Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 16 May 2026
Revised 12 June 2026
Accepted 04 July 2026

Natural Resources for Human Health 2026, Vol. 6 (4s): 485–498

KEYWORDS:
Portulaca oleracea, Angiogenesis, Bone tissue engineering, gold nanoparticles, Osteogenesis

Anti-inflammatory and biocompatibility effects of Portulaca oleracea and nanoparticles on the bone

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ABSTRACT:

Background: Bone healing depends on a well-balanced and highly coordinated process of inflammation, repair, and bone remodeling. Portulaca oleracea and gold nanoparticles (Au-NPs) have demonstrated potential applications in wound healing in soft tissues; however, their potential in hard-tissue bone regeneration has yet to be studied in comparison with each other and within the context of biocompatibility.

Objective: to assess and compare the anti-inflammatory and biocompatibility effects of Portulaca oleracea extract and Au-NPs on early bone healing in a standardized defect model of tibia of the rabbit.

Materials and Methods: Cortical bone defects were surgically created in the tibiae of rabbits and assigned to three independent groups: topical Portulaca oleracea extract treatment, Au-NP treatment, and untreated control. Histological and histomorphometric assessments were conducted at critical early time points (days 3 and 7 post-surgery) to determine the inflammatory cell dynamics, proliferation of fibroblasts, osteoblast and osteocyte activity, and neovascularization.

Results: Morphometric analysis of the bone defect area showed that the application of Portulaca oleracea extract and gold nanoparticles (Au-NPs) had a significant effect on the process of tissue healing and osteogenesis. All experimental groups had a significant decrease in the number of inflammatory cells and a significant increase in blood vessel

Natural Resources for Human Health
eISSN: 2583-1194

density and in the number of fibroblasts by day 7, when compared with the control group. Importantly, the treatment with Portulaca oleracea achieved the highest vascularization at day 3, and reduced inflammation significantly at day 7. In addition, both interventions resulted in early recruitment of osteoblasts at day 3 and Au-NP treatment resulted in the highest osteocyte density at day 7.

Conclusion: Results suggest that the bone defect repair process is promoted by the extract of Portulaca oleracea and Au-NPs in independent but synergic cellular mechanisms during early stages. Both Au-NPs and Portulaca oleracea are highly biocompatible and are potential therapeutic agents for bone tissue regeneration.

INTRODUCTION

Research in bone tissue engineering and regeneration is a key interest in orthopedics and dentistry and enhancement of bone healing after complicated surgical procedures and traumatic injuries. The healing of bone is a complex process that occurs in three stages that occur concurrently and in sequence: inflammation, repair and remodeling [1-2]. For accelerating functional bone repair, induction of the initial inflammatory phase and biocompatibility of therapeutic interventions are two important challenges to be overcome. As a result, scientists have been attracted to the study of different therapeutic methods such as bioactive extracts from plants as well as more advanced nanomedicines [3-4], however, there is a critical need for systematic comparison of the effectiveness of these different therapeutic paradigms in a common experimental framework. Purslane (Portulaca oleracea) is a warm-temperate and warm-tropical herb that is one of the most common traditional medicinal plants, according to the World Health Organization (WHO) [5-6]. *Portulaca oleracea* has strong anti-inflammatory, antioxidant and wound-healing activity [7-11] due to a wide range of bioactive compounds such as polysaccharides, alkaloids, terpenoids, omega-3 fatty acids and flavonoids, which all help improve tissue health, stimulate fibroblast proliferation and reduce the production of pro-inflammatory cytokines [12-15], while the anti-oxidative stress effect of the extract from Portulaca oleracea and the increase in superoxide dismutase activity and the down-regulation of interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) have been reported in previous studies [16], the biocompatibility of the extract with bone tissues and its direct effect on bone tissue regeneration remain largely unknown, particularly in vivo. The metallic nanoparticles such as gold nanoparticles (Au-NPs) are the most recent developments in nanomaterials that have shown the most promise for use in bone tissue engineering because of their inherent osteoconductive properties [8, 17-18]. The mechanism of how Au-NPs can promote osteoblast differentiation and the local inflammatory microenvironment has been proven to change in favor, while inhibiting the activity of osteoclasts [4, 19-21] The mechanisms of Au-NPs involved in bone healing have been proposed to occur by the uptake into cells via phagocytic and non-phagocytic pathways and receptor mediated endocytosis at cell membrane. The extracellular signal-regulated kinase 1/2 pathway is an important cell signaling pathway that is activated by Au-NPs. The bone regenerative potential of Au-NPs is attributed to activation of alkaline phosphatase, upregulation of Runx-2 and inhibition of pro-inflammatory cytokines. Additionally, Au-NPs might also affect the expression of osteocalcin and collagen type I that are essential for mineralisation and extracellular matrix composition [22]. However, the response of the body to Au-NPs and their integration with tissues are regulated by the physical properties of Au-NPs which can trigger different immunological reactions, including their size, surface charge, and coating materials [23-24]. Although bulk gold is thought to be biologically inactive, this characteristic is only noticeable at the macroscopic level. Due to its surface plasmon resonance stimulation properties, however, gold has a number of nanoscale features. The toxicity of the gold nanocrystals is being explored and further studies are required to investigate the effect of gold nanocrystals on the healing of bone [22]. Previous studies have concentrated on either bioactive materials or Au-NPs or on one material alone and comparative studies have not evaluated the properties and pathways of action of these materials for bone healing. The data on the bioactive properties of P. oleracea and Au-NPs have indicated their potential application in bone tissue engineering, however, the previous studies were based on bioactive materials or Au-NPs only and the study is still not comprehensive enough to have a comparative study of the properties and pathways of action in bone healing. Both portulaca oleracea and Au-NPs exhibit therapeutic potential, which are totally different therapeutic strategies [25-27]. Since their different actions have different effect on fibroblastic, osteogenic, angiogenic and inflammatory responses, it is important to compare these physical effects to determine the relative clinical usefulness and safety in bone defect management [28]. Therefore, the present research aimed to evaluate and compare the anti-inflammatory and biocompatibility activities of P.

