOD (U/mL)	T-AOC (µmol/mL)
Negative control, untreated defect	238.8 ± 48.2^{a}	1035 ± 458^{d}	0.576 ± 0.058^{e}
Sumac extract, 1 month	220.0 ± 28.3^{ab}	1073 ± 548^{d}	0.881 ± 0.028^{d}
Sumac extract, 2 months	140.0 ± 28.3^{c}	1735 ± 64^{c}	1.498 ± 0.027^{b}
Bio-synthesized SiO_2 NPs, 1 month	105.0 ± 28.3^{d}	1848 ± 46^{bc}	1.431 ± 0.007^{b}
Bio-synthesized SiO_2 NPs, 2 months	97.0 ± 20.0^{d}	2925 ± 120^{a}	1.971 ± 0.050^{a}
p-value	<0.001	<0.001	<0.001

Different superscript letters indicate Tukey grouping at p ≤ 0.05.

Table 3. Radiographic Densitometric Values of Tibial Bone Defects.

Experimental Group	1 Month	2 Months
Control	2087	1493
Sumac Extract	2248	1734
Bio-Synthesized SiO_2 NPs	1494	2103

groups. The sumac extract as well as the bio-synthesized SiO_2 nanoparticles have the potential to decrease the levels of inflammatory mediators and to increase the antioxidant capacity in comparison to the control group. The nano-SiO_2 bio-synthesized group, however, presented the most favorable profile of all the parameters of assessment especially after two months of the experiments where the lowest values of the inflammatory markers, MDA, and the highest values of the antioxidant capacity and radiographic density were recorded.

Bio-synthesised SiO_2 nanoparticles could make better environment for bone regeneration compared to untreated defects and defects treated with sumac extract.

To develop new sites for dental implants and to apply guided bone regeneration (GBR), we have investigated the local application of Rhus coriaria extract and bio-synthesised SiO_2 nanoparticles to bone defects in preclinical sheep tibia models of bone deficiency. The bone defects of interest were created in the tibia rather than in the alveolar bone, however, the model still has relevance given that the sheep tibia is a large animal model that has been used in a very large number of studies that have investigated the bone regeneration and osseointegration of dental implants using a very wide range of biomaterials [1,2]. Thus this study was a pilot study to investigate a range of bioactive materials for their potential use in a variety of clinical applications including alveolar ridge preservation and augmentation.

The inflammatory profile of the untreated and treated osseous defects was also evaluated and the results are presented in Table 1. As shown in Table 1, the untreated defects exhibited the highest levels of IL-6 and TNF-α. However, the two treated defects showed a significant decrease in the levels of the two inflammatory cytokines. The decrease in the levels of the two cytokines was more pronounced in the osseous defects treated with SiO_2 nanoparticles after 2 months. It is well established that in the early phases of bone healing, inflammation is a necessary process for healing to occur. However, a persistent increase in the levels of IL-6 and TNF-α is known to inhibit the differentiation of the cells into osteoblasts, to increase the activity of osteoclasts, and to impede the formation of a mineralized matrix by these cells [3, 4]. In implant dentistry, an excessive inflammatory response in the tissues surrounding an implant is a concern as it can interfere with the osseointegration process and lead to increased marginal bone loss around the implant [15, 16]. Thus, the decrease in the levels of IL-6 and TNF-α in the two treated defects suggests that sumac extract as well as SiO_2 nanoparticles can favor a shift from a destructive type of inflammation to a regenerative type of inflammation during the

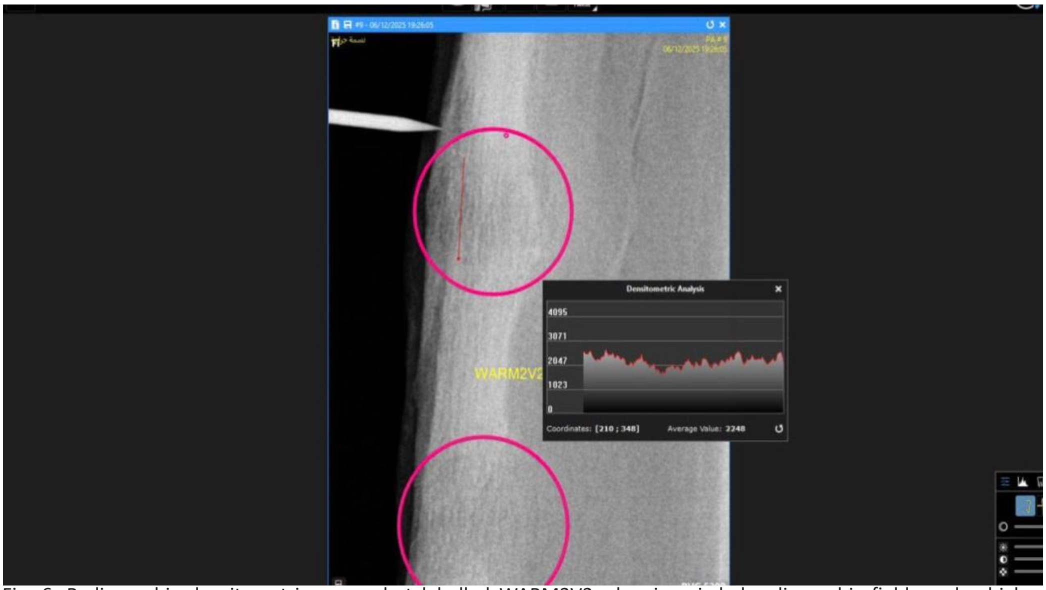

Fig. 6. Radiographic densitometric screenshot labelled WARM2V2, showing circled radiographic fields and a higher average value of approximately 2248.

osseous healing process.

