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The role of bone morphogenic protein 2 in composite scaffolds in tissue engineering: Narrative review

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Abstract

Background: Tissue engineering is currently used as an alternative treatment to accelerate bone tissue regeneration. Composite scaffolds play a role in osteoinduction and can enhance cell proliferation. The addition of bone morphogenetic protein-2 (BMP-2) to the scaffold can promote cell migration, cell proliferation, and the differentiation of genes related to osteogenesis.

Methods: This paper employs a narrative review and searches through PubMed, Sage Journal, and Science Direct for studies published in the last 5 years, using keywords such as "Bone Morphogenetic Protein-2," "BMP-2," "Composite Scaffold," and "Tissue Engineering," resulting in the identification of 20 relevant journals.

Discussion: The release of BMP-2 on composite scaffolds enhances osteogenic differentiation and cell proliferation to accelerate bone tissue regeneration. Osteogenic differentiation occurs through the activation of the WNT/β-catenin pathway by BMP-2, which then promotes the migration of endothelial cells and osteoblasts to the surrounding tissue, thereby speeding up bone formation.

Conclusion: The application of BMP-2 on composite scaffolds can be used for tissue engineering.

Keywords: Tissue engineering; Composite scaffold; BMP-2; Osteogenic differentiation

1. Introduction

The use of biomaterials and tissue engineering in dentistry has significantly transformed clinical practices.[1] A major challenge in dentistry is the regeneration or repair of damaged or lost tissues. Various regenerative techniques have been applied to repair dental structures damaged by caries, pulpitis, fractures, and periodontal diseases.[2] Mild bone damage can naturally heal itself, but extensive bone damage exceeding 2 cm or tissue loss greater than 50% requires a relatively long healing process and increases the risk of pathological fractures and incomplete bone function, necessitating additional treatment.[3] Initially, tissue repair in the maxillofacial area due to trauma or other diseases was performed using autologous tissue transplantation, heterologous materials for bone and mucosal repair, or biocompatible materials for dental tissue repair.[1]

Autologous bone grafts are considered the gold standard for promoting bone regeneration, but they have several limitations, including limited donor tissue availability and the risk of secondary defects at the harvest site. These limitations make autologous grafts less suitable for pediatric and elderly patients. Allografts and xenografts present additional risks, such as pathogen transmission and immune rejection. Tissue engineering, which mimics natural tissue

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development processes, offers a promising alternative for complex tissue regeneration.[2] This field has rapidly advanced, providing new methods to accelerate bone tissue regeneration. The core components of tissue engineering—scaffolds that support stem cell adhesion, growth factors, and stem cells—are essential for forming new tissue and speeding up the regeneration process.[4]

In tissue engineering, biomaterials can be organic, inorganic, or composite, and they are characterized by properties such as biocompatibility, biodegradability, osteoconductivity, osteoinductivity, ease of use, safety, and cost-effectiveness.[4] Composite scaffolds, which blend polymers and ceramics, are noted for their superior mechanical and biological properties compared to other scaffold types.[5] These scaffolds mimic natural bone tissue by incorporating porous ceramic materials, with porosity being crucial for cell attachment and nutrient distribution.[6] Research by Zhang et al. showed that HAp/PLGA scaffolds with bone marrow stem cells accelerated bone defect regeneration in rats, demonstrating faster osteogenesis and mineralization than controls and PLGA alone.[7] Similarly, Fu et al. found that HAp/PLGA scaffolds had better mechanical strength, osteoconductivity, and enhanced cell adhesion and proliferation compared to PLGA scaffolds.[8]

Bone Morphogenetic Protein (BMP) is a vital growth factor in bone tissue engineering, part of the transforming growth factor β (TGF-β) superfamily, recognized for its ability to induce osteogenic differentiation.[9,10]. Various BMPs, including BMP-2, BMP-7, BMP-9, and BMP-6, can initiate osteogenic differentiation in mesenchymal stem cells (MSCs). BMP-2 is crucial in maintaining bone balance by directing osteogenic progenitor cells to become osteoblasts and osteoclasts, thus enhancing bone mineralization and osseointegration.[11] Additionally, BMP-2 stimulates neural cell growth and promotes the differentiation of chondrocytes and osteoblasts. The activation of the Smad/non-Smad pathway by BMP-2 facilitates the differentiation of MSCs into osteoblasts[12], which is essential for bone formation through the differentiation of immature MSCs into osteogenic cells.[13] Research by Li et al. demonstrated that administering BMP-2 to MSCs increases cell differentiation, marked by heightened ALP activity.[10] Martin-Iglesias et al. also found that adding BMP-2 promotes MSC osteogenic differentiation and speeds up mineralization in bone regeneration.[14] Given these findings, further analysis of the role of BMP-2 in composite scaffolds for tissue regeneration is warranted.