oleracea extract with the untreated group. A standardized rabbit tibial defect model was used and extensive histological and histomorphometric analyses were conducted at critical time points (3 and 7 days after surgery). In this way, we sought to distinguish the specific impact of the various therapeutic protocols on the early phase dynamics of inflammatory cells, fibroblastic activity, osteogenic reactions, and vascularization during the first stages of bone regeneration.

MATERIALS AND METHODS

Portulaca oleracea extraction

Portulaca oleracea plant were collected from north of Iraq at March / 2023. Leaves separated from stem and dried by microwave at 70-80 ℃ for 3mints, then grinded by grinder, 9 gm., of grinned leaves dissolved in 90 ml of ethanol using the maceration method for 48 hr. During this time, the mixture was stirred intermittently. The solutions were then filtered through Whatman filter paper. To remove the excess of solvent the rotary evaporator was used. Then stored at -20°C until used.

Preparation of Gold nanoparticles Au-NPs

3 mL of 0.02 mM hydrogen tetrachloroaurate (III) (HAuCl4·4H2O, 99.99%; Direvo Industrial Biotechnology, Germany) was added to 1 mL of olive leaf extract, and stirred for 15 minutes at 50°C on a heater-stirrer. Successful formation of Au-NPs was indicated by a color change to dark yellow [29]. The UV-visible spectroscopy, X-ray diffraction (XRD), and atomic force microscopy (AFM) were used to characterize the resulting Au-NPs. The UV-visible absorption was measured in a range of 400 to 800 nm with UV-1650 PC spectrophotometer (Shimadzu Corporation, Japan). The structure of the produced Au-NPs was examined via XRD (XRD-6000; Shimadzu Corporation, Japan). The XRD patterns were recorded at a scan speed of 4°/min, and the AFM was performed with DX-700HS spectrometer (Shimadzu Corporation, Japan). A total of 0.3 mL of Au nanoparticle solution was diluted to 10 mL of distilled water for this analysis

Experimental Design and procedures

All animal handling and experimental protocols were conducted in strict accordance with the European Parliament and Council Directive 2010/63/EU on the protection of animals used for scientific purposes. Official ethical approval for this study was granted by the institutional animal care and use committee at the College of Veterinary Medicine, University of Mosul, Iraq (Approval Ref No: UM.VET.2023.042).

Sample grouping

A total of 12 adult male white New Zealand rabbits (aged 10–12 months, body weight 2–2.5 kg) were obtained from the College of Veterinary Medicine, University of Mosul, Iraq. The animals were housed under standard laboratory conditions with free access to water and a commercial pellet diet (Purina Lab Diet ® 5326) and berseem clover (*Trifolium alexandrinum*). The rabbits were randomly divided into three groups: an untreated control, a gold nanoparticle (Au-NP) group, and a *Portulaca oleracea* extract group. The healing progress for each group was then evaluated at 3- and 7-days post-surgery. At each scheduled interval, six rabbits were sacrificed. A total of six holes were created in each animal, three in the right tibia and three in the left using a 2 mm round diamond burr (H1 006, Germany) to ensure a uniform diameter of 2 mm [29]. Across the entire study, 72 surgical holes were generated, the untreated control group comprised 12 holes per healing interval. The remaining 48 holes were assigned to the active study group based on the local intervention applied. For these treated groups, a 0.3 mL volume of either the *Portulaca oleracea* extract or the Au-NPs suspension was precisely added into each hole using a sterile Pasteur pipette.

Surgical Procedure

The rabbits were given seven days to settle into their new environment before any surgeries took place. Animal facility staff provided continuous care and monitoring throughout the study. Animals were weighed prior to surgery to determine appropriate dosage of anesthesia and antibiotics for each animal. Surgical instruments and towels were sterilized in the autoclave at 120°C and 15 bar/cm² for 30 minutes. General anaesthesia was obtained by giving intramuscular injections of ketamine hydrochloride (50mg; 1mL/kg body weight) and 2% xylazine (0.2mL/kg body weight). The main surgical steps undertaken in the present study are shown in Figure 1. The *Portulaca oleracea* added in the superior hole while the gold nanoparticles added in the inferior hole and the middle holes left for normal healing as control group. Both tibiae were shaved using a depilatory spray (Surgi Spray®) and the skin was disinfected with ethanol-iodine solution before the skin was stripped. The shaved area was then covered with a piece of cotton that was soaked in alcohol and left for 10 minutes [29].

