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Current knowledge on e.rh-BMP2 in oral and maxillofacial surgery and implantology. A comprehensive literature review

Conocimientos actuales sobre la e.rh-BMP2 en cirugía oral y maxilofacial y en implantología. Una revisión exhaustiva de la literatura

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Palabras clave:

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ABSTRACT

This review examines the current knowledge and clinical applications of engineered recombinant human bone morphogenetic protein-2 (e.rh-BMP2) in oral and maxillofacial surgery and implantology. It synthesizes recent findings on e.rh-BMP2's osteoinductive properties, which enhance bone regeneration in procedures such as alveolar ridge augmentation, sinus floor elevation, periodontal regeneration, and mandibular reconstruction. Comparative analyses evaluate various production methods—including mammalian, insect, and *Escherichia coli* systems—with particular emphasis on *E. coli*-derived BMP-2, noted for its cost-effectiveness and scalability despite the need for additional refolding to ensure bioactivity. The review also contrasts BMP-based therapies with other regenerative modalities such as platelet concentrates, ozone therapy, lactoferrin, and autologous bone grafts, outlining their relative clinical outcomes. Special attention is given to Cowell-BMP formulations, which have shown promise in reducing surgical morbidity and accelerating bone healing across diverse clinical scenarios. Overall, the evidence supports the adaptability of e.rh-BMP2 as a pivotal tool in regenerative medicine. Future investigations should focus on optimizing delivery systems and standardizing treatment protocols to broaden the therapeutic applications of BMP-based strategies in complex oral and maxillofacial reconstructions.

RESUMEN

Esta revisión examina el conocimiento actual y las aplicaciones clínicas de la proteína morfogenética ósea humana recombinante (e.rh-BMP2) en cirugía bucomaxilofacial e implantología. Se sintetizan hallazgos recientes sobre sus propiedades osteoinductoras, que potencian la regeneración ósea en procedimientos como la ampliación del reborde alveolar, la elevación del seno maxilar, la regeneración periodontal y la reconstrucción mandibular/maxilar. Se evalúan diversos métodos de producción—desde sistemas en células de mamífero e insecto hasta *Escherichia coli*—destacando en especial el BMP-2 derivado de *E. coli*, reconocido por su rentabilidad y escalabilidad, pese a requerir repliegamiento adicional para asegurar su bioactividad. Asimismo, la revisión contrasta las terapias basadas en BMP con otras modalidades regenerativas, como concentrados plaquetarios, ozonoterapia, lactoferrina e injertos óseos autólogos, analizando sus respectivos resultados clínicos. Se presta especial atención a las formulaciones Cowell-BMP, que han mostrado resultados prometedores al reducir la morbilidad quirúrgica y acelerar la cicatrización ósea en distintos escenarios. La evidencia respalda la versatilidad de e.rh-BMP2 como herramienta fundamental en la medicina regenerativa. Se recomienda que futuras investigaciones optimicen los sistemas de administración y estandaricen los protocolos de tratamiento para ampliar sus aplicaciones terapéuticas en reconstrucciones orales complejas.

INTRODUCTION

The literature surrounding e.rh-BMP2 and its applications in oral and maxillofacial surgery,

particularly in implantology, has garnered considerable attention in recent years. This review synthesizes findings from various studies that explore the efficacy, production methods,

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and comparative advantages of BMPs, particularly focusing on rhBMP-2 and its derivatives.^{1,2}

Balaji SM³ conducted a comparative study on the use of rhBMP-2 versus traditional iliac crest grafts for alveolar cleft defect closure, highlighting the significant benefits of rhBMP-2 in reducing postoperative morbidity and surgical invasiveness. This pivotal work underscores the potential of rhBMP-2 to facilitate bony union in alveolar defects while sparing patients from the complications associated with autogenous bone harvesting.

In the same year, Herford AS⁴ performed a systematic review emphasizing the lack of comparative studies on rhBMP-2 and autogenous bone grafts for mandibular continuity defects. This highlights a gap in the literature that necessitates further investigation into the comparative effectiveness of these regenerative strategies in clinical practice.

