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Original Article

Exploring the Green Potential of Quercetin-Enhanced Strontium Oxide Nanoparticle Scaffold on Mesenchymal Stem Cells BMP-2 Expression

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ABSTRACT

Aim: The study aimed to create a scaffold infused with Quercetin-enhanced strontium oxide nanoparticles and assess its impact on BMP-2 expression in MSCs. **Materials and Methods:** Scaffold fabrication involved mixing 1% Hyaluronic acid, 0.5% carrageenan and 2% gelatin in a ratio of 6:1:3, adding 10 mg of quercetin-doped SrO nanoparticles and freezing at -20ºC for 12 hr and -80ºC for 24 hr. Dental Pulp Stem Cells (DPSC) cultured in DMEM F12 supplemented with 10% FBS were seeded onto the scaffolds treated with UV radiation. Osteogenic marker gene expression was analyzed using qPCR at 1, 3 and 5 days post-seeding, comparing control and test groups. The comparative Ct method was used to quantify gene expression using normalization of GAPDH. Experiments were conducted in triplicate and repeated thrice for reliability. **Results:** On Day 1, the control group showed a BMP-2 concentration of 5.8 ng/µL, decreasing slightly to 5.1 ng/µL by Day 3 and increasing to 9.6 ng/µL by Day 5. In contrast, the experimental group displayed a higher BMP-2 concentration of 7.4 ng/µL on Day 1, dropping to 0.3 ng/µL by Day 3, but significantly increasing to 27.3 ng/µL by Day 5. **Conclusion:** Combining green-synthesized strontium oxide nanoparticles with Quercetin enhances bone regeneration and differentiation, creating a microenvironment conducive to tissue repair. Quercetin's anti-inflammatory and antioxidant properties align with greener biomedical trends, promising to address bone defects and improve patient outcomes.

Keywords: Bone Morphogenetic Protein 2, Mesenchymal Stem Cells, Nanoparticles, Quercetin, Tissue Scaffolds.

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INTRODUCTION

Green synthesis of nanoparticles offers a sustainable and eco-friendly approach to producing nanomaterials with reduced environmental impact. Unlike traditional methods that often involve harsh chemicals and high-energy processes, green synthesis harnesses the power of natural sources such as plant extracts, microorganisms and biopolymers to fabricate nanoparticles.[1] This method not only minimizes the use of hazardous reagents but also utilizes renewable resources, making it cost-effective and scalable. Furthermore, green synthesis typically occurs under mild reaction conditions, leading to better control over particle size, morphology and surface properties.[2] Additionally, the biomolecules present in the natural extracts act as reducing and stabilizing agents, facilitating the formation and stabilization of nanoparticles. Green synthesis offers a promising path toward creating sustainable nanomaterials applicable across diverse fields such as biomedicine, catalysis and environmental remediation.

Quercetin, a natural flavonoid found in fruits and vegetables, offers potential health benefits and shows promise in oral health. Its anti-inflammatory and antioxidant properties help in reducing gingival inflammation and counteract oxidative stress in periodontitis.[3] Additionally, Quercetin exhibits antimicrobial activity against periodontal pathogens and research suggests its potential to modulate bone metabolism and promote periodontal tissue regeneration, offering prospects for tissue repair and regeneration in periodontal therapy.[4]

In nanoparticle synthesis, Quercetin's properties make it suitable for green synthesis methods, serving as a reducing and stabilizing agent. Overall, Quercetin's diverse properties make it valuable in healthcare and nanotechnology, suggesting avenues for further research and development.

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Strontium oxide nanoparticles possess intriguing properties with wide-ranging potential applications, from biomedicine to environmental science, making them a burgeoning field in nanotechnology.[5] Nanoparticles composed of strontium and oxygen atoms at the nanoscale exhibit distinctive properties attributed to their diminutive dimensions and remarkable surface area-to-volume ratio. Within the realm of biomedicine, they demonstrate potential in drug delivery, bioimaging and tissue engineering applications, featuring notable biocompatibility and precise controlled release capabilities.[6] Additionally, strontium oxide nanoparticles hold potential in catalysis and environmental cleanup, highlighting their versatility across diverse fields.

