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Review Article

# Advances in Collagen Biomaterials for Dental Applications: A Review from Biofabrication to Clinical Practice

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**ABSTRACT**
This review article provides a comprehensive examination of collagen-loaded dental applications, focusing on collagen dental plugs used for socket preservation and tissue regeneration following tooth extraction. It explores the biofabrication and development of these biomaterials, emphasizing advanced manufacturing techniques, material characterization, and innovative technologies such as electrospinning and 3D printing. The review evaluates the clinical efficacy of collagen dental plugs through systematic analysis of clinical trials and case studies, highlighting their effectiveness, patient outcomes, and challenges. Regulatory and quality control aspects are discussed, including compliance with international standards and ensuring safety and biocompatibility. Future directions in collagen-based biomaterials are explored, including advancements in personalized and precision dental care, integration of nano- and micro-technologies, and the development of eco-friendly and sustainable products. The article underscores the significant impact of these advancements on patient care and the potential for ongoing innovation in dental biomaterials.

**Keywords:** Collagen dental plugs, Socket preservation, Biofabrication, Advanced manufacturing, Clinical efficacy, Regulatory aspects, Sustainability, Personalized medicine.

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## INTRODUCTION

### Overview of Collagen in Dentistry

#### *Role of Collagen as a Critical Biomaterial in Dental and Regenerative Applications*

Collagen is the main structural protein in connective tissues, which plays a crucial role for maintaining extracellular matrix structure and function thus being an essential biomaterial used in dental and regenerative applications. Collagen is an excellent material for a variety of dental purposes, due to its high compatibility with human tissues and ability to promote cell deposition while remaining completely resorbable. Collagen-based products enhance wound healing and improve human tissue repair; hence it fronts as a fundamental biomaterial in dentistry for its use in bone regeneration during implantation or periodontal procedures. These features render collagen an attractive biomaterial for use in both surgical and non-surgical dental fields, from simple wound dressing to targeted regenerative strategies (Patino *et al*., 2002; Ghaffar *et al*., 2024).

### Historical Context and Development of Collagen in Dentistry

Up until the 20th century, collagen in dentistry was used strictly as simple wound dressings and grafts. Since then, major breakthroughs have been made in the fields of material science and bioengineering that broadened both applications for collagen use in dental practice. The enhancement of the mechanical properties, stability and functionality of collagen through research and development has assisted in making it an effective biomaterial for regenerative dentistry. Collagens are now keys in advanced dental practices: from socket preservation to guided tissue regeneration and bone grafting. While collagen-based products have a long history of use as the wound healing matrix in dentistry, these recent discoveries reflect a rapidly evolving understanding that has positioned collagen within our clinical domain not just as an antiquated shield with which to bolster

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conventional therapies but rather into one of sophisticated tissue regeneration and repair (Mahesh *et al*., 2015; Gaffney *et al*., 2018).

### Global Challenges in Dental Health and Collagen-Based Solutions

Portion of the population around the world is at risk from dental health issues such as periodontal disease, tooth loss and other conditions. These problems frequently result in challenges that need to be addressed through some form of oral rehabilitation. A great answer for overcoming this challenge is collagen solutions, particularly the utilization of Collagen plugs. Specially designed to promote socket preservation after tooth extraction, as well as tissue regeneration marketing. These materials are also beneficial in reducing the risk of complications that is most associated with it, namely alveolar bone loss and delayed healing as they promote wound healing even at areas such as bony defects for new regenerated tissues. This natural integration allows collagen to work in sync with the body, leading not only to supplement healthier patient outcomes but also decreases time-of recovery and substantially enhances its overall psychology genic results of dental pathology. As a result, the use of collagen-based materials is an integral part of modern-day dentistry and provides valuable answers to some long-standing issues affecting dental health globally (Berisio *et al*., 2002).

## FOCUS ON COLLAGEN DENTAL PLUGS

### Definition and Characteristics of Collagen Dental Plugs

Collagen based dental plugs are specific implantable devices intended to be placed into extraction sockets after teeth removal treatment in order achieve the best post-extraction healing process and prevent eventual side effects like dry socket. The plugs are composed of collagen, a major structural protein sourced from bovine or other animal tissues that is designed to be fully aligned with the oral environment. Collagen dental plugs are biocompatible, meaning that they interact effectively with the body tissues without causing allergic responses and suitable for provoking hemostasis as well stimulating tissue regeneration. Collagen dental plugs, which mirror the natural extracellular matrix and provide a supportive scaffold for stable blood clot formation (Nisar *et al*., 2020).