Huh JB⁵ contributed to the understanding of rhBMP-2 by investigating its efficacy when combined with β -TCP/HA in extraction sockets. Their findings indicated that while rhBMP-2 is effective in promoting ossification, the cost associated with CHO-cell-derived rhBMP-2 remains a concern, prompting exploration into alternatives like *E. coli*-derived rhBMP-2.

The work by Cicciu M⁶ further delved into the optimization of BMP-2 delivery systems, suggesting that biphasic calcium phosphate (BCP) could serve as a more effective carrier than collagen for BMP-2, thus enhancing its osteoconductive properties. This study emphasizes the importance of carrier materials in maximizing the therapeutic potential of BMP-2.

Cicciu M⁶ presented a case report that demonstrated the clinical effectiveness of rhBMP-2 in treating critical size defects, reinforcing the notion that rhBMP-2 can significantly reduce patient discomfort and surgical time by eliminating the need for donor site harvesting.

The comparative landscape of regenerative products was expanded by Albanese A⁷ and Roffi A,⁸ who explored the mechanisms and clinical outcomes of platelet-rich plasma (PRP) and its efficacy in enhancing bone integration with grafts. Their findings suggest that while PRP has beneficial properties, BMPs like rhBMP-2 may offer superior outcomes in specific contexts.

In subsequent years, studies such as those by Kim MS⁹ and Baek WS¹⁰ continued to evaluate the effectiveness of e.rh-BMP2, comparing it to traditional grafting materials in sinus augmentation procedures. These investigations revealed that while e.rh-BMP2 is comparable to deproteinized bovine bone, it does not always enhance bone regeneration, indicating the need for careful consideration of BMP application in clinical settings.

The exploration of Cowell-BMP and its unique properties in bone regeneration was further elaborated by Hwang DY,¹¹ who reiterated the potential of rhBMP-2 in specific oral and maxillofacial applications, while also referencing historical studies that laid the groundwork for current BMP research.

Emerging studies, such as those by Mumcuoglu D¹² and Park SY¹³ have begun to focus on innovative delivery systems

and gene therapy approaches to enhance the effectiveness of BMP-2 in clinical settings. These advancements indicate a shift towards more sophisticated methods of utilizing BMPs for bone regeneration.

Recent reviews by Fiorillo L¹⁴ and Zaki J,¹⁵ have highlighted the ongoing developments in regenerative strategies, emphasizing the need for robust clinical trials to establish the efficacy of BMPs relative to other biomaterials.

Finally, the latest research by Chantiri M¹⁶ has brought attention to the role of rhBMP-2 in accelerating gingival healing, further underscoring the multifaceted applications of BMPs in oral surgery. This body of work collectively illustrates the evolving landscape of BMP research, revealing both the promise and challenges associated with their use in bone regeneration and implantology.

LITERATURE REVIEW

Bone morphogenetic proteins (BMPs) are integral and influential members of the transforming growth factor- β (TGF- β) superfamily, widely recognized for their remarkable and unique capability to induce *de novo* bone formation while significantly accelerating the complex process of tissue healing in various clinical situations associated with bone loss. The osteoinductive effect of BMPs was first characterized and meticulously studied back in the year 1965 when researchers successfully identified a specific bone extract derived from calcified bovine bone, which was subsequently and aptly named BMPs due to its profound biological effects (Figure 1).¹⁷⁻²⁰

This groundbreaking discovery marked a pivotal advancement in our comprehensive understanding of bone biology and