Bone Morphogenetic Protein-2 (BMP-2), a crucial member of the Transforming Growth Factor-beta (TGF-β) superfamily, plays a pivotal role in bone formation and regeneration.[7] It stimulates osteogenesis, triggering mesenchymal stem cells to differentiate into osteoblasts that form bone tissue. By enhancing osteogenic gene expression and promoting bone matrix mineralization, BMP-2 facilitates bone healing and regeneration. Its therapeutic potential is significant in clinical settings for bone repair, often integrated into biomaterials and scaffolds, or administered locally to injury sites. In orthopedics and dentistry, BMP-2 holds promise for improving bone regeneration and repair outcomes.[8]

Incorporating these green-synthesized nanoparticles into a scaffold creates a versatile platform with potential applications in bone regeneration, offering a multifunctional approach to tissue repair and restoration. Thus, the study aimed to create a scaffold infused with Quercetin-enchanced strontium oxide nanoparticles and assess its impact on BMP-2 expression in Mesenchymal Stem Cells [MSCs].

MATERIALS AND METHODS

The study is an experimental *in vitro* investigation conducted between June-August 2023 in Saveetha Dental College and Hospitals, Chennai.

Scaffold Fabrication

To create the scaffold, stock solutions of 1% Hyaluronic Acid (HA), 0.5% carrageenan and 2% gelatin were prepared. These solutions served as base materials. The stock solutions of HA, carrageenan and gelatin were mixed in a specific ratio of 6:1:3. After blending these base materials, 10 mg of Quercetin-doped Strontium oxide nanoparticles were added to the solution. Following this, 3 mL of the homogeneous mixture was transferred to six-well plates and 100 µL of the crosslinking agent Triphenylphosphine [TPP 15%] was added to each well. The plates were then stored at -20ºC for 12 hr and subsequently at -80ºC for 24 hr to solidify the scaffold and enhance its structural stability. To prevent degradation or contamination, the plates were stored under dry conditions after freezing (Figure 1).

Culture of Human Dental Pulp Stem Cells (DPSCs)

Informed consent and ethical approval from the SIMATS ethics committee was obtained and after that DPSCs were extracted from molars. Dental pulp tissue was collected from the pulp chamber of extracted teeth. The extracted DPSCs were cultured in Dulbecco's Modified Eagle Medium F12 supplemented with 10% Fetal Bovine Serum (FBS) and 1% Penicillin. Cell cultures were regularly maintained by changing the culture medium as needed and passaging the cells upon reaching confluence.

Detection of Osteogenic Marker Gene[BMP-2] Expression in DPSCs Using Quantitative Real-time PCR Assay

The goal was to assess how the fabricated scaffolds influence the early gene expression of osteogenic marker genes in DPSCs using Quantitative real-time PCR (qPCR). DPSCs were seeded onto fabricated scaffolds treated with UV radiation to promote cell growth and differentiation. The cells were then treated with differentiation media containing DMEM F12 supplemented with 10 mM β-glycerophosphate and 0.05 mM ascorbic acid to induce osteogenic differentiation and promote the expression of osteogenic marker genes. Gene expression levels were analyzed at three time points: 1, 3 and 5 days after cell seeding and treatment. Total RNA was isolated using the Trizol reagent and reverse transcription into Complementary DNA (cDNA) was performed using oligo (dT) primers. Quantitative real-time PCR reactions were conducted to quantify the expression levels of osteogenic marker genes such as BMP 2 forward [GGAATGACTGGATTGTGGCT] and BMP 2 reverse [TGAGTTCTGTCGGGACACAG]. The relative mRNA expression levels of target genes were calculated using the comparative Ct method, normalizing to the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase [GAPDH] with forward primer sequence [TCTCCTCTGACTTCAACAGCGAC] and reverse primer sequence [CCCTGTTGCTGTAGCCAAATTC]. The expression levels of target genes between DPSCs cultured under regular conditions (control) and DPSCs cultured on scaffolds impregnated with strontium oxide nanoparticles (test group) were compared. All experiments were repeated three times to ensure reliability and consistency.