All operations have been made under sterile conditions with gentle surgical technique. Once the cotton was removed a sterile towel was placed around the area of the operation. The surgical procedure involved skin incision and reflection of the fascial and periosteal flap followed by the exposure of the proximal tibial metaphysis. By intermitted drilling and continuous cooling with irrigated normal saline, bone preparation was performed by microengine (Z500L, Nakanishi Inc., Japan) that was set at rotary speed at 2500 rpm and reduction ratio of 20/1, the opening was made by 2 mm round burr, then 3 holes were prepared with 10 mm distance between them, then the operation sites were washed with normal saline to remove the debris from the drilling sites. Sterile Pasteur pipettes were used to introduce treatments into the defects. The surgical site was then flushed with saline and the muscle layer was closed with absorbable catgut suture with the skin closed using black silk suture. The surgical area was treated with an antibiotic spray (Oxytetracycline) locally. All animals were treated with one dose of long acting systemic antibiotic (20% oxytetracycline 0.7 mL/kg) on the day of surgery. This was followed by daily local and systemic antibiotic treatments for the next five days. Following scarification, the tibiae were dissected to expose the surgical sites and strip away the remaining soft tissue. The experimental holes were isolated from each other by using carbide disc mounted on a straight handpiece (ST-01, NSK Japan) to release cuts. The surrounding bone was then harvested 5 mm away from the defect borders using a disk cutter at 6,000 rpm under vigorous irrigation. The harvested specimens were fixed in fresh 10% formalin for three days then transferred to 50% formic acid for decalcification. During solution changes every 3–4 days, decalcification progress was monitored by probing the bone with a fine needle; the process was deemed complete when the needle passed through the tissue without resistance. Once fully decalcified, a sharp scalpel was used to bisect each bone sample longitudinally through the center of the defect. Finally, the specimens were washed under running water for 30 minutes to wash out any residual acid before processing for histological analysis across all experimental and control blocks [29]

Histological and Histomorphometric Evaluation

Histological examinations were performed on a total of 72-hole sites across all experimental groups. Bone samples were dehydrated for 2 hours in a series of ethanol (60%, 80%, 90%, and 100%). They were then cleared in two changes of xylene (Sigma-Aldrich, 534056) and embedded in molten paraffin wax. Samples were placed in a constant temperature water bath of 53-60 ℃ for 1-2 hours and then transferred to 2-3 more paraffin wax water baths for the complete removal of xylene and for complete paraffin infiltration. The specimens were placed in the middle of the paraffin blocks and cut into serial sections 5 µm thick with a Leitz microtome (Germany). After hematoxylin and eosin (H&E) staining, sections were placed on clean glass slides (Sail Brand, China) and viewed with a light microscope (CX23, Olympus, China). Histomorphometric analysis was conducted on S EYE 2.0 software at 40X magnification and five randomly selected fields on each slide were counted to obtain mean values for statistical comparison.

Statistical analysis

Data are expressed as the mean ± standard deviation. Statistical significance was evaluated via a one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test using GraphPad Prism software (version 8.4.3). Differences were considered statistically significant at $P < 0.05$.

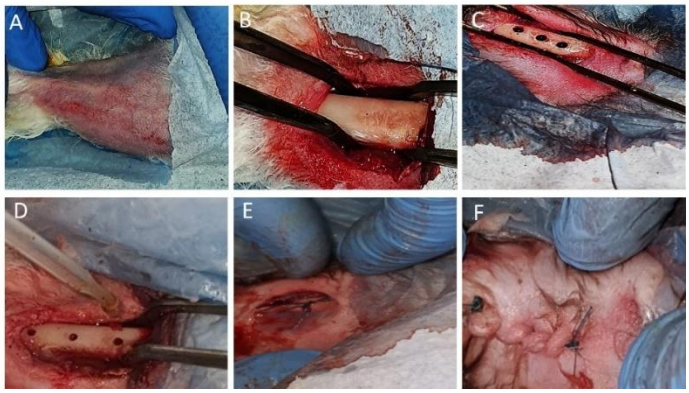

Figure 1: Sequential stages of the surgical procedure evaluating the effects of gold nanoparticles (Au-NPs) and *Portulaca Oleracea* extract on rabbit bone healing: (A) skin shaving; (B) reflection of skin and fascia; (C) hole preparation; (D) application of experimental materials; (E) muscular suturing; and (F) cutaneous closure.

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eISSN: 2583-1194

Results

Histological images of various magnifications of the bone defect site after 3 days of treatment with Portulaca oleracea extract and Au-NPs compared with the control group are shown in figure 2. Histological scans of the control group revealed an abundance of adipocytes and fibroreticular tissue, accompanied by abundant blood vessels, as illustrated in Figure 2 (A-C). Notably, the group of animals treated with Portulaca oleracea extract, by contrast, showed woven bone formation in the defect with the presence of progenitor cells and fibroreticular tissue. Osteoblasts were found in a single layer at the margins of the thin newly formed bone trabecular filling the defect, while large lacunae containing osteocytes were more numerous in the newly formed bone (Figure 2 (D–F)). The defect area treated with Au-NPs showed a significant presence of newly deposited woven bone, fibroreticular tissue and adipocytes. At the edge of the trabecular, osteoblast cells were arranged and many osteocytes in the new bone as seen in Figure 2 (G–I).