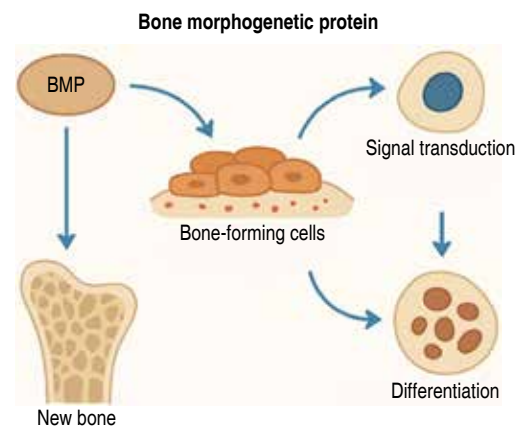


Figure 1: How does bone morphogenetic protein (BMP) works: a BMP molecule binding to receptors on a mesenchymal stem cell. Arrows indicate the intracellular signaling cascade triggered by the BMP-receptor interaction, which leads to the differentiation of the stem cell into an osteoblast. Labels highlight key stages: BMP binding, signal activation, osteoblast differentiation, and subsequent bone regeneration.

molecular mechanisms, which led to numerous innovative applications in the expansive fields of regenerative medicine and orthopedic surgery, effectively revolutionizing treatment options and outcomes for patients suffering from various bone-related ailments and conditions such as fractures, osteoporosis, and nonunion. The ongoing research surrounding BMPs continues to shed light on their potential therapeutic effects, contributing significantly to the advancement of medical science and enhancing patient care practices in orthopedics and beyond.²¹⁻²⁴

Over the years, a diverse range of bone morphogenetic proteins (BMPs) has been isolated, studied, and characterized in laboratory and clinical settings. These proteins have gained significant importance in preclinical and clinical studies focused on advancements in bone repair, healing, and regeneration. Recombinant human BMP, or rhBMP-2, has emerged as the most widely used osteoinductive product in various surgical specialties. Its extensive applications in medical interventions are due to its unique properties and effectiveness in promoting rapid bone healing, greatly benefiting patients undergoing surgical procedures. Thus, rhBMP-2 is seen as a critical resource for surgeons and medical professionals, improving patient outcomes and the effectiveness of surgical interventions in healthcare.^{12,25}

Other versions of bone morphogenetic proteins (BMPs) –specifically e.rh-BMP2, Cowell-BMP, and Cowell-BMP-E– have been thoroughly refined for numerous vital medical applications. This development underscores their significant role in contemporary medicine. Cowell-BMP-E, in particular, has gained widespread usage in oral and maxillofacial surgeries and implantology over the last decade. Its notable adoption showcases its effectiveness in promoting healing and versatility across specialized medical fields. Highlighting its contribution to patient outcomes and treatment efficacy exemplifies its importance in critical healthcare practices.¹²

The advancements achieved through the integration of these advanced BMP variants signify a key step forward in addressing the complex challenges faced in modern surgical procedures and the ever-evolving field of regenerative medicine. Bone morphogenetic proteins (BMPs) represent a dynamic group of growth factors that belong to the TGF- β superfamily, which is widely regarded and utilized in regenerative medicine and innovative applications within the area of bone tissue engineering. The synthesis of these proteins is variable and depends significantly on the production system employed, with recombinant expression in bacterial, mammalian, and insect cells being the most common approaches now widely used in the field today. Among these various methods, *E. coli*-derived BMP-2 has gained significant attention and appreciation due to its excellent cost-effectiveness and impressive scalability, which have made it a preferred option for many researchers and practitioners within the medical sector.¹²

The continuing evolution, enhancement, and refinement of BMPs underscore their critical importance in progressing surgical techniques and further advancing the field of

regenerative medicine. The effective integration of BMPs into clinical practices represents a transformative shift in the treatment landscape, allowing for greater innovation and success in therapeutic interventions aimed at rebuilding and regenerating bodily tissues. As research continues to expand our understanding of these remarkable proteins, the future holds great promise for their application in addressing diverse medical challenges, paving the way for breakthroughs that could significantly improve patient care and surgical outcomes across a multitude of specialties.¹²

Production methods for different types of BMPs

BMPs can be synthesized through a variety of expression systems, each offering unique advantages and presenting distinct limitations. For example, mammalian cell expression systems, such as CHO (Chinese hamster ovary) and HEK293 (human embryonic kidney 293), are capable of producing glycosylated and properly folded BMPs. This method ensures a high level of bioactivity; however, it comes at a high cost and often results in a lower yield. It is commonly utilized in the production of clinical-grade BMPs, such as the INFUSE bone graft, which demonstrates the efficacy of this approach (Table 1).