The stronger late anti-inflammatory response observed in the SiO_2 nanoparticle group may be explained by the biological activity of silicon-based biomaterials. Silicon has been associated with collagen synthesis, osteogenic differentiation, and mineral deposition, which are essential events during new bone formation [17]. Recent reviews on nanoparticles in bone regeneration have emphasized that nanoscale materials may enhance cell adhesion, scaffold bioactivity, angiogenesis, and osteogenic signaling, particularly when their surface chemistry supports interaction with the extracellular matrix [7]. Therefore, the lower IL-6 and TNF-α values in the SiO_2 group may reflect not only a passive reduction in inflammation but also a more organized transition from the inflammatory phase toward tissue remodeling and mineral maturation.

The oxidative-stress results further support this interpretation. The untreated control group exhibited the highest MDA level and the lowest antioxidant capacity, indicating persistence of lipid peroxidation and insufficient antioxidant defense. By contrast, the SiO_2 nanoparticle group, particularly at two months, showed the lowest MDA value together with the highest SOD and T-AOC levels. This pattern is consistent with the concept that oxidative stress negatively affects bone regeneration by impairing osteoblast function, promoting cellular apoptosis, and disrupting extracellular matrix deposition [8,9]. In oral bone regeneration, this mechanism is clinically meaningful because oxidative stress has been increasingly recognized as a limiting factor in periodontal and peri-implant bone repair, especially under inflammatory or metabolically compromised conditions.

The improvement in antioxidant defense observed in the treated groups may also be related to the phytochemical properties of *Rhus coriaria*. Sumac is rich in phenolic compounds, flavonoids, tannins, and organic acids, which have been reported to exert antioxidant and anti-inflammatory effects [10,11]. In a periodontal context, Sağlam et al. reported that sumac extract reduced alveolar bone loss and influenced oxidative status and RANKL/OPG balance in an experimental periodontitis model [12]. This previous finding is particularly relevant to the present study because it links sumac not only to systemic antioxidant activity but also to oral bone preservation. However, in the current results, sumac produced a moderate improvement compared with the more pronounced late response observed in the SiO_2 nanoparticle group. This difference may indicate that sumac primarily improves the biochemical microenvironment, whereas SiO_2 nanoparticles may provide both biochemical modulation and a bioactive mineral-supporting interface.

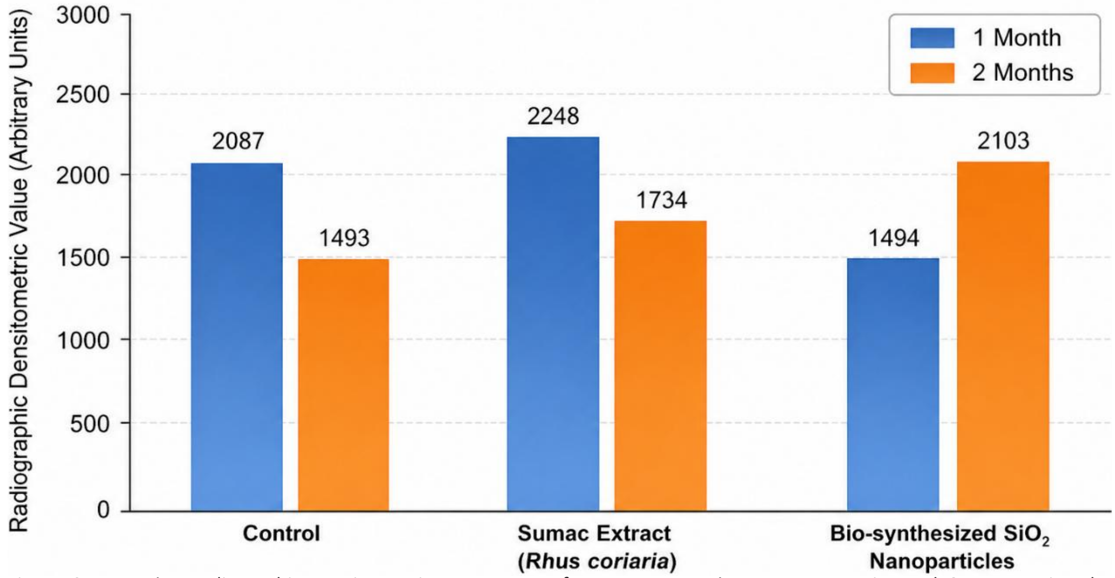

Fig. 7. Comparative Radiographic Densitometric Assessment of Bone Regeneration Among Experimental Groups During the Healing Period.