2. Method

This paper uses a narrative review design as the scientific framework because this type of design encompasses various aspects of a specific topic. Moreover, it provides comprehensive information on health issues from multiple perspectives. Articles were searched through several databases, namely PubMed, Sage Journal, and Science Direct, for studies published in the last five years. In the initial general search, the keywords and synonyms combined were "Bone Morphogenic Protein-2" OR "BMP-2" OR "The Role Of BMP-2" OR "Composite Scaffold" OR "Tissue Engineering." The search results from the databases yielded a total of 3,023 articles. These articles were then screened based on inclusion criteria, which included full-text articles, open access, and publications from the last five years, focusing on the role of BMP-2 in composite scaffolds or tissue engineering. The exclusion criteria were literature reviews, systematic reviews, books, and non-English articles. After screening the articles according to the inclusion criteria, 20 relevant articles were identified. The collected data will be analyzed, and conclusions will be drawn based on the research findings.

2.1. Article Screening

Table 1 List of articles according to inclusion criteria

No.	Tittle	Author	Results
1	The role of VEGF and BMP-2 in stimulation of bone healing with using hybrid bio-composite scaffolds coated implants in animal model.[15]	Rady et al., 2020	BMP-2 levels increased significantly in the treatment group compared to the control group at week 2 and decreased at week 3
2	Exfoliated Human Deciduous Tooth Stem Cells Incorporating Carbonate Apatite Scaffold Enhance BMP-2, BMP-7 and Attenuate MMP-8 Expression During Initial Alveolar Bone Remodelling in Wistar Rats (Rattus norvegicus).[16]	Prahasanti et al., 2020	BMP-2 and BMP-7 levels were higher in the treatment group than in the control group.
3	Effect of inducible bone morphogenetic protein 2 expression on the osteogenic	Toth et al., 2020	Osteogenic differentiation occurred on day 21 in the dental pulp stem cells (DPSC)-BMP-2 line, especially

	differentiation of dental pulp stem cells in vitro.[17]		in control medium (CM) and osteoinductive medium (OM) compared to the control line.
4	Accelerating Bone Healing by Decorating BMP-2 on Porous Composite Scaffolds.[18]	Li et al., 2019	BMP-2 induced on scaffolds can increase proliferation, cell attachment, and osteogenic differentiation compared to controls
5.	Immobilization of BMP-2 and VEGF within Multilayered Polydopamine-Coated Scaffolds and the Resulting Osteogenic and Angiogenic Synergy of Co-Cultured Human Mesenchymal Stem Cells and Human Endothelial Progenitor Cells.[19]	Godoy-Gallardo et al., 2020	BMP-2 is induced into human mesenchymal stem cells (hMSCs) scaffolds, there is an increase in osteogenic differentiation and in human EPCs (hEPCs) there is an increase in angiogenesis.
6.	The combination of PLLA/PLGA/PCL composite scaffolds integrated with BMP-2-loaded microspheres and low-intensity pulsed ultrasound alleviates steroid-induced osteonecrosis of the femoral head.[11]	Zhu et al., 2020	The administration of BMP-2 to composite scaffolds combined with low-intensity pulse ultrasonic (LIPUS) can increase the regeneration of bone experiencing osteonecrosis by increasing angiogenesis and the expression of transcription of osteogenic factors.
7.	Dental Pulp Stem Cell Differentiation Potential Of BMP-2 and BMP-4.[20]	Li et al., 2023	Dental pulp stem cells (DPSCs) supplemented with BMP-2 induced increased cell proliferation and viability.
8.	Clarifying the Tooth-Derived Stem Cells Behavior in a 3D Biomimetic Scaffold for Bone Tissue Engineering Applications.[21]	Salgado et al., 2020	The scaffold combination of collagen, nano hydroxyapatite, and phosphoserine was able to encourage the proliferation and differentiation of human dental follicle stem cells (hDFMSC) and was able to increase ALP levels and the expression of RUNX-2, BMP-2, and osteopontin (OPN) compared to the control group.
9.	Osteogenic Potential of Sheep Mesenchymal Stem Cells Preconditioned with BMP-2 and FGF-2 and Seeded on an nHAP-Coated PCL/HAP/β-TCP Scaffold.[22]	Stamnitz et al., 2022	The addition of BMP-2 and FGF-2 to the scaffold can enhance the osteogenic potential of ovine BM-MSCs. FGF-2 plays a role in MSC proliferation, while BMP-2 promotes osteogenesis.
10.	Three-Dimensional Printed Polylactic Acid Scaffold Integrated with BMP-2 Laden Hydrogel for Precise Bone Regeneration.[23]	Cha et al., 2021	In vitro: scaffold cage/Biogel group released BMP-2 to maintain osteoinductivity for 14 days. In vivo: the cage/Biogel/BMP-2 scaffold group had the highest bone regeneration compared to the other groups.
11.	A novel nano-hydroxyapatite/synthetic polymer/bone morphogenetic protein-2 composite for efficient bone regeneration.[24]	Bal et al., 2021	Implantation of a hydroxyapatite/PLA-PEG nanoscale scaffold combined with BMP-2 at a dose of 3 μg and 10 μg was able to increase bone formation and density in lumbar bone defects (91.6%) in Sprague-Dawley rats at 8 weeks post-surgery.
12.	BMP-2 and VEGF-A modRNAs in collagen scaffold synergistically drive bone repair through osteogenic and angiogenic pathways.[25]	Geng et al., 2021	The combination of BMP-2 and VEGF-A on the collagen scaffold is able to encourage osteogenic differentiation and angiogenesis, thereby stimulating bone formation.
13.	Dual delivery of bone morphogenetic protein-2 and basic fibroblast growth factor from nanohydroxyapatite/collagen for bone tissue engineering.[26]	Hu et al., 2019	Cell adhesion, proliferation and differentiation of bone marrow mesenchymal stem cells (BMSCs) in the scaffold group added with BMP-2 and basic fibroblast growth factor (bFGF) were compared with the control group ($P<0.05$).