RESULTS

Measurement of BMP-2 Concentration in the Control Group

Table 1 illustrates that on Day 1, the BMP-2 concentration in the control group was recorded at 5.8 ng/µL and by Day 3, there was a slight decrease in concentration to 5.1 ng/µL. However, by Day 5, the BMP-2 concentration notably increased to 9.6 ng/µL.

Effect of Strontium Oxide Nanoparticle-Impregnated Scaffold

On Day 1, the BMP-2 concentration in the experimental group was notably higher than the control, measuring at 7.4 ng/µL. In contrast, by Day 3, there was a substantial decrease in BMP-2 concentration to 0.3 ng/µL, but remarkably, by Day 5, there was a substantial increase in BMP-2 concentration to 27.3 ng/µL, representing a remarkable elevation compared to both the control group and the earlier time points in the experimental group (Figure 2).

DISCUSSION

Scaffolds play a critical role in tissue engineering by furnishing a supportive milieu conducive to cell proliferation and tissue regeneration.[9] The green synthesis of nanoparticles offers a sustainable method for scaffold fabrication, enhancing mechanical properties, biocompatibility and bioactivity.[10] Harnessing the advantages of green synthesis, such as cost-effectiveness and reduced toxicity, researchers are developing innovative scaffold designs tailored for various tissue engineering applications, promising biocompatible and sustainable solutions that promote efficient tissue regeneration while minimizing the environmental footprint of biomedical materials.

In this context, a novel Quercetin-enhanced strontium oxide nanoparticle scaffold was developed, combining bioactive and biocompatible components from natural sources to improve osteogenic differentiation and bone formation. Quercetin, chosen for its anti-inflammatory and antioxidant properties,[11] and strontium oxide nanoparticles, selected for their enhanced biocompatibility and osteogenic properties,[12] constitute the scaffold's key components.

Previous studies have demonstrated the individual benefits of Quercetin and strontium oxide nanoparticles. Oral administration of Quercetin in animal models of osteoporosis showed promising results, partially reversing osteopenia likely through its antioxidant, anti-inflammatory, osteogenesis-promoting, osteoclast-inhibiting and estrogen-like effects.[13]

Another study explored the effectiveness of Quercetin in mitigating alveolar bone loss and reducing apoptosis in a Wistar rat model of experimentally induced periodontitis. The study's findings suggest that administering Quercetin leads to a reduction in alveolar bone loss by enhancing osteoblastic activity, diminishing osteoclastic activity, apoptosis and inflammation in the experimental periodontitis model.[14]

Studies have shown that Quercetin-impregnated alginate-chitosan scaffolds show biocompatibility, making them promising for dental regenerative therapies.[15] Quercetin-coated biogenic Titanium oxide Nanoparticles (HQTN) demonstrated strong antioxidant and antimicrobial activity with minimal hemolytic potential, positioning them as safe dental biomaterials.[16] Additionally, quercetin-mediated copper oxide nanoparticles incorporated into electrospun polycaprolactone scaffolds effectively eradicated Pseudomonas aeruginosa biofilms, offering the potential for combating biofilm-related infections.[17]

Additionally, numerous studies have explored the properties of strontium oxide nanoparticles. In one study, researchers conducted green synthesis and characterization of strontium nanoparticles from green tea leaf extracts. They investigated the antimicrobial and anti-inflammatory activities of these nanoparticles against oral pathogens, revealing their effectiveness against *Enterococcus faecalis, Streptococcus mutans* and *Candida Albicans.*[18]

Figure 1: The formulated Quercetin-Enhanced Strontium Oxide Nanoparticle Scaffold.

It has also been shown that strontium nanoparticles synthesized from *Acacia nilotica* and green tea extracts exhibit excellent antioxidant, antimicrobial and anti-inflammatory activity, outperforming selenium and zinc oxide nanoparticles in comparison.[19,20]

Another study assessed the osteogenic potential of mesoporous bioactive glass ceramics doped with strontium nanoparticles. *In vitro* cell culture experiments unveiled that the incorporation of strontium selectively influences osteoblasts, facilitating their early differentiation towards the osteoblast phenotype while impeding osteoclastogenesis.[21]

In our study, we analyzed the influence of green-synthesized nanoparticles on Mesenchymal Stem Cell BMP-2 expression. The results revealed a notable difference in BMP-2 concentration between the control group, where DPSCs were cultured under regular conditions and the test group, where DPSCs were cultured on scaffolds impregnated with strontium oxide nanoparticles. By Day 5, the BMP-2 concentration in the control group reached 9.6 ng/µL, while in the test group, it dramatically increased to 27.3 ng/µL. This substantial increase in BMP-2 concentration in the test group suggests that incorporating strontium oxide nanoparticles into the scaffold significantly influences BMP-2 expression compared to the control group.