### Rationale Behind Using Collagen in Dental Plugs

Collagen was employed for dental plugs because of its natural characteristics that make it well suited to the environment needed. One of the main benefits is that collagen biodegrades within human tissue and this means it integrates with surrounding tissue, increasing healing capability as well minimizing risk for complications (Ghaffar *et al*., 2024). It is nice for bone and soft tissue growth in the socket because it helps to assist with cellular healing so that we can create new cells. Collagen dental plugs stabilize the blood clot, which is a critical factor in developing dry socket and provide it with collagen matrix scaffolding type of material that helps to grow new tissue there which leads to better recovery purposes (Kotsakis *et al*., 2014).

## COLLAGEN AS A BIOMATERIAL IN DENTISTRY

### Fundamental Properties of Collagen

#### *Biochemical and Mechanical Properties*

The unique biochemical and mechanical attributes of collagen's basic traits favor its utilization in different dental treatments. Collagen is chemically characterized by the presence of a triple-helix structure and its molecular signature. This triple-helix assembly, of three polypeptide chains intertwined together, is responsible for collagen being so resilient and flexible. This structure enables collagen to create a flexible matrix, supporting cellular grow and connecting with the substrate that contributes to repair tissue. The above biochemical properties are important in dental applications as they allow collagen-based materials to withstand the mechanical impacts experienced within the oral environment and therefore promote proper healing and tissue regeneration. Collagen, mechanistically speaking, acts as a sturdy scaffolding wherein the maintenance of strength is vital for structure resiliency through healing. It included excellent mechanical stability and biocompatibility, so that it is a good potential candidate as dental materials to assist in cellular adhesion-proliferation properties. Due to the mechanical properties along with its triple-helix structure, collagen is able of providing an adequate spatial scaffold in order to promote tissue repair and regeneration processes associated to successful dental treatments (Kannus, 2000).

### Structural Aspects of Collagen

Collagen is structured at multiple hierarchical levels. Collagen is made of amino acids, which at a molecular level combine to form triple helices that assemble into fibrils and again organize further as fibers. It is this same kind of hierarchical structure that endows the material with its mechanical strength and resilience. Properties of collagen at the fibrillar level play a crucial role in its utility for dental applications. The porosity of an FGF rapamycin structure is a function, among other factors, on the degree to which fibrils are aligned in that sample and this tends to influence how well it could support new tissue growth or blend with native biological tissues. Further, the turnover rate of collagen in the human body is critical to determine its viability and longevity when used as a dental material (Bella & Hulmes, 2017).

### Comparison of Natural and Synthetic Collagen

An application of natural vs synthetic collagen provides advantages and disadvantages for each type. Collagen that is derived from animal tissues, such as bovine or porcine sources would also be ideally suited to humans because it has a natural compatibility with human tissue. Nevertheless, it could potentially expose problems such as the variability of product quality and disease transmission. The use of recombinant DNA technology to produce synthetic collagen might alleviate some of these concerns related, owing to more reliable quality and reduced risk for zoonotic infections. Despite offering these advantages, however, the biological properties of synthetic collagen may never fully emulate its natural counterpart and are inherently limited by such divergence in structure, a limitation that could affect how they function under application. For natural vs. synthetic collagen, the selection depends on what properties are desired for your dental application e.g., consistency and functionality of the synthesized material as well as safety considerations (Shoulders & Raines, 2009).

## TYPES AND SOURCES OF COLLAGEN FOR DENTAL USE

### Types of Collagens

Collagen is a family of proteins in connective tissues and there are several types of collagens, but Type I, II which the two have appropriate functions for dental applications belonged to fibrillar collagens and type III (Ramachandiran & Jomhari, 2015). Further, Type I collagen, the most common in man is mainly located within bone: skin and tendons. It is exceptionally beneficial for procedures such as dental bone grafting and socket preservation since it supports the structural integrity of surrounding tissues, reabsorbs into the body until artificial scaffolding fully integrates with native tissue to restore function. Cartilage is of obvious relevance to cartilage repair and regeneration but does have more specialized use in dental applications, as they are tissues rich in type II collagen. Collagen III, which is generally present in the early wound repair process plays a very important part in extracellular matrix restoration and new tissue (Gelse *et al*., 2003).