14.	Alveolar bone repair of rhesus monkeys by using BMP-2 gene and mesenchymal stem cells loaded three-dimensional printed bioglass scaffold.[27]	Wang et al., 2019	The addition of BMP-2 to the bioglass scaffold was able to encourage the proliferation of rBMSCs in a paracrine/autocrine manner, while also increasing bone regeneration in bone defects. BMP-2 is produced to induce mesenchymal stem cells (MSCs) to differentiate into osteoblasts and promote bone regeneration.
15.	Enhanced bone regeneration of the silk fibroin electrospun scaffolds through the modification of the graphene oxide functionalized by BMP-2 peptide.[28]	Wu et al., 2019	Peptide-BMP-2 in graphite oxide shows increased osteogenic and bone tissue regeneration so that it can accelerate healing.
16.	Bioinspired gelatin/bioceramic composites loaded with bone morphogenetic protein-2 (BMP-2) promote osteoporotic bone repair.[29]	Echave et al., 2022	The gelatin/HA composite scaffold added with BMP-2 was able to support cell proliferation and differentiation and encourage increased ALP activity and transcription factor gene expression in human bone marrow derived mesenchymal stem cells (hBM-MSCs). The combination of scaffold and BMP-2 was able to accelerate new bone formation in mouse models with osteoporosis.
17.	A non-invasive smart scaffold for bone repair and monitoring.[30]	Huang et al., 2023	The addition of BMP-2 is able to stimulate osteogenic differentiation of cells. Proteins related to osteogenesis were expressed highest in the group with the addition of BMP2
18.	BMP-2-releasing gelatin microspheres/PLGA scaffolds for bone repairment of X-ray-radiated rabbit radius defects.[31]	Xia et al., 2019	The combination of PLGA/GM scaffold with BMP-2 was able to increase the proliferation and osteoblastic differentiation of BMSCs and accelerate the fusion and formation of new bone in rabbit radial bone defects.
19.	BMP-2 Delivery Strategy Modulates Local Bone Regeneration and Systemic Immune Responses to Complex Extremity Trauma.[32]	Vantucci et al., 2020	Implantation of a scaffold made from heparin methacrylamide microparticles (HMP) which has been added with BMP-2 is able to induce the formation of bridging bone and increase the volume of the defective rat femur bone. HMP can also inhibit the inflammatory process so that the healing process runs faster.
20.	Evaluation of BMP-2 and VEGF loaded 3D printed hydroxyapatite composite scaffolds with enhanced osteogenic capacity in vitro and in vivo.[33]	Chen et al., 2020	Scaffolds with the addition of BMP-2 and VEGF promoted osteogenic differentiation, as well as mineral deposition and osteogenesis gene expression. Implantation of a combination of scaffold and BMP-2 in mouse bone defects showed the formation of new bone with a higher bone matrix composition compared to the control group.

