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Portulaca Oleracea and gold nanoparticles biocompatibility and osseointegration of dental mini-implant in rabbits

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Aim: this study aimed to identified the biocompatibility and osseointegrative effect of Portulaca Oleracea in comparing to the Au nanoparticles by using histological and histomorphometric analysis.
Materials and methods: Leaves of plants dried by using dryer under 43℃ for 24 hours then grinded, 10gm the grinned leaves dissolved in 100ml of ethanol by using method of maceration for 48hr. A dilution of gold nanoparticles was used in this research by dilute 0.3 ml of Au nanoparticles in 10 ml of distal water. titanium implants of 2 mm width and 8.5 mm length were used in this study. Twelve white male adult healthy New Zealand rabbits used, animals were divided into three groups according to the time of healing as follows; 3 days and week and 2weeks after operation. The coated implants were inserted following the applying one drop of Portulaca Oleracea extraction in the superior osteotomy and one drop of diluted Au nanoparticles in the inferior osteotomy, whereas the uncoated implants were inserted immediately in the middle one. Histological and histomorphometric analysis measured the RLT, OTT, BTT and FC number by LSD test.
Result: Portulaca Oleracea group showed enhancement the healing and bone formation in comparing to the other groups in all intervals, the PO group showed $p<0.05$ with both Au and control group for OTT, BTT and FC in 2weeks interval.
Conclusion: PO coating material is biocompatible, and the acceleration of the osteoid tissue and bone trabeculae formation indicate the Portulacea Oleracea coating material is osteoinductive material accelerate osseointegration.

Keywords: dental implant, Portulaca Oleracea, gold nanoparticles, osseointegration, biocompatibility.

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Introduction

The reaction that cells and tissues respond to the biomaterials is known as a biocompatibility, and this is impacted by the material's characteristics, surface topography, structural makeup, and behaviour when it becomes into touch with body fluids. Commercially, pure titanium implants develop a titanium oxide coating on their surface at milliseconds of the metal coming into contact with the water, air, or other electrolytes. By increasing the surface free energy, this formed oxide layer facilitates the adsorption of the biomolecules and so, the subsequent cellular binding and diffusion.[1]

"A close structurally and functionally junction between organised, living bone and the top surface of a load-bearing implant" was considered the original definition of osseointegration about the light microscopic level.[2] The direct fracture healing is regarded one of the complex physiological mechanisms that is responsible for the make up osseointegration. Similar to a traumatic damage in the bone, drilling an implant cavity lead to cause the different stages of the wound healing. Initially, the fibrin polymerisation and the formation of a blood clots are the outcomes of the cellular and plasmatic haemostasis processes. New angiogenesis appearing, extracellular of matrix deposition, and invasion by bone-forming cells, all these processes are facilitated by this clot which lead to newly formed bone will be generated.[3]

Dental implants have been developed and altered over time. In order for achieving the best possible relationing between this implanted material and the body, numerous techniques have been used for changing the bulk material composition as well as the implant surface topography, chemistry, energy, and charge properties in order to produce the best as possible as bone-implant interaction.[4] There are two methods for incorporating materials onto the surfaces of biological implants include, the collagen deposition and the biomaterial coatings.[5] The aim of the modern dental implant researches are to create surfaces that can encourage higher and quicker of tissue osseointegration.[6] The using of biomaterials in the field of osseous regeneration is increasingly essential due to the numerous shortcomings of the conventional techniques in the orthopaedic implants. [7]

The surface features and the morphology have shown to be important influencing effects at the different stages of osseointegration.[8] Many new generations of the implant surfaces have been developed in order for improving the bone formation at the interface with implants, where these surfaces can be altered at the level of nanoscale and differentiation of cells in the way of osteogenesis, can be induced by a variety of biochemical treatments.[9] The chemical changing in the surfaces of dental implants can be have a direct impact on the way of cells interact with the implant and the implantation site.[10] This process is aided by cellular adhesion, proliferation and then differentiation.[11] and in actuality, all these biological processes are vital.[12] The formation and the quality of this resultant bone are directly impacted by the surface properties which are necessary for triggering a certain cellular response at the interface between the bone and the implant surface.[13]