On the other hand, the insect cell expression system, which operates via the Baculovirus system, permits post-translational modifications that closely resemble those found in mammalian cells. While this method can achieve a higher yield compared to mammalian systems, it also introduces complexities in the purification process that can be challenging to navigate.

Lastly, the *E. coli* expression system stands out as the most cost-effective and scalable option available. It produces non-glycosylated BMPs, which necessitate a subsequent refolding process to ensure proper configuration and functionality. This system has been utilized for the production of Cowell-BMP and other recombinant BMPs, demonstrating its effectiveness in generating BMPs despite its limitations. Each of these systems plays a crucial role in the synthesis of BMPs, highlighting the diversity of methods available in biotechnology for producing these important proteins.^{1,26-34}

Synthesis of BMP-2 in *E. coli*

E. coli is widely recognized and extensively utilized for BMP-2 production primarily due to its rapid growth rate and exceptionally high protein yield. However, there are significant challenges associated with this process, as BMP-2 is a disulfide-rich protein, making its correct folding particularly difficult. The entire synthesis process involves several intricate steps:³⁵⁻³⁸

1. Gene cloning and expression.
 - a. The **BMP-2 gene** is inserted into a **plasmid vector** with a strong promoter.

- b. Transformed *E. coli* cells express BMP-2 in the **cytoplasm or periplasm**.
2. Formation of inclusion bodies.
 - a. BMP-2 often forms **insoluble inclusion bodies** in the cytoplasm.
 - b. These aggregates require **denaturation and refolding** to regain bioactivity.
3. Refolding and purification.
 - a. Inclusion bodies are **solubilized using urea or guanidine hydrochloride**.
 - b. The protein is **refolded** using **redox buffers** to restore its disulfide bonds.
 - c. Purification is done via **affinity chromatography (heparin column)**.
4. Periplasmic expression (alternative method).
 - a. Some strategies use **signal peptides** to direct BMP-2 to the **periplasm**, where it folds correctly.
 - b. This avoids **inclusion body formation**, leading to **higher bioactivity**.

Applications of BMP

The focus centers on the applications and implications within oral and maxillofacial surgery, where innovative methodologies are integrated into clinical practice for better outcomes. We will also examine its essential use in implantology, with advancements improving procedural efficiency and patient safety. Exploring how e.rh-BMP2 can revolutionize these fields is vital, offering solutions that promote bone regeneration, restore functionality, and enhance patient outcomes. Its potential to alter clinical paradigms and treatment strategies significantly raises the standard of care, impacting surgical practice and recovery processes. Continued research and application of e.rh-BMP2 are crucial, as its contributions may define the future of surgical interventions, improving healing times, reducing complications, and optimizing recovery for countless patients in need of advanced medical procedures.^{17-20,39,40}

These are some applications of BMPs in oral and maxillofacial surgery and implantology:

- **Alveolar ridge augmentation:** BMPs stimulate bone formation in cases of severe ridge resorption, improving

Table 1: General information for BMP.