### Sources of Collagen

Collagen occurs in different shapes and forms, all of which enjoy a variety of benefits along with unique challenges. Bovine and porcine collagen from cow and pigs are commonly applied because they have a high abundance, relatively easy in extraction procedure both of which have structures identical to that with human collagen. As a result of their great effectiveness and compatibility with human tissues, all these categories have been thoroughly investigated for applications in dentistry (e.g., grafting, wound healing) (Ghaffar *et al*., 2024; Luo *et al*., 2024). Because marine collagen is taken from fish, especially their skin and scales like those of salmon or cod relatives, it seems to be an ideal type for use as a therapy since the risk of transferring diseases with this material doesn't seem too large compared to using animal derived collagens. Marine collagen is also usually more biocompatible in clinical applications as it typically has a lower antigenicity and may cause fewer immune responses. However, by far the most recent advancement in collagen technology is recombinant collagen that comes from genetic engineering. This type of collagen can be generated by genetically engineered bacteria to make unique properties that are formulated for targeted clinical utilizations. It is recently that the recombinant collagen has been stabilized, introduced with functional groups for bioconjugation and ultimately made biocompatible. These advancements enable the production of completely new dental materials with engineered properties including enhanced mechanical strength, circumscribed erosive behavior and functionalizing into hard-soft-mediate integrated tissue architectures. This means very hopeful advances for dental therapies and the possibility of more effective therapeutic methods being better individualized (Cruz *et al*., 2021).

## COLLAGEN-LOADED DENTAL APPLICATIONS

### Collagen in Guided Tissue and Bone Regeneration (GTR and GBR)

#### *Role in Periodontal and Bone Regeneration*

Collagen is required for Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR) as a main scaffold because it promotes the repair and reconstruction of periodontal and alveolar tissues. To avoid the migration of non-periodontal cells into the defect area, collagen membranes are used as physical barriers during periodontal regeneration. That specificity of the barrier effect is essential to allow only those cells from the regenerative periodontal region to expand and repair any damaged tissue in our gums. This in effect forms a biological chamber that guides the natural process of wound healing, promoting new cell growth (particularly periodontal cells) whilst preventing unwanted non-ideal cellular invasion into the GTR area therefore ensuring proper and desirable tissue regeneration (Cho *et al*., 2021; Kida *et al*., 2021).

### Mechanisms Supporting Osteoconductive and Cell Proliferation

A nano-structured biopolymer scaffold consisting of a porous, interconnected collagen matrix is capable to mimic the native collagen skeleton and ensure that osteogenesis has both spaces on which it can proceed. For this purpose, scaffolds are fabricated which resemble the natural extra cellular matrix and hence create a favorable osteoconductive environment for attachment of osteoblast cells to scaffold surface where they grow successively (Ghaffar *et al*., 2024; Chang *et al*., 2023). One of the biggest advantages to using collagen scaffolds, since they have an inherent porosity itself and therefore allows blood vessels to grow in allowing for nutrients and oxygen to reach neighboring bone. The importance of this vascularization cannot be underestimated as it is necessary for new bone tissue to form and the regenerative process to take hold successfully. (Rodrigues *et al*., 2003).

### Recent Clinical Evidence on GTR and GBR

Recent clinical data support the use of collagens in GTR and GBR Practice. Numerous clinical trials have shown that treatments with collagen additives can improve tissue regeneration resulting in shorter healing times than are observed with other materials such as silicates and induce the development of stronger new bones. What emerges from these studies is that collagen plays a role in promoting the success of periodontal and bone regeneration, validating its importance as an essential element in dental regenerative protocols. The development of collagen-based technologies is still currently underway, where they will be driving technological growth in this field and facilitating clinical efficacy as well additionally the range of these materials also covers preventive orientation for regenerative dentistry (Rodriguez *et al*., 2018).

## COLLAGEN IN WOUND HEALING AND HEMOSTASIS

### Promoting Hemostasis and Wound Healing

Collagen is very important in the healing of wounds and stopping hemorrhage, especially during dental surgeries. The same properties that make it useful for managing bleeding allow its use to help glue tissues back together. The native process of hemostasis would result from the propensity to bind with platelets viscous system through direct interaction between collagen fibrils and platelet-surface glycoprotein VI, which will be followed by packed-focal a clot stabilization without an excess bleeding. This is especially important in dentistry, where the ability to control hemorrhage has significant implications for patient safety and procedure completion. In addition, collagen-based matrices serve as a 3D scaffold that supports cellular migration and proliferation, creating an ideal environment for tissue regeneration. This scaffold effect help in quicker wound healing and also reduces post operative inflammation enhancing the recovery moreover (Stein *et al*., 1985).

### Clinical Outcomes of Collagen-Based Matrices

Collagen-based matrices offer specific advantages in oral surgery, including their use following tooth extractions and for periodontal interventions, as demonstrated by clinical studies as well as real-world applications. Studies have seen that they improve the healing process by lowering post-surgery infections, promoting faster tissue repair and speed up recovery time. Patients tend to be more satisfied since the incision is less painful and the return to normal function occurs earlier. Clinical data from multiple studies is consistent in indicating that collagen matrices provide a more favorable host site response than traditional approaches, therefore supporting the use of these materials for regenerative purposes (Barrientos *et al*., 2008).