There are great attention which directed toward the natural products that can be used as therapeutic materials with less adverse results. [14] The Portulacaceae family, includes the annual herbaceous plant Portulaca oleracea (PO), which is found worldwide but particularly in the tropical and also subtropical areas. It has

reddish stems and alternate leaves.[15] PO, of green or yellow leaves, is a herb that is widely utilised in many nations.[16] Proteins, minerals, fatty acids, polysaccharides, vitamins, sterols, terpenoids, and other natural chemical classes are among Portulaca oleracea's chemical contents, which mostly fall under the flavonoid .[17] alkaloid, terpenoid, and organic acid groups.[18] Numerous of Portulaca oleracea's biological activities, including antibacterial, bronchodilator, neurotoxic, renoprotective, muscle relaxant, hepatoprotective, antiulcerogenic, and anti-fertility effects, have been demonstrated by contemporary pharmacological scientific researches.[19]

In the rapidly developing field of biotechnology, nanomedicine presents a viable solution to the issues with various medication delivery and bone regeneration techniques.[20] One type of the nanomaterials that is easily synthesised by a one-step, and environmentally friendly green chemistry process is the gold nanoparticles (GNPs).[21] They are renowned for being biocompatible and non-toxic particles. Gold nanoparticles are a great choice for biomedical applications because of their properties.[22] Targeted medicine, tissue engineering, gene transport, biosensing, diagnostics, molecular imaging, and peptide are regarded as just a few of the many uses for the gold nanoparticles.[23] This is due to their unique structural, optical, chemical, and electrical properties.[24] In the field of tissue engineering, these particles have been described as materials which can be used as osteogenic agents to achieve bone tissue regeneration.[25] After being absorbed intracellularly, these particles have been demonstrated in numerous studies to positively impact in osteogenic differentiation of osteo-progenitor cells.[26]

Materials and methods

Portulaca Oleracea extraction

The plant was collected in northern Iraq in March 2023. After being separated, the leaves were dried for 24 hours at 43°C in a drier before being pulverised in a grinder. The maceration method was used to dissolve 10 grams of the smiling leaves in 100 millilitres of ethanol over the course of 48 hours.[27] The liquid was now intermittently blended. The solutions were filtered with Whatmann filter paper. The excess solvent was removed using a rotary evaporator. It is then stored at -20°C until it is used.[15]

Preparation the gold nanoparticles

In a test tube, combine 1 mL of olive leaf extract and 3 mL of 0.02 mM hydrogen tetrachloroaurate (III) (HAuCl4.4H2O, 99.99%) to create gold nanoparticles (AuNPs). The liquid is then aggressively stirred for 15 minutes at 50 °C using a thermal stirrer. The colour shift to dark yellow is a reliable indicator of AuNP production. Ten millilitres of distal water were used to dilute 0.3 millilitres of gold nanoparticles during this investigation.[28]

Preparing Implants

In this investigation, prefabricated titanium screw implants (TAD Mini Orthodontic implants, China) measuring 2 mm in width and 8.5 mm in length were utilised. Before being used, they were autoclaved and kept in airtight containers.

Description of an Experimental Animal

The study used twelve white male adult healthy New Zealand rabbits that were between 10 and 12 months old to ensure that the proximal epiphysis of the tibia was completely closed, weighed between 2.25 and 2.5 kg, were housed in standardised, separate cages, fed standard pellets and berseem, and had free access to tap water. All animals were given seven days to become used to their new surroundings before undergoing any surgery. The animal

house crew provided nursing care and oversight for the animals.

Sample grouping:

The animals were split into three groups based on when they healed: three days, one week, and two weeks following surgery (four rabbits were utilised in each interval). Three mini-implants (two coated) and (one uncoated) were positioned in the right tibia. They were divided into three groups based on the type of coating:

1-control group (uncoated implants): include twelve implants (4 implants for each interval).

2. Experimental group (coated implants): consists of 24 implants (8 implants per interval, 4 for each coating material) 12 implants coated with 1 drop of Au nanoparticles, and 12 implants coated with 1 drop of portulaca oleracea extraction. The coated material is applied using a Pasteur pipette. For both experimental and control implants, all bone blocks were subjected to histomorphmetric assessment and histological investigation.