The initial rise in concentration observed in the treated group could be attributed to the introduction of strontium oxide nanoparticles, which likely stimulated the expression of BMP-2. The subsequent further increase in BMP-2 concentration by Day 5, surpassing even the control group, indicates a delayed but enhanced response to the treatment, possibly due to a compensatory mechanism or a delayed release of BMP-2 triggered by the strontium oxide nanoparticles impregnated scaffold. Our study findings are consistent with those of a previous investigation involving a chitosan-agarose-gelatin scaffold, modified with nanoparticles, aimed at achieving sustained release of Stromal cell-Derived Factor 1 (SDF-1) and Bone Morphogenetic Protein 2 (BMP-2). In this prior study, the scaffold loaded with BMP-2 exhibited heightened levels of Alkaline Phosphatase (ALP) activity, indicative of enhanced osteogenic differentiation.[22]

These findings suggest that increasing BMP-2 levels through scaffolds represents a promising strategy for promoting tissue regeneration and repair in a controlled and site-specific manner. Such an approach holds potential applications in various fields, including orthopedics, dentistry and regenerative medicine. Literature proves that BMP-2 stimulates bone remodeling, as well as restoring bone density around dental implants.[23] Higher levels of BMP-2 can enhance the success rate of dental implant procedures by promoting osseointegration and reducing the risk of implant failure. Moreover, increased BMP-2 levels can improve the efficacy of tissue engineering strategies, leading to the development of more functional and durable tissue substitutes.[24]

Table 1: The control and strontium oxide nanoparticle-impregnated scaffold on BMP-2 expression in dental pulp stem cells over 1,3 and 5 days.

Group	Day 1 (ng/µL)	Day 3 (ng/µL)	Day 5 (ng/µL)
Control	5.8	5.1	9.6
Strontium Oxide nanoparticles impregnated scaffold on the expression of BMP 2	7.4	0.3	27.3

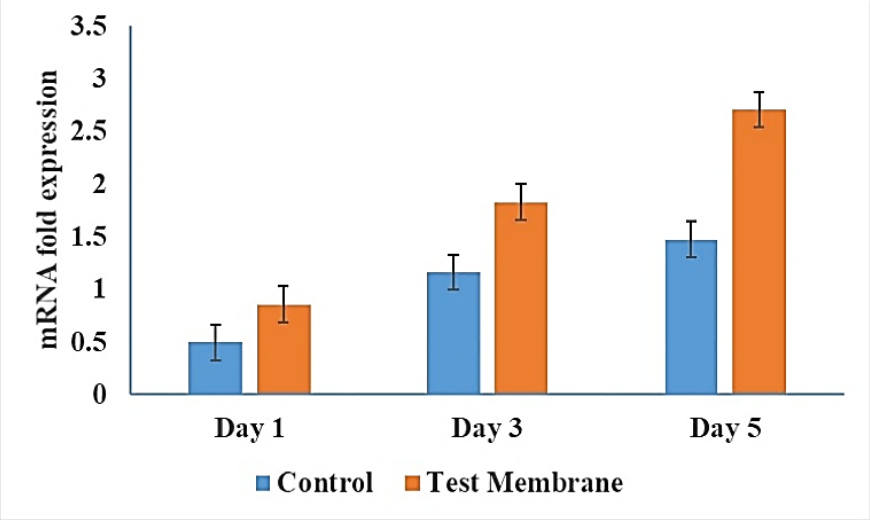

Figure 2: The X-axis represents the mRNA fold expression of the control and strontium oxide nanoparticle-impregnated scaffold[test membrane] over Days 1,3 and 5 and the Y-axis represents the change in the mRNA fold expression.