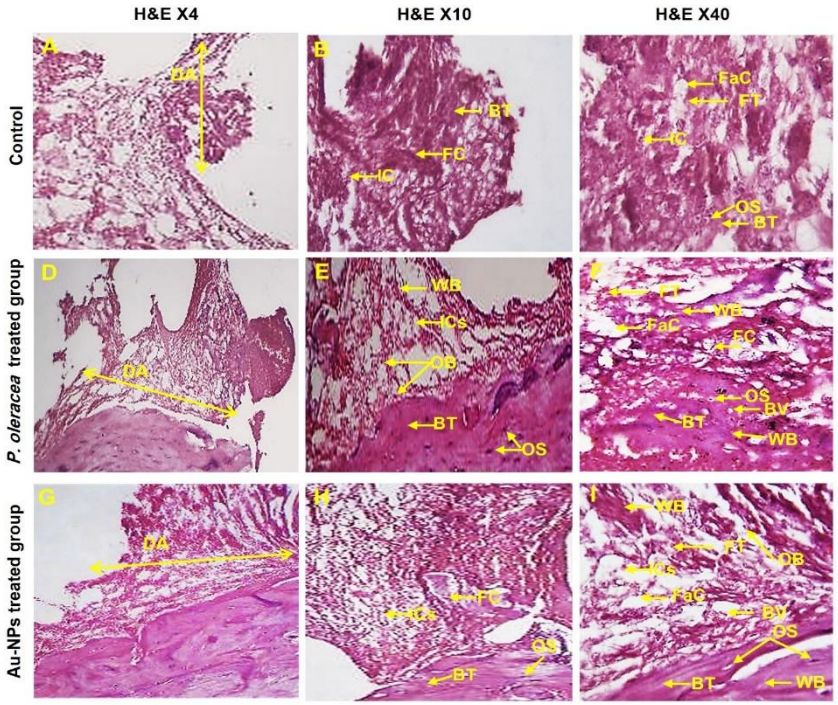

Figure 2: Representative H&E-stained histological images illustrating bone morphology within the defect area at various magnifications after 3 days. Low-magnification images (4×; A, D, G) show the defect area (DA) in the untreated control (A), *Portulaca oleracea* extract -treated (D), and Au-NPs-treated (G) groups. High magnification images (10×; B, E, H) demonstrate woven bone (WB) formation within the defect area, along with inflammatory cells (ICs), fibroreticular tissue (FTs), fibroblasts (FCs), osteoblasts (OBs), and osteocytes (OSs) in the untreated control (D), *Portulaca oleracea* (E), and Au-NPs-treated (H) groups. Higher magnification images (40×; C, F, I) reveal bone trabecular (BTs), blood vessels (BV), osteoblasts (OBs), and osteocytes (OSs) in the untreated control (C), *Portulaca oleracea* (F), and Au-NPs treated (I) groups

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eISSN: 2583-1194

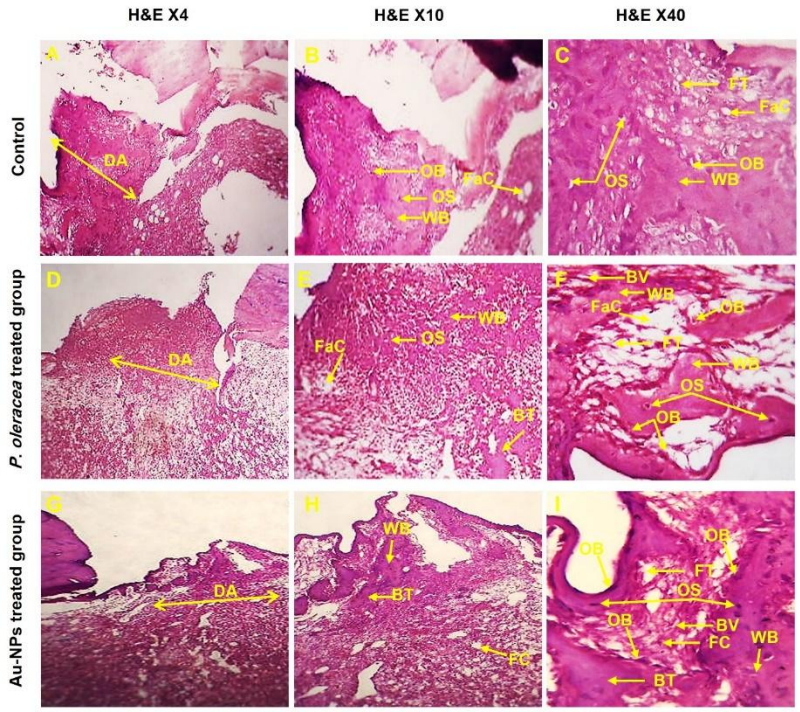

Figure 3: Representative H&E-stained histological images illustrating bone morphology within the defect area at various magnifications after 7 days. Low-magnification images (4×; A, D, G) show the defect area (DA) in the untreated control (A), *Portulaca oleracea* extract -treated (D), and Au-NPs-treated (G) groups. High magnification images (10×; B, E, H) demonstrate woven bone (WB) formation within the defect area, along with inflammatory cells (ICs), fibroblasts (FCs), fibroreticular tissue (FTs), osteoblasts (OBs), and osteocytes (OSs) in the untreated control (D), *Portulaca oleracea* (E), and Au-NPs-treated (H) groups. Higher magnification images (40×; C, F, I) reveal bone trabecular (BTs), blood vessels (BV), osteoblasts (OBs), and osteocytes (OSs) in the untreated control (C), *Portulaca oleracea* (F), and Au-NPs treated (I) groups

The Portulaca oleracea extract-treated group and the Au-NPs-treated group showed improvement in the bone defect area after 7 days when compared to the untreated control group, and this improvement was observed at various magnifications (Figure 3). In the control groups, only thin bone trabecular with preosteocytes and osteocytes, and scattered active osteoblasts and progenitor cells within the woven bone were seen in the histological sections as seen in Figure 3 (A–C). Specifically, the group of animals that were treated with Portulaca oleracea had significantly more bone trabecular in the defect site surrounded by fibroreticular tissue and there were many more osteocytes, osteoblasts, and fibroblasts in this group as seen in Figure 3 (D–F). Bone trabecular and fibroreticular tissue were seen filling almost the entire area of the defect in the Au-NPs-treated group, with plenty of osteoblasts and osteocytes present as seen in Figure 3 (G—I).