BMP type	Classification	Manufacturer	Synthesis	Usage vehicle	Estimated price in Latin America (USD)	Availability in Latin America
rhBMP-2 (Infuse®)	Human recombinant (CHO)	Medtronic	Produced in CHO cells (Chinese hamster ovary)	Absorbable collagen matrix	\$4,500-7,000 per kit	Available in some countries
rhBMP-7 (OP-1 Putty)	Human recombinant (CHO)	Stryker	Produced in CHO cells	Collagen and carrier protein vehicle	\$3,500-5,500 per dose	Limited availability
BMP-2 in hydroxyapatite	Human recombinant (CHO)	Geistlich Pharma	Recombinant production with synthetic hydroxyapatite	Hydroxyapatite and collagen matrix	\$3,000-5,500 per kit	Available in some countries
e.rh-BMP2 (Cowell BMP)	Human recombinant (<i>E. coli</i>)	Cowellmedi	Recombinant production in <i>E. coli</i>	BCP (biphasic calcium phosphate) matrix	Up to \$2,000 per unit	Available in several countries
Bongros-BMP	Human recombinant (<i>E. coli</i>)	Bioalpha (Korea)	Recombinant production in <i>E. coli</i>	Combined with hydroxyapatite	\$2,500-4,500 per unit	Limited availability in Latin America
e.rh-BMP2/BioCaP/β-TCP	Human recombinant (<i>E. coli</i>)	Shanghai Ninth People's Hospital (China)	Recombinant production in <i>E. coli</i>	Biomimetic calcium phosphate (BioCaP/β-TCP) matrix	Not commercially available	Not available in Latin America
e.rh-BMP2 in hydroxyapatite	Human recombinant (<i>E. coli</i>)	Geistlich Pharma	Recombinant production in <i>E. coli</i>	Hydroxyapatite and collagen matrix	\$3,500-6,000 per kit	Available in some countries

implant stability. This is particularly useful for patients with significant bone loss who require additional volume before implant placement.

- **Sinus floor elevation:** in maxillary sinus augmentation, BMPs enhance bone regeneration, allowing for successful implant placement in areas with insufficient bone height. They help integrate graft materials and accelerate new bone formation.
- **Periodontal regeneration:** BMPs promote the repair of periodontal defects by inducing osteogenesis and soft tissue healing. They are used in cases of severe periodontitis where traditional regenerative techniques may be insufficient.
- **Mandibular and maxillary reconstruction:** BMPs are applied in trauma cases, tumor resection, or congenital defects to regenerate lost bone. They provide an alternative to autologous bone grafts, reducing donor site morbidity.
- **Implant site preparation:** BMPs accelerate bone formation in deficient areas, ensuring optimal conditions for implant placement. This is particularly beneficial for patients with compromised bone quality or insufficient volume.
- **Treatment of cystic and tumor-related bone defects:** BMPs help regenerate bone lost due to odontogenic cysts or tumor excision. They enhance healing and reduce the need for extensive grafting procedures.
- **Guided bone regeneration (GBR):** BMPs improve the effectiveness of barrier membranes by stimulating new bone growth. They are often combined with collagen membranes to enhance bone regeneration in implant sites.
- **Distraction osteogenesis:** BMPs improve bone formation in cases requiring gradual bone elongation, such as mandibular advancement procedures. They enhance the quality and speed of new bone formation.
- **Management of osteonecrosis of the jaw (ONJ):** BMPs aid in bone healing and regeneration in patients with medication-related ONJ, particularly those affected by bisphosphonate therapy. They help restore bone integrity and reduce complications.
- **Enhancement of autologous bone grafts:** BMPs improve the osteoinductive potential of autologous grafts, reducing donor site morbidity. They enhance the integration and longevity of grafted bone, making procedures more predictable.

When comparing best management practices (BMPs), it is essential to focus on their production methods and overall efficiency. A thorough analysis will help us understand the advantages and limitations tied to each type of BMP. Each BMP has unique features that significantly impact effectiveness in various applications. By examining their production methods, we uncover the processes that contribute to operational efficiency in real-world situations.