Based on our study, the Quercetin-Enhanced Strontium Oxide Nanoparticle Scaffold shows promise for periodontal regenerative therapy. Further comparative studies with other green-synthesized scaffolds would provide a comprehensive understanding of their effectiveness and clinical benefits in real-world scenarios.

LIMITATIONS

The study was conducted *in vitro*, which may not fully replicate the complex *in vivo* environment. Factors such as interactions with the immune system, blood supply and mechanical forces could influence the scaffold's performance differently *in vivo*. While the study is completely focused on MSC BMP-2 expression, other factors and signaling pathways involved in osteogenic differentiation and bone formation should also be investigated to gain a comprehensive understanding of the scaffold's effects.

CONCLUSION

The study shows that scaffolds infused with green-synthesized strontium oxide nanoparticles and quercetin significantly enhanced BMP-2 expression, particularly by Day 5. This highlights their potential to create a favorable microenvironment for bone regeneration and osteogenic differentiation. The synergistic effects of these components, coupled with their anti-inflammatory and antioxidant properties, enhance bone repair. Additionally, the green synthesis approach supports sustainable biomedical advancements.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BMP-2: Bone Morphogenic protein; **MSC:** Mesenchymal Stem Cells; **SrO:** Strontium oxide; **DPSC:** Dental Pulp Stem Cells; **TGF-β:** Transforming growth factor-beta; **HA:** Hyaluronic acid; **TPP:** Triphenylphosphine; **FBS:** Fetal Bovine Serum; **PCR:** Polymerase Chain Reaction; **DMEM:** Dulbecco's Modified Eagle Medium.

AREAS OF FUTURE RESEARCH

Conducting clinical trials to evaluate the efficacy and feasibility of the scaffold in human patients would be the goal of future research. Assessing its performance in various clinical scenarios, such as bone defects, fractures and non-unions, would provide valuable clinical data to guide its use in routine practice.

ETHICAL CONSENT

Ethical approval was obtained from the SIMATS ethics committee.

SUMMARY

The study aimed to develop a scaffold infused with Quercetin-enhanced strontium oxide nanoparticles and assess its impact on BMP-2 expression in MSCs. Scaffold fabrication involved mixing hyaluronic acid, carrageenan and gelatin, along with quercetin-doped SrO nanoparticles. Dental Pulp Stem Cells were cultured on the scaffolds and gene expression was analyzed over several days. Results showed that the experimental group exhibited significantly higher BMP-2 expression compared to the control group, indicating enhanced bone regeneration potential. This suggests that combining green-synthesized nanoparticles with Quercetin holds promise for promoting tissue repair in bone defects, aligning with greener biomedical approaches and offering potential improvements in patient outcomes.