### Interaction with Other Hemostatic Agents

Collagen is also made more effective in the presence of other hemostatic agents. Collagen combined with tranexamic acid or hemostatic powders significantly improved clot strength and time to complete hemostasis. For instance, tranexamic acid helps in blood clot stabilization by inhibiting fibrinolysis which complements collagen's role to form and stabilize the clots. Similarly, when combined with collagen, hemostatic powders can help to improve the coagulation process and achieve faster bleeding cessation. These combinations work Synergistically to provide a better character and effects of hemostatic management in dental surgeries, leading into best clinic outcomes during surgery that contributes towards an efficient surgical process (Products *et al*., 1992; Stein *et al*., 1985).

## COLLAGEN AS A DRUG DELIVERY VEHICLE

### Local Delivery of Therapeutics

Among other naturally occurring polymer sequences, the potential of collagen to act as a versatile drug delivery platform in dental settings through its unique properties such as biocompatibility, degradability and functionalization capabilities has increasingly been recognized. With its potential to include and provide therapeutics directly from specific regions of the oral cavity, this platform has the aptitude for holistic treatment. The delivery of drugs, growth factors or bioactive molecules could be delivered in a collagens matrix and thus this technique will act as focalized localized therapy. By delivering treatments locally, systemic exposure is minimized side-effects reduced and therapeutic efficacy increased. Moreover, collagen can naturally degrade *in vivo* helping to present a slow and controlled delivery of the growth factors which will lead for prolonged therapeutic effects. Changes to the collagen formulation and/or incorporation of specific additives enable us to adjust delivery kinetics with great precision in terms of time or drug release dose. Such flexibility in treatment is invaluable for chronic dental disorders requiring long-term therapeutic strategies, specifically (Selvaraj & Perumal, 2022).

### Controlled Release Profiles and Biocompatibility

With advancements in nano and micro encapsulation techniques, the delivery of drugs based on collagen is now possible at an increased capacity. These include electrospun and microencapsulated MATs, often employed by incorporating nanocarriers for enhanced stability, controlled release or targeting of the cargo. For example, nano-encapsulation yields tiny drug-carrying bundles which can dive through the depths of tissues better and with more precision. On the other hand, micro-encapsulation is effective for producing larger therapeutic levels over longer range of time-designations (Guillamat-Prats, 2021). The child can then swallow her or his saliva along with the drug encapsulates, which reach their target areas in the oral cavity through sophisticated well-designed persorption/delivery mechanisms protecting such agents from adverse effects, while facilitating burst and sustained release at specific targeted sites within dental tissues. All this means that people get healthier faster, inflammation is reduced and patients are generally closer to being satisfied all the way down. These technological advancements mean that collagen-based systems are poised to be an important and integral part of the forthcoming spectrum of dental therapeutics, providing more efficient, treatment options with substantial patient compliance (Raftery *et al*., 2013).

## DENTAL PLUGS: DEFINITION, TYPES, AND CLINICAL APPLICATIONS

### Overview of Dental Plugs

Dental plugging is a specific medical device for the treatment of dental-oral tissue resection, filled in areas where teeth are removed to speed up recovery and prevent complications after extraction such as dry sockets. Physical plugs act as a barrier to the outside world and help prevent food, bacteria or foreign objects from getting into your bone and tissue while it heals. Dental plugs are categorized according to the material they are made of their design or use. Collagen dental plugs are worth mentioning here as they have the unique ability to incorporate themselves effectively into surrounding tissues. Collagen is a natural protein of connective tissues and acts as biocompatible scaffold for cellular activities responsible or vital to process of tissue regeneration. This integration also results in quicker recoveries and better clinical outcome as a whole (Kotsakis *et al*., 2014; Zaky *et al*., 2020).

### Comparison with Other Socket Preservation Techniques

Compared to other socket preservation methods, collagen dental plugs have numerous benefits that make them the most suitable for many clinical conditions. There are several traditional methods which have been used for active recovery such as synthetic materials, autografts (using the patient tissue), and allografts using donor tissues. Although more resistant to degradation, these materials also sometimes do not bond as well with the body and thus could theoretically take longer to heal or in some cases produce adverse reactions. Autografts are biocompatible; however, they necessitate another surgical site which can cause more patient discomfort and increases recovery time. Allografts suffer from the risk of immunological rejection or pathogen transmission (Pagni *et al*., 2012). Collagen dental plugs, in contrast, offer ready-made products that also take advantage of the added benefits exclusive to natural tissue integration. Not only are they biocompatible, but the materials mimic natural ECMs in driving rapid regeneration of tissues. Due to the simplicity of deployment and minimized rate of complications, collagen plugs are particularly well-suited for a broad range of patients, especially those with comorbidities that compromise wound healing (Alasqah *et al*., 2024). Three, restraining the soft tissue in order that it does not occupy bone healing space splinting Survival rate of a collagen plug after tooth extraction depends on multiple factors including wide variety clinical situations as well understanding basic biology in return quality care must be rendered (Rodriguez *et al*., 2018; Kim, 2020).