Additionally, providing a comprehensive understanding of these practices is crucial for making informed decisions about their implementation and usage. This examination enhances our knowledge for practical application, leading to better outcomes and improved organizational performance. Thus, scrutinizing BMPs is vital for fostering sustainable practices across industries.³⁹⁻⁴³

Additionally, in contrast BMPs with other notable regenerative products, such as platelet-rich fibrin and platelet-rich growth factor, discussing their distinct mechanisms and clinical outcomes in regenerative medicine. It is important to include studies on Cowell-BMP and its significant role in bone regeneration, highlighting not only its effectiveness but also its unique properties that set it apart from other growth factors. This comparison will offer valuable insights into their applications and performance in clinical settings, which can guide future research and treatment options.⁴⁴⁻⁴⁶

Comparative analysis of bone morphogenetic proteins (BMPs) and other regenerative products in oral and maxillofacial surgery

Regenerative medicine in oral and maxillofacial surgery has evolved significantly, incorporating various biomaterials and biological agents to enhance tissue repair and bone regeneration. Among these, bone morphogenetic proteins (BMPs) have gained prominence due to their osteoinductive properties. However, other regenerative products, such as platelet concentrates, ozone therapy, lactoferrin, and autologous bone grafts, also play crucial roles in clinical applications. This review compares their mechanisms, efficacy, and clinical outcomes.⁴⁷⁻⁵¹

BMPs, particularly BMP-2 and BMP-7, are members of the TGF- β superfamily and are widely used in bone regeneration. They stimulate mesenchymal stem cell differentiation into osteoblasts, promoting new bone formation. Recombinant human BMP-2 (rhBMP-2) has been extensively studied for its ability to induce bone growth in alveolar defects and implantology. However, concerns regarding ectopic bone formation, inflammation, and cost have led researchers to explore alternative regenerative strategies.⁵²⁻⁵⁶

BMP vs platelet concentrates (PRF, PRGF, PRP)

Platelet concentrates, including platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and plasma rich in growth factors (PRGF), are autologous blood derivatives rich in growth factors such as PDGF, TGF- β , and VEGF3. These factors accelerate wound healing, enhance angiogenesis, and improve soft tissue regeneration. PRF, in particular, has shown superior results in periodontal regeneration due to its fibrin matrix, which sustains growth factor release over time. Compared to BMPs, platelet concentrates are less osteoinductive but offer better soft tissue healing and reduced inflammatory response.⁵⁷⁻⁶¹

BMP vs ozone therapy

Ozone has been explored for its antimicrobial and bio-stimulatory properties in oral surgery. It enhances wound healing by increasing oxygenation and stimulating fibroblast activity. While ozone therapy does not directly induce bone formation like BMPs, it reduces infection risk and promotes tissue repair, making it a valuable adjunct in regenerative procedures.⁶²⁻⁶⁶

BMP vs lactoferrin

Lactoferrin, a multifunctional glycoprotein, has demonstrated osteogenic and anti-inflammatory properties. It stimulates osteoblast proliferation and inhibits osteoclast activity, contributing to bone homeostasis. Studies suggest that lactoferrin may enhance BMP-induced bone regeneration by modulating inflammatory responses and improving cell viability.^{4,67-71}

BMP vs autologous bone grafts

Autologous bone remains the gold standard for bone regeneration due to its osteoconductive, osteoinductive, and osteogenic properties. Unlike BMPs, which rely on signaling pathways to induce bone formation, autologous grafts provide live osteogenic cells, ensuring predictable outcomes. However, donor site morbidity and limited availability are significant drawbacks.⁷²⁻⁷⁶

Clinical applications and potential of Cowell-BMP-E in surgical procedures

Cowell-BMP-E has been extensively studied for its vital role in bone regeneration and tissue engineering, especially in oral and maxillofacial surgery. As a recombinant human bone morphogenetic protein-2 (rhBMP-2), it facilitates osteoinduction by promoting mesenchymal stem cells' differentiation into osteoblasts, essential for new bone formation. Research has demonstrated its effectiveness in surgical applications like alveolar ridge augmentation, sinus floor elevation, and implant site preparation, showing a remarkable ability to enhance bone regeneration compared to traditional grafting techniques with limitations. Its integration with biocompatible carriers, such as β -tricalcium phosphate (β -TCP) and hydroxyapatite, improves BMP stability and optimizes clinical outcomes. Recent advancements in delivery systems aim to refine Cowell-BMP-E's application and reduce complications, such as ectopic bone formation and unwanted inflammatory responses. Comparative analyses with other regenerative materials, including autologous bone grafts and synthetic substitutes, showcase its distinct advantages in osteogenic potential and long-term stability. Ongoing