Table 1: The mean number of blood vessels in the bone defect areas on 3 and 7 days after treatment in the three groups (control, extract-treated, Au-NPs-treated)

Duration	Groups	Mean number of blood vessels	Standard deviation	Standard error of the mean	Minimum	Maximum
3 Days	Control	3.10	0.74	0.23	2	4
	P. oleracea	5.30	1.64	0.52	3	8
	Au-NPs	4.20	1.55	0.49	3	8
7 Days	Control	3.10	1.29	0.41	2	5
	P. oleracea	2.60	0.84	0.27	2	4
	Au-NPs	4.60	0.70	0.22	4	6

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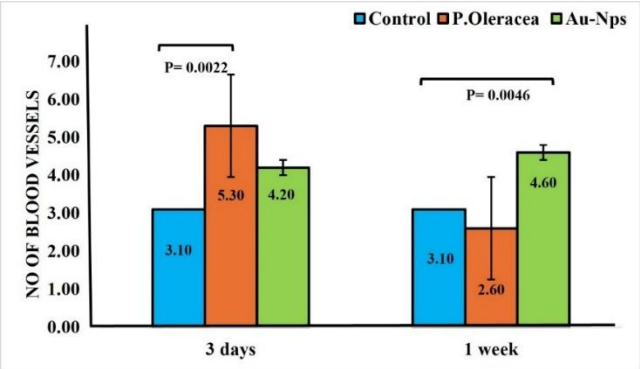

Figure 4: Mean blood vessel counts in bone defect areas following treatment with *Portulaca oleracea* extract, Au NPs, or no treatment (control) for 3 and 7 days, Horizontal lines represent statistically significant differences P<0.05

Table 2: The mean number of inflammatory cells in the bone defect areas on 3 and 7 days after treatment in the three groups (control, extract-treated, Au-NPs-treated)

Duration	Groups	Mean number of inflammatory cells	Standard deviation	Standard error of the mean	Minimum	Maximum
3 Days	Control	50.11	2.93	0.98	45	55
	P. oleracea	18.20	4.54	1.44	13	25
	Au-NPs	30.30	11.91	3.77	14	45
7 Days	Control	6.00	2.16	0.68	3	10
	P. oleracea	2.73	2.83	0.85	0	7
	Au-NPs	10.09	2.51	0.76	6	15

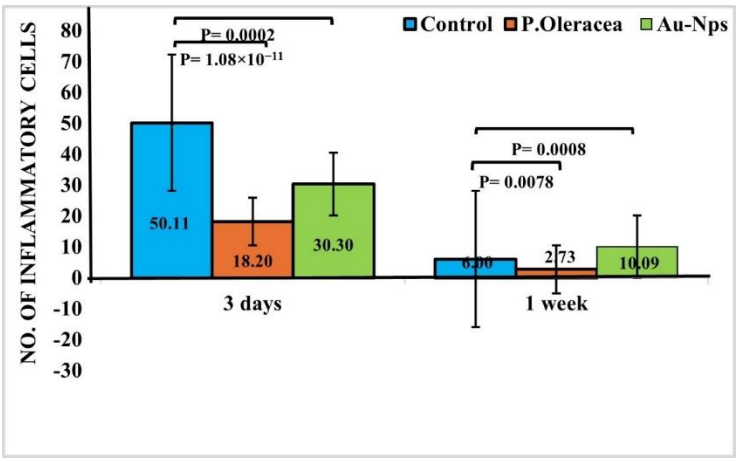

Figure 5: Mean inflammatory cell counts in bone defect areas following treatment with *Portulaca oleracea* extract, Au NPs, or no treatment (control) for 3 and 7 days, Horizontal lines represent statistically significant differences P<0.05

Table 3: The mean number of fibroblast cells in the bone defect areas on 3 and 7 days after treatment in the three groups (control, extract-treated, Au-NPs-treated)

Duration	Groups	Mean number of fibroblast cells	Standard deviation	Standard error of the mean	Minimum	Maximum
3 Days	Control	10.40	2.59	0.82	5	14
	P. oleracea	19.10	9.27	2.93	9	30
	Au-NPs	17.70	4.60	1.45	10	27

7 Days	Control	8.90	2.23	0.71	5	12
	P. oleracea	33.30	6.06	1.92	25	42
	Au-NPs	14.70	1.49	0.47	13	17

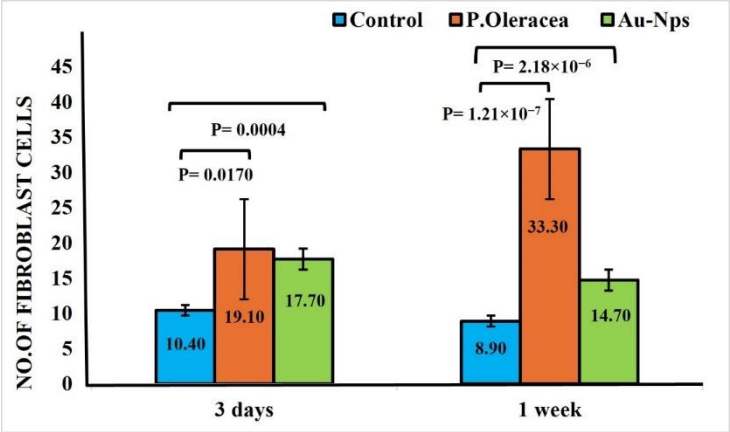

Figure 6: Mean fibroblast cell counts in bone defect areas following treatment with *Portulaca oleracea* extract, Au NPs, or no treatment (control) for 3 and 7 days, Horizontal lines represent statistically significant differences P<0.05

Table 4: The mean number of osteoblast cells in the bone defect areas on 3 and 7 days after treatment in the three groups (control, extract-treated, Au-NPs-treated).