## TYPES OF COLLAGEN-BASED DENTAL PLUGS

### Commercial and Custom-Fabricated Plugs

Commercial and custom-made dental plugs based on collagen are broadly divided into two types, which work as separate entities in the field of medicine. Commercial collagen plugs are premanufactured in readily available sizes and shapes to accommodate most people. Under tough regulations, quality dental accessories are well produced to maintain their reliable standards among different types of dental procedures. They are the most readily available and can be used for tooth extractions to socket preservation. Customizable: As opposed to off-the-shelf silicone plugs, custom-fabricated collagen plug prototypes are not only designed on a patient-specific basis but also restyled to be anatomically and therapeutically ideal for each unique case. When the plug is customized, it can be in different dimensions (size and shape), materials composition to match better with patient's oral structure or clinical conditions (Akbari & Rasouli-Ghahroudi, 2018). That personal touch often results in better fit and function, especially with more convoluted situations or cases that are out of the ordinary. This extended in-house manufacturing capability to developed customized collagen plugs represents a great advantage that helps achieving better patches, mainly for those cases where the commercial standard ones could not be good enough. Advanced imaging and manufacturing techniques like 3D printing help deliver tailored solutions based on the unique needs of each patient in fast, accurate brands (Kotsakis *et al*., 2014; Nisar *et al*., 2020).

### Clinical Success Rates and Patient Outcomes

The clinical success rate and patient outcomes would indicate that collagen based dental plugs are very effective. The performance of these plugs in a variety of dental procedures has been widely documented through multiple case studies and clinical trials, informative as to how well they actual perform. Generally, success rates are evaluated based on criteria such as the period of healing, graft incorporation with surrounding tissues and patient overall satisfaction towards treatment. Two additional studies more formally showed that commercial and custom fabricated collagen plugs contribute significantly to decreased healing times as well as increased tissue regeneration, leading to an overall higher quality of postoperative care (Steiner *et al*., 2008). Follow-up exams, typically up to a year or more after plug implantation at intervals sufficient to capture long-term stability of the plug, absence of complications such as infection and re-bleeding in high-risk cases; patient-reported satisfaction postpartum. Impressive success rates, along with positive patient feedback serve as the testament of collagen plugs for being a consistent choice within dental surgery. The data indicates that when these plugs are correctly selected and used, they can have a major impact on clinical outcomes by accelerating the healing process with less morbidity as well greater patient comfort level leading to improved satisfaction (Ba *et al.*, 2014; Huang *et al.*, 2012).

## INDICATIONS, CONTRAINDICATIONS, AND LIMITATIONS

### Clinical Indications

Collagen dental plugs have been growing in popularity due to their adaptability across several different aspects of clinical applications within dentistry (Wang, 2023). They are especially recommended to preserve the alveolus following extraction as they aid in preventing collapse of the sock, controlling hemorrhage and allow it to proceed with normal healing. Furthermore, they are used for periodontal surgeries that need to promote soft tissue regeneration and decrease the chance of postoperative complications. Another indication for collagen plugs is with bone grafting procedures, where they support new bone formation acting as a scaffold in addition to improving the overall outcomes of regenerative treatments by adding stability to the graft. They are biocompatible with the surrounding tissue, and this feature is really important in clinical situations which require quicker recovery or patient outcomes (Park *et al.*, 2019).

### Contraindications and Patient-Specific Considerations

Although collagen dental plugs have their advantages, when to use them, they still depending on each patient. The plugs are contraindicated in cases where there is an active infection that could get worse with the presence of the plug, or where they would not function properly. Collagen plugs are probably best avoided in patients with severe allergies, especially if they have known hypersensitivity to bovine-derived products and would be at risk of experiencing an allergic response. Those with impaired ability to heal, such as uncontrolled diabetics or patients on immunosuppressive therapy, may not be ideal for collagen-based therapies. On the other hand, there are patient specific considerations of their own, such as medical history reconciliation and verifying any possible allergic reactions or systemic conditions to determine a safe use for collagen plugs. Personalized treatment planning, including a detailed assessment of these factors, is crucial in determining the suitability of collagen dental plugs for each patient (Naomi & Fauzi, 2020; Park *et al.*, 2019).