The article screening results yielded 20 journals regarding the role of BMP-2 in composite scaffolds for tissue engineering. From Table 1, it is evident that BMP-2, as a growth factor added to composite scaffold biomaterials, enhances osteogenic differentiation in the treatment group compared to scaffolds without BMP-2. Additionally, BMP-2 increases cell proliferation, cell viability, cell adhesion, angiogenesis, and bone regeneration while reducing osteonecrosis. Some studies also combined BMP-2 and VEGF growth factors on scaffolds, resulting in a significant increase in osteogenic differentiation and angiogenesis, thus stimulating bone formation. In vitro studies showed that BMP-2 maintains osteoinductivity, increases osteogenesis gene expression, and enhances mineral deposition. In vivo studies on animal models receiving BMP-2-enhanced scaffolds demonstrated better and greater bone formation or regeneration compared to scaffolds without the growth factor. Using BMP-2 at physiological doses in humans is associated with side effects such as inflammation, osteolysis, edema, adipogenesis, and ectopic bone formation. Therefore, accurate dosing of BMP-2 is necessary to ensure efficient local drug delivery systems that enhance osteogenic and osteoinductive properties.

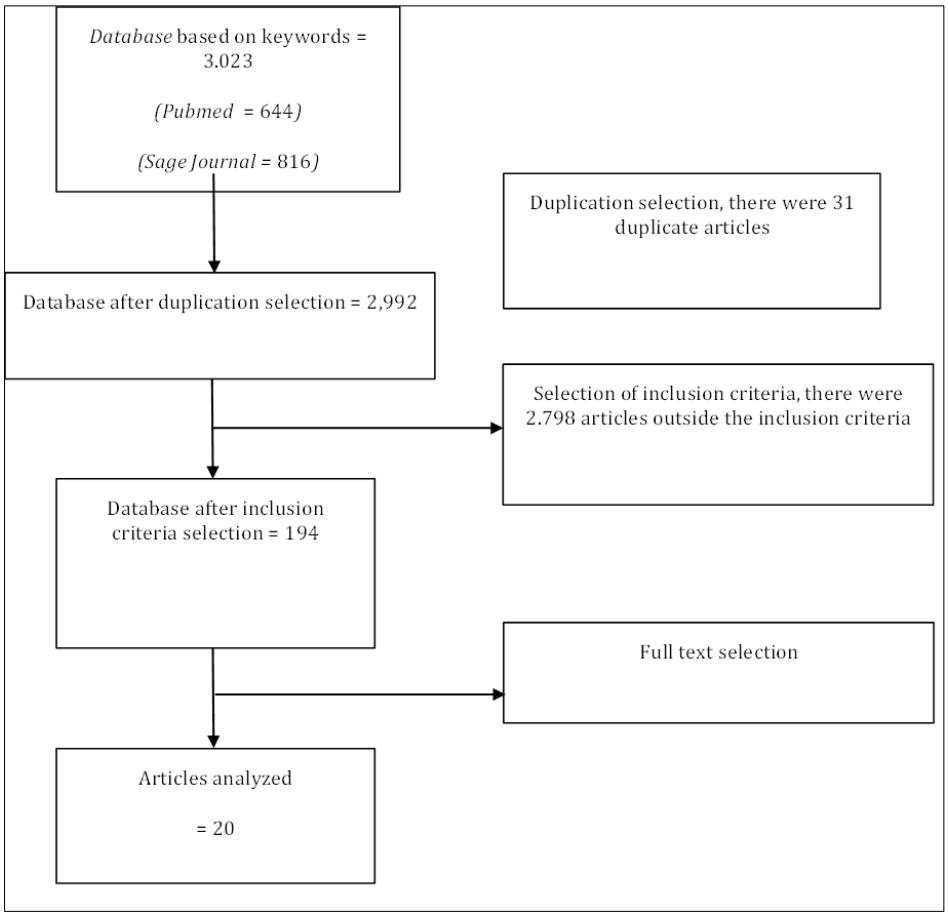

Figure 1 Article screening

3. Discussion

Tissue engineering aims to restore, maintain, or enhance the function of tissues damaged or lost due to physiological, pathological, mechanical, or traumatic conditions by developing biological replacements or reconstructing tissues. There are three critical components in tissue engineering, often referred to as the tissue engineering triad: biomaterial scaffolds, cells, and growth factors.[34] Scaffolds serve as a 3D microenvironment for cells, providing structural support that must match the mechanical properties of native bone tissue.[35]