Duration	Groups	Mean number of osteoblast cells	Standard deviation	Standard error of the mean	Minimum	Maximum
3 Days	Control	0	0	0	0	0
	P. oleracea	5.00	6.55	2.07	0	16
	Au-NPs	3.30	4.32	1.37	0	10
7 Days	Control	35.60	3.47	1.10	30	40
	P. oleracea	14.33	1.80	0.60	12	17
	Au-NPs	30.10	3.60	1.14	24	35

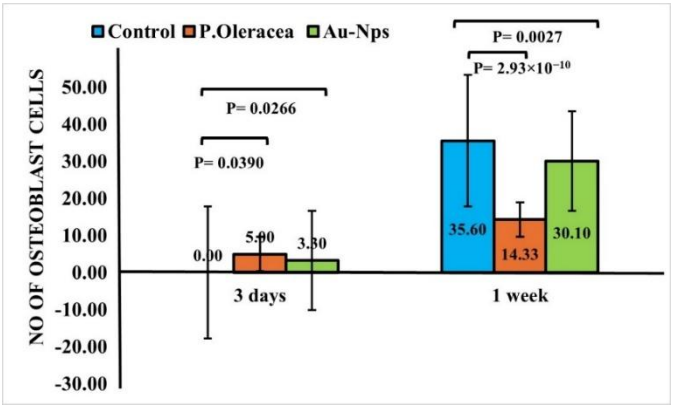

Figure 7: Mean osteoblast cell counts in bone defect areas following treatment with *Portulaca oleracea* extract, Au NPs, or no treatment (control) for 3 and 7 days, Horizontal lines represent statistically significant differences P<0.05

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eISSN: 2583-1194

Table 5: The mean number of osteocyte cells in the bone defect areas on 3 and 7 days after treatment in the three groups (control, extract-treated, Au-NPs-treated)

Duration	Groups	Mean number of osteocyte cells	Standard deviation	Standard error of the mean	Minimum	Maximum
3 Days	Control	0.45	1.04	0.31	0	3
	P. oleracea	4.45	5.92	1.79	0	17
	Au-NPs	1.64	2.01	0.61	0	5
7 Days	Control	19.30	2.54	0.80	14	22
	P. oleracea	16.30	4.32	1.37	13	22
	Au-NPs	48.10	3.28	1.04	44	53

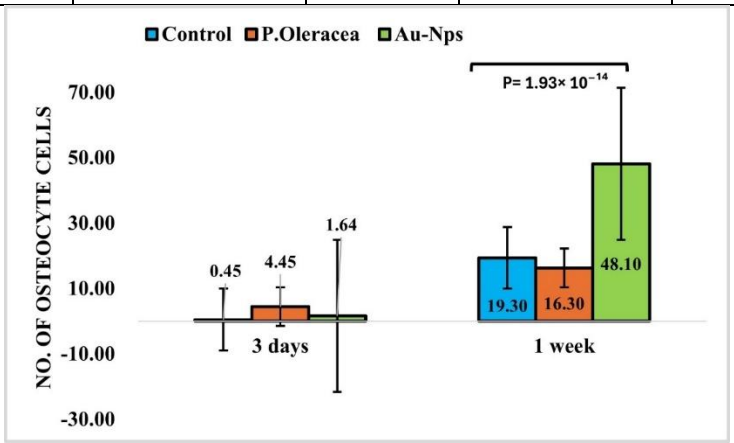

Figure 8: Mean osteocyte cell counts in bone defect areas following treatment with *Portulaca oleracea* extract, Au NPs, or no treatment (control) for 3 and 7 days, Horizontal lines represent statistically significant differences P<0.05

Morphometric analysis of blood vessel number in the bone defect area revealed a higher mean value in both experimental groups than in the control after 3 days. The number of blood vessels was significantly higher in the Portulaca oleracea group (5.3 ± 0.52) than in the control (3.1 ± 0.23) group. At 7 days, the Au-NPs-treated group also had more blood vessels (4.60 ± 0.22) compared to the control group, table (1) and figure (4). Analysis of inflammatory cell counts in the bone defect region showed an overall decrease in mean values across all experimental groups after 7 days. In the Portulaca oleracea-treated group, inflammatory cell counts were significantly reduced compared with the control at both 3 and 7 days (18.2 ± 1.44 and 2.73 ± 0.85, respectively), table (2). Similarly, the Au-NPs-treated group showed a significant decrease in inflammatory cells (30.3 ± 3.77) relative to the control group at 3 days. However, the Au-NPs-treated group showed a significant increase in inflammatory cells (10.09 ± 0.76) compared with the control group after 7 days, as shown in table (2) and figure (5). Analysis of fibroblast counts in the bone defect region showed an overall increase in mean values across all experimental groups after 3 and 7 days. The Portulaca oleracea-treated group exhibited a significant increase in fibroblast counts compared with the control at both time points (19.1 ± 2.93 and 33.3 ± 1.92, respectively) (Table 3). Similarly, the Au-NPs-treated group showed a significant increase in fibroblast counts relative to the control after 3 and 7 days (17.70 ± 1.45 and 14.70 ± 0.47, respectively), as shown in table (3) and figure (6). Examination of osteoblast numbers in the bone defect region showed an overall increase in mean values across all experimental groups after 3 days. Both Au-NPs and Portulaca oleracea extract appeared to stimulate osteogenic activity, with significant increases in osteoblast counts observed in the Portulaca oleracea- and Au-NPs-treated groups (5.00 ± 2.07 and 3.3 ± 1.37, respectively) compared with the control at 3 days. However, osteoblast numbers were significantly reduced in comparison with the control group after 7 days, as shown in table (4) and figure (7). Analysis of osteocyte counts in the bone defect region revealed a significant increase in mean values in the Au-NPs-treated group after 7 days. Osteocyte activity was significantly higher in the Au-NPs-treated group (48.10 ± 1.04) than in the untreated control group (19.3 ± 0.80), as shown in table (5) and figure (8).