## LIMITATIONS AND CHALLENGES

While collagen dental plugs provide numerous benefits, there are also some limitations and challenges that should be acknowledged. One of the reasons for this is that natural degradation rates are so variable and can contribute to an unpredictable treatment outcome. This variability has the potential benefit of either early resorption via unnecessary degradation or prolonged presence of a plug, which may affect healing as well (Perumal, Ramasamy, A, *et al.*, 2018). In addition, there is a risk of adverse responses including inflammation and hypersensitivity especially in people who are sensitive to collagen or the sources thereof. The issue of cost: Importantly, collagen-based products are more expensive than their synthetic counterparts. It might also restrict their availability and use in clinical practice. Investigation and development efforts continue to focus on optimizing the predictability, safety, and cost of collagen dental plugs. It will be possible to improve the broader clinical utility and patient outcomes with these improvements (Boateng *et al.*, 2008).

## BIOFABRICATION AND DEVELOPMENT OF COLLAGEN DENTAL PLUGS

### Advanced Manufacturing Techniques

#### *Biofabrication Processes*

The biofabrication of collagen dental plugs require multi-step material performance optimization. Genetically engineered Collagen is sourced from animal sources such as bovine tendons using acid extraction and enzymatic treatment technology, which are further purified to make them safe for use. This purified collagen is crosslinked using chemical agents or physical methods like lyophilization in order to improve their structural integrity, and stability. With the use of more advanced methods like electrospinning and 3D bioprinting, we can take this even a step further; creating an environment closer to that found in nature with nanofibrous mats resembling extracellular matrix architecture for better cell integration or exact customized geometries using 3d printing. These methods work together to optimize the mechanical behavior and malleability of collagen dental plugs, facilitating better clinical results (Selvaraj & Perumal, 2022; Sivakumar *et al.*, 2021).

### Integration of Technologies

This mode of collagen dental plugs entering the IoT world with electrospinning, 3D printing and bioactive agents represents an important step forward. Electrospinning produces nanofibrous scaffolds that recapitulate the native extracellular matrix of tissue, leading to improved cell adhesion and biointegration. Printers have enabled high-resolution design of multi-layer structures that can be optimized for the healing dynamics at a specific anatomical site in any given patient. Moreover, the integration of bioactive agents such as antimicrobials and growth factors to collagen matrix in turn improves its performance offering certain therapeutic advantages like infection reduction or equitable tissue regeneration. These bioactive agents with advanced manufacturing techniques make the collagen dental plugs of higher quality, which enhances their behavior in clinical applications (Liu *et al*., 2023; Perumal *et al*., 2017).

## MATERIAL CHARACTERIZATION AND PROPERTIES

### Physicochemical Properties

Collagen dental plugs have desirable physiological properties, which are extremely important for effective and proper clinical application. This bio printed implants share "porosity" for sharing cells, tensile strength to ensure they do not fall apart in the body and degradation rate to naturally degrade within a suitable time frame. The porosity of the fabric affects the capacity to enable cell infiltration and tissue increase, which is critical for hit tissue regeneration. The high tensile strength of these takes again means that they have a robust consistency in respect to the mechanical forces experienced with an oral environment, and thus will hold their structure intact throughout healing. In addition, the degradation rate of collagen plugs is another important factor in consideration; an ideal saturation ensures that support by material for tissue regeneration lasts long enough before it becomes eventually absorbed or integrated into surrounding tissues. These properties collectively influence the plugs' ability to support healing and integration with the host tissues, impacting their clinical effectiveness (H. Kang *et al*., 2020).

### Advanced Characterization Techniques

Advanced characterization methods are used to thoroughly comprehend collagen dental plugs and also optimize their potential. High-resolution images of surface morphology and internal structure, including pore size distribution as well as overall textural characteristics are depicted using Scanning Electron Microscopy (SEM). By Fourier-Transform Infrared Spectroscopy (FTIR) The results of FTIR reflect the information about chemical composition, and molecular structure of collagen whereas provide answers to questions regarding existence as well as bonds between functional groups present in it (Dolafi Rezaee *et al*., 2024). Three-dimensional collagen fiber network structure was analyzed, with X-ray Diffraction (XRD) technique used to evaluate the crystalline and structuring of the individual fibers, which determines its mechanical properties as well as stability. Known as orthogonal techniques, they are essential in determining the physical and chemical attributes of collagen dental plugs with an eye towards ultimately formulating optimized materials for better clinical performance (Asran *et al*., 2010; Ba *et al*., 2014; H. Kang *et al*., 2020).