Cells have significant therapeutic potential due to their unique mechanisms of action on tissues, which cannot be replicated by chemical compounds. A critical aspect of therapeutic success is the method of cell transplantation. Scaffold-based tissue engineering aims to create efficient cell delivery systems and produce three-dimensional (3D) tissues. Composite biomaterials, whether natural or synthetic, are designed to improve stability and mechanical properties. Many combinations of natural and synthetic composites are used in tissue engineering, such as Poly-E-caprolactone (PCL) combined with various natural biomaterials like collagen, gelatin, and cellulose.[34] Zhu et al. (2020) found that PLLA/PLGA/PCL composite scaffolds have a microscopic porous structure with excellent channel connectivity, making them ideal for cell adhesion and growth, thus functioning as biomimetic scaffolds.[11]

Tissue engineering shows promise for enhancing bone healing without relying on native bone tissue. Mesenchymal stem cells (MSCs) from various tissues have demonstrated potential in bone repair due to their osteogenic capabilities. Research indicates that effective osteogenesis of MSCs requires continuous stimulation with osteoinductive biofactors such as bone morphogenetic protein-2 (BMP-2).[36] BMP-2, part of the TGF-β superfamily, promotes bone formation by differentiating MSCs into osteoblasts and osteocytes, thereby producing the necessary extracellular matrix. BMP-2 enhances the expression of osteogenic markers such as ALP and osteocalcin through the MAPK pathway and regulates osteoblastic genes via SMAD-mediated signalling.[37]

Several studies have shown that composite biomaterial scaffolds supplemented with BMP-2 significantly increase BMP-2 levels in treatment groups compared to controls. This increase occurs because BMP-2 released from the scaffold stimulates the migration of endothelial cells and osteoblasts from nearby tissues, enhancing bone formation and accelerating bone tissue regeneration. Additionally, biomaterials like bioglass/chitosan used in these scaffolds exhibit osteogenic effects, promoting new bone formation in bone defects.[15,16]

Research by Toth et al. (2020), Li et al. (2019), Godoy-Gallar et al. (2020), Salgado et al. (2020), and Hu et al. (2019) further indicates that BMP-2 aids in osteogenic differentiation, cell proliferation, cell adhesion, and cell viability.[17–19,21,26] BMP-2 can activate the WNT/β-catenin pathway, enhancing β-catenin expression, which then translocates to the cell nucleus to form the β-catenin T cell factor (TCF)/lymphoid enhancement binding factor (LEF) complex. BMP-2 can also trigger the canonical WNT pathway by activating the p38 MAPK pathway during cartilage formation. As a ligand, BMP-2 binds to BMP receptors, initiating BMP signaling. This binding leads to the phosphorylation and activation of Smad1 by MAPK, which further stimulates BMP signaling. The p38 MAPK pathway can inhibit GSK3β, a BMP ligand inhibitor, thus maintaining Smad1 activity and prolonging BMP signaling. Smad1 then moves to the cell nucleus and induces the expression of bone transcription factors like Runx2 and osterix (Osx). Along with TCF and LEF, these factors initiate the transcription of osteoblast differentiation marker genes such as ALP, OCN, OPN, and Col-1.[38,39]

Composite scaffolds enhanced with BMP-2 can significantly improve bone formation and repair. For example, Zhu et al. (2020) investigated the effects of combining low-intensity pulsed ultrasound (LIPUS) with BMP-2 release from PLLA/PLGA/PCL scaffolds. Their findings revealed that this combination increases the levels of calcium (Ca) and phosphorus (P), as well as the expression of osteoblastic factors like RUNX2, Col I, and OCN, all of which are crucial for bone repair. LIPUS aids in bone repair by promoting osteogenesis and neovascularization, thereby enhancing angiogenesis. Additionally, BMP-2 can stimulate angiogenesis in human endothelial progenitor cells. BMPs play a vital role in regulating angiogenesis and maintaining blood vessels, making BMP-2 effective in addressing angiogenesis-related issues caused by bone ossification or necrosis.[11,40]

4. Conclusion

In tissue engineering, BMP-2 within composite scaffolds facilitates bone formation and repair by promoting osteogenic differentiation and enhancing cell proliferation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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