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eISSN: 2583-1194

DISCUSSION

The therapeutic herbs and nanotechnology are often used in regenerative medicine [30]. The utilization of natural products for bone repair, like *Portulaca oleracea* extracts, and the less harmful side effects of Au NPs have attracted more attention [8] his study directly compared the anti-inflammatory and biocompatibility effects of *Portulaca oleracea* extract and gold nanoparticles (Au-NPs) on early cortical bone healing in a standardized rabbit tibial defect model. At 3 and 7 days after treatment, our histological and histomorphometric findings showed that both treatments were able to induce a quicker transition from the inflammatory to the proliferative phase of the bone repair process than untreated bones, and shed some light on the effects of these agents on inflammation, cellular reactions and tissue formation. The findings indicated that both treatments were able to significantly lessen inflammatory cell infiltration in comparison with the control group, especially at day 7. These findings are consistent with previous studies reporting anti-inflammatory activity of P. oleracea, attributed to its ability to inhibit pro-inflammatory mediators and to modulate cell signaling pathways, such as NF-ϰB [13]. Furthermore, numerous triterpenoids from all over the structure of *Portulaca oleracea* were found to effectively inhibit the activity of cyclooxygenase, a key enzyme in the inflammatory pathway. Cyclooxygenase enzymes, particularly COX-2, play a key role in the production of pro-inflammatory mediators, such as prostaglandins [13, 19, 31]. The process of healing involves sequential but overlapping events of inflammation, angiogenesis and osteogenesis. The size and severity of the primary inflammatory response has been shown to influence the quality of the repair response [32-33]. Inflammatory cell infiltration may be excessive or prolonged and result in a delay in fibrovascular phase and affects endochondral and intramembranous ossification, or it may be controlled and self-limited, serving to recruit osteoprogenitor cells in time [34]. The extracts from P. oleracea have been shown to affect the NF-ϰB and MAPK signaling pathways, which inhibit pro-inflammatory cytokine transcription in LPS-stimulated macrophages, containing flavonoids like luteolin, kaempferol and quercitrin as well as omega-3 fatty acids and alkaloid components [35]. P. oleracea has been shown to inhibit the activation of NF-ϰB and subsequent adhesion molecule expression in endothelial cells upon stimulation with TNF-α [36] and to decrease the levels of IL-1β, TNF-α, IL-6 and PGE2 in an LPS-induced lung injury model, while increasing the level of anti-inflammatory cytokine IL-10 [37]. The present bone-healing data demonstrate an extension of this well-established anti-inflammatory profile, from soft tissue and cell culture systems, to an in vivo model of hard tissue defect in bone, and thus indicate that the same mechanisms of action of the phytochemicals on NF-ϰB/MAPK suppression likely underlie the accelerated resolution of inflammation observed histologically at the fracture margin. Similarly, Au-NPs have been found to have anti-inflammatory effects, partly by inducing the anti-inflammatory M2 macrophage phenotype and growth factors such as TGF-β and VEGF, which are beneficial for osteogenesis and angiogenesis. In these two treatment groups, there were more fibroblasts, indicating active deposition of extracellular matrix and granulation tissue formation. This is supported by previous investigations in which substances from *Portulaca oleracea* were found to stimulate migration and proliferation of fibroblasts [13] which are responsible for collagen production and thus play a role in the structure of the repaired tissue. In addition, Au-NPs can enhance fibroblast activity and collagen production which are both necessary for fracture repair [27, 38]. In addition, the early vascularization noticed in the treatment with *Portulaca oleracea* at day 3 was consistent with previous studies reporting its pro-angiogenic effect in models of skin wound, which demonstrated that the extract of *Portulaca oleracea* stimulated neovascularization, increased the proliferation of fibroblasts and increased collagen deposition in injured skin [39]. Angiogenesis and osteogenesis are closely linked in the process of bone repair. In the injured site, hypoxia induces the release of HIF-1α-dependent VEGF from osteoblasts and macrophages that attract endothelial cells and osteoprogenitors to the defect and create the nutrient and oxygen supply necessary for matrix mineralization [40-41]. In the present study, *Portulaca oleracea* did not have such a strong effect on the maturation of terminal osteocytes as Au-NPs; however, it is plausible that *Portulaca oleracea* was also having a functional role other than just anti-inflammatory since it accelerated microvascular recruitment at the most earliest time point examined here, thereby reducing the time before establishment of the fibrovascular phase. Interestingly, defects that were treated with Au-NPs showed enhanced osteoblast activity and early bone matrix mineralization suggesting that they may be used to facilitate osteogenesis [23, 42]. The Au-NP group showed a higher osteocyte density on day 7, which is in line with a number of studies that have found that the anti-inflammatory effects of gold nanoparticles are not the primary factor in their osteoinductive properties, but are accompanied by direct osteoinductive effects on bone-forming cells. It has been demonstrated that Au-NPs can penetrate into the cells and stimulate the Wnt/β-catenin signaling pathway, promoting osteogenic differentiation of human mesenchymal stem cells in Au-NPs/HA composites [18, 42]. The parallel mechanism is mediated by mechanical stress that Au-NPs exert to the cell membrane that triggers p38 MAPK signaling and promotes osteogenic rather than adipogenic lineage commitment [43]. Au-NPs have also been reported to induce osteogenic differentiation of periodontal ligament stem cell sheets by increasing autophagy-related protein expression with 45 nm being