### *In vitro* and *in vivo* Studies

*In vitro* as well *in vivo* studies are required for the biocompatibility, efficacy and safety evaluation of collagen dental plugs. In a laboratory with *in vitro* studies, the plug is tested for biomedical characteristics associated with cell adhesion and cytotoxicity or proliferation using mammalian cells. The tests data suggests how the material affects biological cells and possible cellular processes. *In vivo*, or animal, studies give a much broader view of how the plugs perform in an entire living organism. These studies examine things such as tissue integration, healing response and if any inflammatory reactions might arise. Investigating how the collagen plugs function in controlled and live systems will give insight into their properties, tolerability status determining its clinical application (Boyan *et al*., 1996; Hanas *et al*., 2017; H. J. Kang *et al*., 2020).

## INNOVATIONS AND FUTURE DIRECTIONS IN DENTAL PLUG DESIGN

### Recent Innovations

Collagen dental plug progress: new collagen design is poised to usher in better, more versatile uses of dentistry to promote mechanical strength and biological compatibility of dental plugs, multi-layered structures have been developed (Di *et al*., 2019). For example, such structures often contain layers made of different collagenous materials each tailored for a specific purpose: porous layer conducive to tissue penetration and ingrowth on one hand and denser various mechanical supportive firmware laminations. Novel hybrid materials combining collagen with synthetic polymers or other biomaterials have also been investigated to enhance the durability and functionality of such devices. Innovations also consist of incorporation substances as growth factors, antimicrobial peptides or hemostatic agents into collagen matrix. This bioactivity is designed to further increase the plugs natural abilities for healing reduce risk of infection and enhance tissue regeneration. Collectively, these advancements are designed to optimize the performance of collagen dental plugs, leading to better clinical outcomes and increased patient satisfaction (Chen *et al*., 2017; H. J. Kang *et al*., 2020; Nisar *et al*., 2020; Perumal, Ramasamy, Nandkumar, *et al*., 2018).

### Personalized Approaches

The direction for collagen dental plugs lies in personalized solutions, made to fit each threatening wound of CCGs. Digital technologies, such as 3D-imaging and Computer-Aided Design (CAD), have developed significantly to be able create custom-fabricated dental plugs that are patient specific based on the individualized anatomical and clinical indications. Clinicians can easily create and fabricate dental plugs that uniquely fit each patient, for example, bone structure, extraction site morphology. By personalizing them, they not only better match mechanically with plugs but also functionally integrate into the tissue in which it is placed. Customization for each patient tends to promote more successful healing with fewer complications and better results overall. As technology continues to evolve, the ability to create bespoke dental plugs will likely become a standard practice, providing tailored solutions for diverse clinical scenarios (Binlateh *et al*., 2022; Kida *et al*., 2021).

### Multifunctional Collagen Plugs

Multifunctional collagen plugs are developed as a major breakthrough in dental biomaterials. These therapeutic plugs are engineered to deliver much more than just simple tissue support. This would allow for the addition of features like controlled drug release systems to collagen plugs so that therapeutic agents such as anti-inflammatory drugs or growth factors be may targeted delivery directly at their site (Ghaffar *et al*., 2024; Visalli *et al*., 2024). This localized delivery will lead to shortening times and less dependence on systemic medications. Responsive behaviors to surrounding environmental cues (e.g., pH and temperature changes) are further added for dynamic tunability of the properties within the plugs. Plugs that stiffen with changes in environmental conditions or release drugs depending on the physical cues of surrounding environment. These multifunctional features are expected to greatly advance the field of dental biomaterials, offering more comprehensive solutions for complex dental and oral health issues (Almadani *et al*., 2021; Amtha & Kanagalingam, 2020).

## CLINICAL EFFICACY AND REAL-WORLD APPLICATIONS

### Review of Clinical Trials

Clinical effectiveness and utility of collagen dental plugs are widely supported by Systematic Reviews on Clinical Trials (SRCT) as well as detailed case reports, providing significant knowledge about socket preservation post-extraction thereby validating them for use. All of these studies concluded that the use of collagen plugs is beneficial in preserving alveolar bone volume and accelerates and more complete healing while minimizing potential post-operative complications such as dry socket or infections. Collagen plugs have been shown to be advantageous compared with other socket-preservation methods such as autografts, allografts or synthetic materials. Their biocompatibility, simplicity to use and patient comfort play a great role in their good clinical results whereby most of the patients experience little pain with minimal discomfort during dental procedure resulting shorter recovery period (Binlateh *et al*., 2022; Kida *et al*., 2021).