Surgical procedure

To calculate the amount of anaesthetic needed for each animal, the animals were weighed before implantation. During the procedure, autoclaved towels and tools were used, which were autoclaved for 30 minutes at 120°C and 15 bar/cm. According to their body weight, the animals were anaesthetised by intramuscular injection of 50 mg of ketamine hydrochloride and 2% xylazine (1 ml/kg and 0.2 ml/kg, respectively).

An ethanol and iodine solution was used to clean the skin after the ventral side of the tibia was shaved. A piece of gauze saturated with alcohol was then placed over the shaved area and left there for 10 minutes. The treatment was carried out sterilely and gently using the appropriate surgical technique. The surgical cloths were placed around the procedure site after the gauze was removed. The proximal tibia metaphase emerged when the skin was incised and the fascia and periosteal flap were reflected. The bones were prepared by intermittent drilling, continually chilled, and regularly irrigated with saline. A physio-dispenser was used, with a 20/1 reduction ratio and a bur set to rotate at 2500 rpm. Three holes, spaced 10 mm apart, were bored after the opening was made using a 1 mm round bur. The osteotomy was done gradually using the appropriate drill. To remove the debris from the drilling areas, the operation site was washed using regular saline. The sterilised implants were being placed in the prepared areas. While the uncoated implants were placed right away in the middle osteotomy, the coated implants were placed after one drop of Portulaca Oleracea extraction was applied in the superior osteotomy and one drop of diluted Au nanoparticles was applied in the inferior one. After using a screwdriver to introduce the implants into the osteotomies, the region was cleaned with regular saline. The muscles were also sutured with an absorbable 3-0 chromic catgut suture (MAI Animal Health, USA). The skin was then closed with 3-0 silk sutures (Fisher Scientific, USA), (figure1).

Figure1: surgical operation, implant bed preparation, implant insertion, muscle and skin suturing

The sutured area was next treated with oxytetracycline spray, a topical

antibiotic (Zoetis, USA). The appropriate postoperative care was given. The experimental animals received 0.7 ml/kg of the long-acting systemic antibiotic oxytetracycline after surgery. As part of the postoperative care, a systemic intramuscular drug and an antibiotic (local oxytetracycline spray 2.5%) were given once daily for five days after surgery.

After the animal sacrifice, the tibia was dissected. The implant site became visible once the soft tissue was removed. A carbide disc attached to the straight handpiece made cuts that allowed the implants to be identified and separated from one another. The bone surrounding the implants was sliced using a disc cutter that rotated slowly and cooled vigorously. The osteotomy was performed 5 mm from the implant's head. Specimens of bone-implant blocks were promptly preserved in 10% freshly produced formalin and left to fix for three days. 50% formic acid was applied to the samples. The specimens were checked everyday with a tiny needle. Every three to four days, the solution was altered. Decalcification was achieved once it was finished, which happened when the needle was inserted deeply and without resistance into the specimen. The bone implant block was then sliced in half using a sharp scalpel, and it was run the entire length of the implant deep within the bone until it was in one of the two halves. The implant was then carefully removed from its bed. After the specimens were submerged in running water for 30 minutes to remove any residual acid, histological slides were prepared, and S-EYE 2.0 soft wear was used for the histomorphometric analysis, where the reactive layer thickness (RLT), osteoid tissue thickness (OTT), bone trabecular thickness (BTT), fibroblast cells number (FC). Ten fields take randomly, for each field three measurements take and then the mean calculated for statistic analysis (figure 2).

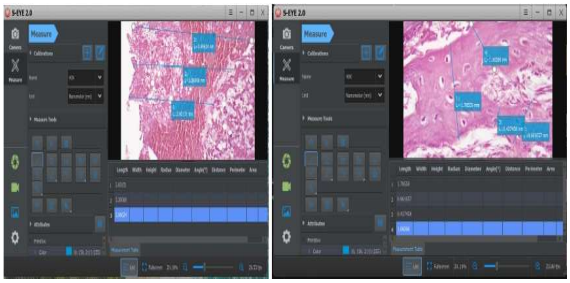

Figure 2: S-EYE 2.0 soft wear used for histomorphometric analysis

Statistic analysis

In the context of analysis of variance, statistical analysis is conducted using the least significant difference (LSD) test, which aids in identifying the populations whose means differ statistically. Comparing the populations collected in pairs is the test's fundamental concept, when there is a significant difference between the means of data for control and experimental groups.