more effective than 13 nm [44], and this relation has also been observed in the differentiation of hMSCs [45]. In addition to these cell-autonomous effects, Au-NPs also alter the local immune microenvironment, mesoporous-silica-based Au-NPs have been seen to induce an anti-inflammatory M2 phenotype in macrophages and induce osteogenic cytokine secretion, creating a positive paracrine signaling environment for osteoblast maturation in a cranial defect model [46]. It has been demonstrated that chiral Au-NPs can induce M2 polarization of macrophages and promote bone regeneration by regulating autophagy [47]. This study supports a model whereby Au-NPs exert a convergent immunomodulatory and direct osteoinductive signaling effect, accelerating the transition from osteoblast to osteocyte, as evidenced by the significant increase in the number of osteocytes in the defects observed here when compared with both control and *Portulaca oleracea*-treated defects. Interestingly, the activity of Portulaca oleracea and Au-NPs does not appear to be on the same interchangeable components of the same coupled pathway of healing; it appears it is on complementary and distinct components of the pathway. The inflammatory-to-vascular transition was the most common transition for the effects of Portulaca oleracea, while the osteoblast-to-osteocyte transition was the most common transition for Au-NP effects. This is consistent with the overall idea of osteogenesis-angiogenesis coupling, where common molecular pathways such as Wnt/β-catenin signaling, MAPK signaling, and the VEGF-HIF-1α signal pathways control both programs, and therefore have dual roles in the regulation of both programs [48-49]. The use of an agent that shortens the inflammatory and vascular phase (Portulaca oleracea) and an agent that directly accelerates the maturation of osteoblasts (Au-NPs) can be used synergically, since the present design with separate groups does not test this, but can be tested in future work. The biocompatibility of all agents in both of these studies is consistent with their reported safety in other studies and is a translation of previous reports [50]. Overall, the toxicity of gold nanoparticles is low, and has been demonstrated at various cell types and concentrations with some very small diameters of gold nanoparticles even reported to be anti-osteogenic [42]. The size dependence suggests that the therapeutic effect of this platform is likely more due to the parameters used to form the Au-NPs than to their simple incorporation and future studies should report the therapeutic effect of AuNPs along with the control of Au-NP size and surface functionalization. *Portulaca oleracea* is a naturally occurring herb in the food chain which has been shown to be Hepatoprotective, antioxidant and metabolically beneficial in other in vivo models [35, 51] and is a low toxicity and cost effective promising topical adjunct in orthopedic wound care. There are several limitations in this study that need to be taken into account. First, the two active groups were not tested in combination, and their synergistic or antagonistic interaction in combination is important future direction for testing; the two active groups were each tested with a common untreated control design. Second, all the endpoints measured in this study using histomorphometry were good surrogate markers of inflammatory resolution, vascularization and cell maturation; future studies would benefit from the process to later time points of defect closure to see if the early improvements seen here lead to improvements in biomechanical strength, bone mineral density or mechanical union at closure. Third and most importantly, the tibial defect model is a well-established and widely used model to study cortical bone healing, but it does not fully mimic the clinical loading environment, healing mechanisms, and comorbidities (such as osteoporosis, diabetes) that are often found in many clinical bone defects, and the applicability to larger animal models or clinical trials should be evaluated carefully. Fourth, the molecular pathways suggested here to explain the observed histological effects (NF-κB/MAPK suppression in Portulaca oleracea, Wnt/β-catenin and autophagy-related osteoinduction in Au-NPs) also have not been directly investigated in the present tissues, but have been described in the literature; immunohistochemical or gene-expression analysis of these cell pathways in the present defects would greatly strengthen the conclusions.

CONCLUSION

We have demonstrated that the extract of *portulaca oleracea* and gold nanoparticles are able to modulate early bone healing in a rabbit model. Both agents proved to be non-toxic and to promote bone regeneration and proliferation of fibroblasts, while reducing the inflammatory cell infiltration. Interestingly, the osteogenic responses were enhanced by Au-NPs and the *Portulaca oleracea* extract exhibited a higher pro-angiogenic effect. The findings highlight the potential application of these natural extracts and nanomaterials in the field of bone repair, particularly as complementary therapies. While *Portulaca oleracea* has proven to be an attractive choice for integrative study and treatment and drug development, mechanistic, medical and translational studies are also needed. The complete therapeutic potential of this would necessitate a collaboration of traditional medicine, the chemistry of natural drugs, pharmaceuticals and medical science. Their mechanism of action and optimization of their dosage treatment and combined usage in clinical applications should be studied further.

Conflict of Interest: The authors have no conflict of interest to declare.

Authors' contributions

Rasha Hatem Dosh: Data curation, Visualization, Formal analysis, Writing- Original draft preparation,; **Najat Mutar Alsallami**: Conceptualization, Methodology, Investigation; **Manar Mudhafar Alnema** Conceptualization, Methodology, Investigation; **Siham Mahmood Al-Rehemi** Conceptualization, Methodology, Investigation; **Bushra Habeeb Al-Maula**: Supervision, Validation, Formal analysis; Writing- Reviewing and Editing; : **Zena Jehad Wally** Conceptualization, Methodology, Investigation; **Wijdan Rajh Al-Kraity**: Visualization, Formal analysis. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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