As defects heal, the level of mineralization within them increases. One way to assess osseointegration is by measuring the time course of the mineral density within a defect. In the present study, the defects that had been filled with sumac had the highest grey-value reading of all the defects at one month post-operatively. This would indicate the highest early mineral response or the highest early radiopacity within that selected region of interest. However, at two months post-operatively, the SiO_2 nanoparticle group had the highest radiographic density of all. The late increase in mineral density of the SiO_2 group was what was expected for a bioactive silicon-containing material. Such a material could potentially aid in the attenuation of the early inflammatory response. More importantly, it could also aid in the late stages of mineralization of bone, or the maturization of the bone structure, late mineralization. This late process of mineralization of bone is more important than early radiopacity because it is this matured bone that will have sufficient primary and secondary stability to allow for the functional loading of an implant [18,19].

Note that the radiographic data have to be viewed with a critical eye. The data were read from the CS Imaging screenshots and aligned with the corresponding handwritten group codes. Thus, the data are not calibrated DICOM values or even micro-CT data but rather a description of the findings. For a serious dental manuscript, the findings of density have to be proven more strongly using a fixed region-of-interest, a set of standardized exposure parameters, blinded measurements, and – if possible – a micro-CT or histomorphometric analysis. Dental journals require robust evidence when density values are used to prove bone regeneration.

Our results concur with previous studies stating that the successful repair of bone by GBR is largely dependent on the applied biomaterial, which has to control the formation of local and mineralized tissue [20, 21]. New GBR concepts therefore are based on regenerative materials that not only maintain the space required for bone augmentation, but that also modulate the immune response, induce angiogenesis and last but not least stimulate osteogenesis while maintaining a redox balance [22-24]. The results of the SiO_2-nanoparticle group support this multifunctional concept of biomaterials. As compared to the control group, treated animals showed a decrease of inflammatory cytokines, a decrease of lipid peroxidation (MDA) and an increase of the antioxidant power. Finally, the late phase radiographic density observed within the defect area was satisfactory.

The current study will also be of translational significance for assessment of bio-synthesised SiO2 nanoparticles against sumac extract using identical experimental setup. Most reports to date have investigated individual plant extracts and silica-based materials independently and thus it is difficult to compare results in terms of evaluation of their bioactivity. Results of the present study showed that bio-synthesised SiO2 nanoparticles possessed a superior and more complete regenerative profile compared to sumac extract especially in the later stages of healing. This in no way reduces the bioactivity of sumac; it only implies that the greatest value of sumac would lie in its phytochemicals used in the green synthesis of materials and to modulate the bioactivity of regenerative materials.

There are a few limitations to the current study. First, the current radiographic analysis is descriptive in nature. Replicate measurements for complete data sets would strengthen the findings. Second, tibial defects were used rather than alveolar defects. The use of a sheep model as a preclinical model for the evaluation of biomaterials for bone repair prior to human clinical trials is, however, acceptable. Third, histological, histomorphometric and immunohistochemical studies of these defects would greatly increase the scientific strength of the current study. In particular, new bone area, and trabecular thickness, collagen type I expression and RUNX2 expression would be of great value in determining whether the improvements in biochemistry translate to real osteogenic repair.

Further research, including histological and immunohistochemical analysis of tissue that has healed using the test material (e.g. using RUNX2 and collagen type I as markers of bone tissue), is necessary in order to verify or refute the assumption that the enhanced biochemanical parameters of a test material can lead to the formation of osteogenic tissue.

CONCLUSION

This study investigated the effect of the local application of bio-synthesized SiO_2 nanoparticles on bone healing. The findings were more pronounced in the treated groups than those of control group. Late regenerative effects of SiO_2 nanoparticles were even greater than sumac extract alone. The improved effects of the SiO_2 nanoparticles were accompanied by decreased levels of pro-inflammatory cytokines and oxidative stress, and elevated activities of antioxidants, and late radiographic bone density. The study demonstrated potential dental applications of green-synthesized SiO_2 nanoparticles as a novel bio-material, and the study can be a basis for future studies on guided bone regeneration, implant-site preservation, and alveolar bone augmentation. The current study was restricted to the assessment of newly forming bone by means of two dimensional radiographs. The Histological and immunohistochemical results of this study are not presented in the current manuscript but will be presented in a separate paper. The use of the sheep tibial defect model for preclinical studies of biomaterials and their possible application to clinical dental material is a limitation of the current study. The use of radiographic density in 2D images from radiographs by means of CS Imaging software has to be interpreted in view of the above mentioned restrictions. Radiographic density measurements were derived from standardized image assessments and were therefore interpreted descriptively within the methodological limitations of two-dimensional radiographic evaluation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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