REFERENCES

1. Vijayaram S, Razafindralambo H, Sun YZ, Vasantharaj S, Ghafarifarsani H, Hoseinifar SH, *et al.* Applications of green synthesized metal nanoparticles-A review. Biol Trace Elem Res. 2024;202(1):360-86.
2. Najahi-Missaoui W, Arnold RD, Cummings BS. Safe nanoparticles: are we there yet? Int J Mol. Sci.2020;22(1):385.
3. Wang Y, Tao B, Wan Y, Sun Y, Wang L. Drug delivery based pharmacological enhancement and current insights of quercetin with therapeutic potential against oral diseases. Biomed and Pharmacother. 2020;128:110372.
4. Mooney EC, Holden SE, Xia XJ, Li Y, Jiang M. Quercetin preserves oral cavity health by mitigating inflammation and microbial dysbiosis. Front Immunol. 2021;12:774273.
5. Mukherjee S, Mishra M. Application of strontium-based nanoparticles in medicine and environmental sciences. Nanotechnol Environ Eng. 2021;6(2):25.
6. Rafeeq M. Synthesis and Characterization of Strontium Oxide Nano Particle by Sol-Gel Method. Orient J Chemi. 2021;37:83-90.
7. Zhu L, Liu Y, Wang A, Zhu Z, Li Y, Zhu C, *et al.* Application of BMP in bone tissue engineering. Front Bioeng Biotechnol. 2022;10:810880.
8. Halloran D, Durbano HW, Nohe A. Bone morphogenetic protein-2 in development and bone homeostasis. J Dev Biol 2020;8(3):19.
9. Kirillova A, Yeazel TR, Asheghali D, Petersen SR, Dort S, Gall K, *et al.* Fabrication of biomedical scaffolds using biodegradable polymers. Chem Rev 2021;121(18):11238-304.
10. Hano C, Abbasi BH. Plant-based green synthesis of nanoparticles: Production, characterization and applications. Biomol. 2021;12(1):31.
11. Ulusoy HG, Sanlier N. A minireview of quercetin: From its metabolism to possible mechanisms of its biological activities. Crit Rev Food Sci Nutr. 2020 ;60(19): 3290-303.
12. Wong SK, Chin KY, Ima-Nirwana S. Quercetin as an agent for protecting the bone: a review of the current evidence. Int J Mol Sci. 2020;21(17):6448.
13. Huang YY, Wang ZH, Deng LH, Wang H, Zheng Q. Oral administration of quercetin or its derivatives inhibit bone loss in an animal model of osteoporosis. Oxid Med Cell Longev. 2020;23:110-123.
14. Taskan MM, Gevrek F. Quercetin decreased alveolar bone loss and apoptosis in experimentally induced periodontitis model in Wistar rats. Antinflamm Antiallergy Agents Med Chem. 2020;19(4):436-48.
15. Hanish D, Priya VV, Gayathri R. Quercetin-infused alginate-chitosan scaffolds for possible use in dental regenerative therapies. International Journal of Medical Dentistry. 2023;27(3).
16. Gandhimathi KA, Francis AP, Rengasamy G, Veeraraghavan VP, Sankaran K. Quercetin-coated biogenic titanium oxide nanoparticles: Synthesis, characterization and *in vitro* biological studies. Particulate Science and Technology. 2024:1-9.
17. Rohatgi N, Ganapathy D, Sathishkumar P. Eradication of Pseudomonas aeruginosa biofilm using quercetin-mediated copper oxide nanoparticles incorporated in the electrospun polycaprolactone nanofibrous scaffold. Microbial Pathogenesis. 2023;185:106453.

18. Agarwal S, Maiti S, Rajeshkumar S, Agarwal V, Deshmukh M, Ganapathy D. Green synthesis and characterization of strontium and zirconium nanoparticles from green tea leaf extracts and studying their antimicrobial activity and anti-inflammatory activity against oral pathogens. J Pharm Negat Results. 2022:539-43.
19. Shanmugam R, Anandan J, Balasubramanian AK, Raja RD, Ranjeet S, Deenadayalan P. Green synthesis of selenium, zinc oxide and strontium nanoparticles and their antioxidant activity-a comparative *in vitro* study. Cureus. 2023;15(12).
20. Agarwal S, Maiti S, Rajeshkumar S, Agarwal V, Deshmukh M, Ganapathy D. Green synthesis and characterization of strontium and zirconium nanoparticles from green tea leaf extracts and studying their antimicrobial activity and anti-inflammatory activity against oral pathogens. Journal of Pharmaceutical Negative Results. 2022:539-43.
21. Kumar A, Banrjee S, Roy P, Xu H, Mariappan CR. Osteogenic commitment of strontium nanoparticles doped mesoporous bioactive glass-ceramics. Mat Sci Engi: B. 2022;286:116068.
22. Wang B, Guo Y, Chen X. Nanoparticle-modified chitosan-agarose-gelatin scaffold for sustained release of SDF-1 and BMP-2. Int J Nanomedicine.2018;13: 7395-408.
23. Eawsakul K, Tancharoen S, Nasongkla N. Combination of dip coating of BMP-2 and spray coating of PLGA on dental implants for osseointegration. J Drug Deliv Sci. Technol. 2021;61:102296.
24. Park SH, Park JY, Ji YB, Ju HJ, Min BH, Kim MS. An injectable click-crosslinked hyaluronic acid hydrogel modified with a BMP-2 mimetic peptide as a bone tissue engineering scaffold. Acta Biomater. 2020;117:108-20.

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