Results

Histological study:

At 3rd day interval, Histological study showed The reaction of the body to the foreign material. In the control group, the thread area filled with RBCs clot and inflammatory cells with area of necrosis and fibrin material. in the Portulaca Oleracea (PO) group, the area showed low congestion of RBCs with newly formed fibroblast cells among numerous collagen fibres and newly formed blood vessels (angiogenesis) with few inflammatory cells, while the gold nanoparticles (Au) group showed more RBCs clumps, inflammatory cells, fibroblast cells with collagen fibres with inflammatory cells.

At 1week interval, the socket of implant in the control group illustrated still areas of congestion with fibrin and large number of fibroblast cells with collagen

fibers, inflammatory cells, with newly blood vessels. The socket of PO group showed reduction in the fibroblast cells and appearing osteoid tissue with some trapped osteocyte within it, in Au group fibrin area still presented with newly formed fibroblast and collagen fibres, in some area the nanoparticle material appeared.

At 2weeks interval, the threads showed some slight congestion areas with more fibroblasts in between collagen fibres and beginning of osteoid tissue appearing in the control group, the PO group illustrated the newly formed bone trabeculae with osteoblast cell on the periphery and osteocyte cells within these trabeculae which enclose large marrow spaces also more osteoid tissue formed , the Au group also illustrated more osteoid tissue with some preosteoblast and trapped osteocyte within it with more fibroblast and collagen fibres (figure 3).

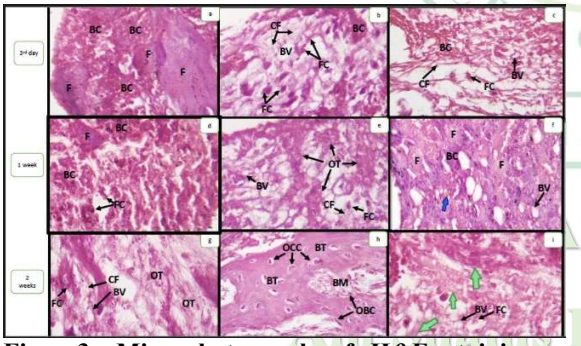

Figure3: Microphotograph of H&E staining bone showing control group (a,d,g), Portulaca Oleracea group (b,e,h) and gold nanoparticles group(c,f,i) in three intervals (3days, 1week, 2 weeks).Blood congestion(BC), fibrin accumulation (F), fibroblast cells (FC),collagen fibre (CF), newly formed blood vessels (BV), osteoid tissue (OT), bone trabeculae (BT), osteocyte cell (OCC) osteoblast cells (OBC), bone marrow space (BM), Gold nanoparticle (blue arrow) in Au group in 1 week interval and osteoid tissue in Au group in 2 weeks interval (green arrows)

Histomorphometric and statistic analysis :

The reactive layer thickness(RLT) measured from the implant tissue interface to the end of reaction of tissue which may be haemorrhage, granulation tissue , fibrous tissue , osteoid tissue or bone trabeculae, the extension and composition of this layer indicate the biocompatibility and Osseointegrative effects of the experimental materials , also the osteoid tissue thickness(OTT), the bone trabecular thickness (BTT) and the fibroblast cells (FC) measurement in the 3 intervals for the three groups (figure 4) and (table 1).

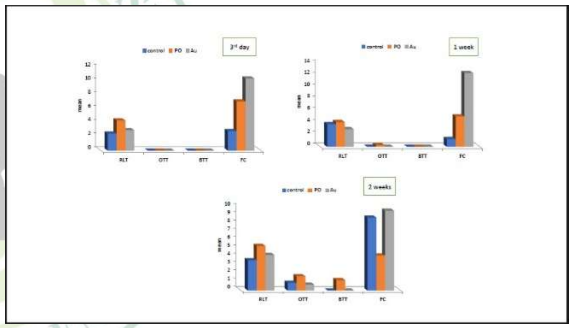

Figure 4: Histogram of histomorphometric analysis of reactive layer thickness (RLT), osteoid tissue thickness (OTT), bone trabeculae thickness (BTT) and fibroblast cell number (FC) for three groups in the three times of healing

At the 3rd day interval, according to the LSD test the PO group showed significant difference with both Au group and control group in RLT but there was no significant difference between Au and control groups while for FC counting the LSD showed significant difference between all three groups.