evaluations of Cowell-BMP-E's clinical efficacy are necessary to establish standardized protocols for its use in varied surgical contexts. Future studies are expected to clarify its role in minimizing surgical morbidity and enhancing patient recovery, emphasizing the importance of exploring Cowell-BMP-E's potential in modern surgical practices for improved patient care and outcomes.⁷⁷⁻⁸²

Recent evidence from García-Guevara et al. demonstrates that guided bone regeneration using recombinant human BMP-2 (rhBMP-2) can effectively treat bone defects associated with uncontrolled orthodontic movements. In the described case, a combination of rhBMP-2 (Cowellmedi's formulation), particulate bone, biphasic calcium phosphate, and a collagen membrane –supplemented with adjunctive activated oxygen and lactoferrin– produced significant improvements in lingual mandibular bone density and volume within 8 to 10 weeks. This successful outcome emphasizes that BMP-2's role extends beyond conventional implant-site development to include diverse regenerative applications in oral and maxillofacial surgery.^{81,82}

These findings suggest a broader therapeutic potential for BMP-based treatments, highlighting their promising utility in scenarios such as orthodontic-induced bone resorption. The rapid bone formation and enhanced clinical outcomes observed reinforce the possibility that BMP formulations, like those offered by Cowellmedi, could broaden the spectrum of treatment options in complex surgical situations. Such applications may ultimately lead to improved patient outcomes and encourage further research into optimized delivery systems and long-term efficacy.^{81,82}

This literature review recommends the use of Cowell-BMP in the oral cavity, especially when a graft is an option, otherwise e.rh-BMP2, once it depends on the clinical condition and the surgical time that each patient presents, might reduce healing problems and additional costs, especially in the periodontitis patient group who require bone augmentation in sequencing implant placement.

CONCLUSION

In summary, e.rh-BMP2 not only has high expectation in various bone regenerative applications thanks to its excellent osteoinductive property but also has high potential for upgrading current oral and maxillofacial surgery and implantology operations. The improvement of the mechanical strength of the e.rh-BMP2 ONP under rigid loading condition from 7.3 to 19.6 MPa with an increasing mass ratio of e.rh-BMP2/ONPs clearly demonstrated the successful adoption of a bioactive hybrid coating on the implantable surface, contributing to direct loading application of e.rh-BMP2 in epigenetic activating orthopedics bone regeneration therapy. Besides, the relatively simple production method and excellent inhibition of osteolysis effects without side-effects on surrounding tissues distinguished the

e.rh-BMP2/ONPs hybrid implant for future clinic application. The overview of recent studies on different BMPs indicates that still up to now, no BMPs could outperform Cowell-BMP in efficiency and *in vivo* evaluation time. Cowell-BMP has the exception of bone regeneration ability from site-to-site and even if the inter-species animal model is used, since its osteogenic activity *in vivo* has been thoroughly proven in the long-term studies which are adequate enough. Cowell-BMP, as a naturally derived sample, surprisingly possesses lower osteogenic activity than BMP-2, BMP-4, and BMP-7, which may be attributed to their sufficient and synthetic production. Further studies including monoclonal hybridoma generation and monoclonal antibody identification as immunoassays for the Wang-1 as well as protein crystallization could enhance the isolation and purification stage. Quantitative methods for proteins and growth factors will be used for their characterization. Integrating directed differentiation with cell-released products of stem cells can develop a biomimetic and organic-enhanced technique in designing composites for an ultra-strong bone substitute. Further considerations regarding these approaches will greatly extend the knowledge of BMPs. While BMP exhibits superior regenerative efficacy relative to other products, its synergistic use with complementary biomaterials may optimize overall treatment outcomes.

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