At 1week interval, the Au group was significantly difference with both other groups OP and control groups, while OP group had no significant difference with control group for RLT. For OTT, the PO group showed significant difference with other two groups while there was no significant difference between Au and control group, for FC counting the LSD

showed significant difference between all three groups.

At 2 weeks interval, the LSD test showed significant difference between all groups for RLT, the PO group differ significantly with both Au and control group for OTT, BTT and FC counting, while there was no significant difference between Au and control groups in OTT, BTT and the FC counting

Table 1: Multiple Comparison LSD test of Reactive layer thickness, Osteoid tissue thickness, Bone trabeculae thickness and Fibroblast cell number for all groups in all intervals

Interval	Groups	RLT	OTT	BTT	FC
3rd day	Control / PO	.000	/	/	.000
	Control / Au	.095	/	/	.000
	PO /Au	.000	/	/	.000
1week	Control / PO	.075	.000	/	.000
	Control / Au	.000	1.000	/	.000
	PO /Au	. 000	.000	/	.000
2weeks	Control / PO	.000	.019	.000	.000
	Control / Au	.002	.511	1.000	.482
	PO /Au	.000	.004	.000	.000

***. The mean difference is significant at the 0.05 level.**

Discussion

The most crucial connection for biocompatibility in vivo is the interface between the implant surface and tissue, particularly for metallic implants and also for other biomaterials since the surface characteristics affect the type and severity of the foreign body reaction, the intensity and extent of this tissue reaction determine the biofunctionality of implant's surface.[29] In this study the reaction layer extend from the implant surface to the end of histological changes, usually the reaction starts within few seconds or some minutes after implantation and differed in it's composition indifferent intervals according to the effects of coating material, at the third day interval the PO group showed greater reaction extension than the other two groups and it's content lesser RBCs congestion, lesser inflammatory cells and more fibroblast cells than the control group, this indicate that the PO is active material, has anti-inflammatory effect with acceleration of healing by acceleration the granulation tissue formation and this agreed with Zhou *etal*.[15] who showed that the aqueous extract of Portulaca oleracea may also play an important role in the suppression of the vascular inflammatory process.

At the 1week interval the reaction layer appeared osteoid tissue in PO group so it is indicate that the PO stimulate the differentiation of the steam cell to osteoblast cell which is mean that the coated material is osteoinductive material, in comparing to that of Au group which characterised by high level of fibroblast cells which may extend to fibrous capsule surrounding the implant and causing it is displacement. By the 2nd week the appearance of osteoid tissue in the Au group indicate slowly beginning osseointegration with high level fibroblast cells, while formation of bone trabeculae in PO group indication that this material is accelerate the osseointegration of bone. And this agree with Guo *etal*.[30] who said that the PO extract administration groups demonstrate high-quality wound healing, characterized by an increase in new blood vessels, collagen deposition, and re-epithelization, as well as a reduction in iron accumulation and inflammatory infiltration. The increase in fibroblast in 2 weeks interval in Au group is indicate that the Au nanoparticles help in wound healing acceleration and this agree with Volkova *etal*.[31] who said the gold nanoparticles aided in burn healing and stimulated regenerative processes in damaged tissues, as evidenced by an increased burn contraction rate and restoration of the skin's histological structure and type I and III collagen content by day 21 post-treatment.

One of the limitations in this study is the lack the renal functional tests like

creatinine and liver functional tests such as alkaline phosphatase which can increase the biocompatibility property of the Portulaca Oleracea..

Conclusion

The low inflammatory reaction and necrotic tissue in the early time interval mean acceleration the healing process so PO coating material is biocompatible, in the other hand, the acceleration of the osteoid tissue and bone trabeculae formation so Portulacea Oleracea coating material is osteoinductive material accelerate osseointegration in shorter time than the Au nanoparticles.

Ethical approval

The study was approved by the institutional animal care and use committee of the College of Veterinary Medicine, University of Mosul, Mosul, Iraq, on March 15, 2023, with reference number UM.VET.2023.012.

Competing interests

The authors declare they have no conflict of interest.

Availability of data and materials

The corresponding author can provide all of the data used in this study upon request.

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