### Clinical Outcomes

Case studies published in the literature illustrate numerous applications of collagen plugs for many clinical circumstances. This includes routine and more complex extractions with multiple teeth or patients who have healing abilities that are not very good. Collagen plugs have a practical benefit in socket preservation and bone regeneration due to their ability to minimize exposure of the alveolar cavity, support enhanced regrowth of new osseous tissue as well as act as scaffold for dental implantation. This is further supported with long-term follow-up data from these studies that help validate the credibility of collagen plugs by establishing prolonged effects on increased bone density as well as better healing results in comparison to other treatments (Buchbender *et al*., 2021).

### Challenges and Limitations

Collagen plugs can be difficult to use in the clinic. One of the main concerns raised by literature is that this cut in patient responses can be due to different factors, and it varies creating a broader aspect between patients according to their genetics, systemic conditions, oral microbiome (Kadivi *et al*., 2024). These differences can influence how long it takes for an injury to heal, and whether treatment is ultimately successful, potentially highlighting the importance of tailored treatments. Furthermore, although the incidence of allergic reactions or sensitivities to bovine collagen has been low, risk due consideration on that perspective along with a suggestion not only for the use synthetic but also porcine derived collagens (Guarnieri *et al*., 2017).

### Future Research Directions

This has also been a major concern and criticism of the method, as well with respect to large scale production where collagen plugs need to be reproducibly made time after time. Nevertheless, the future of collagen dental plugs seems bright with active research on modification of its existing formulations and bioactive agents or growth factors to provide additional regeneration potential. Opportunities for interdisciplinary research collaborations between materials scientists, biologists, and clinical practitioners are additionally identified as a significant impetus toward progress. The collaboration is anticipated to develop next-generation collagen plugs with better clinical performance and wider utility in different dental and maxillofacial surgical facets, thereby expanding the horizons of what can be achieved (Amtha & Kanagalingam, 2020; Buchbender *et al*., 2021; V Sandhu *et al*., 2012).

## REGULATORY AND QUALITY CONTROL ASPECTS

### Regulatory Importance in Ensuring Safety and Efficacy of Collagen Dental Plugs

Regulation and quality control of collagen dental plugs are required to ensure their safety, efficacy, consistency in clinical application especially over the socket preservation procedures which is another prerequisite for successful healing. It must meet the strict standards set by regulatory agencies such as the Food and Drug Administration (FDA) in U.S. and European Medicines

Agency (EMA). The procedures involve placing the collagen plugs into latching contour male part of an artificial joint to determine that the requirements specified in these standards are met for performance without adverse effects (Alasqah *et al*., 2024).

### Certification Process and Documentation for Compliance

The certification process is detailed and meticulous, requiring manufacturers to provide a long list of data that shows compliance with these regulatory standards. This comprehensive standard describes the manufacturing process of the product, by which detailed information was documented on how collagen and other raw materials were being obtained, for instance quality and source, as well as pre-clinical and clinical studies supporting safety/effectiveness. The manufacture of the collagen plugs themselves is tightly controlled and validated to ensure each batch meets the specific requirements for clinical use. This involves strict procurement of ultra-fine collagen from a reliable resource and high-caliber manufacturing practices (lyophilization, primarily) to keep the quality and functionality of the collagen preserved (P. L. Bigliardi *et al*., 2017).

### Critical Role of Sterility in Quality Control

In order to avoid infections during dental procedures, it is important for collagen plugs used in dentistry be sterile using proven sterilization techniques like gamma irradiation or ethylene oxide treatment (Olawumi *et al*., 2024). These techniques need to be capable of completely eradicating all pathogens present but without significantly degrading the collagen structure and function. When collagen plugs are paired with an active pharmaceutical ingredient, vigilance becomes even more critical: such combination products face higher regulatory hurdles and must demonstrate rigorous safety and efficacy testing (Katalinich, 2001).

### Challenges in Achieving Global Regulatory Compliance

There are of course many challenges in navigating through the regulatory landscape and this becomes even more difficult when trying to comply on a global level across different jurisdictions. However, whilst guidelines have been set out in regions such as the FDA and EMA agencies for others, there may be additional requirements which could slow down product approval leading to a delay in when companies enter the market. Furthermore, strong post-market surveillance mechanisms by manufacturers are essential for monitoring the *in vivo* performance of collagen dental plugs. This continued post-marketing surveillance is instrumental in detecting any safety concerns or adverse events that may emerge once the product has launched on the market (P. Bigliardi *et al*., 2017).

### Evolving Regulatory Frameworks for Advancements in Collagen-Based Biomaterials

The field of regenerative dental medicine and biomaterials is a rapidly developing one, and the regulatory scaffold to keep up with these developments must evolve as well. That will include establishing policies for advancing next-generation formulations of collagen, potential combination products and novel manufacturing methods. Collaboration among regulators, researchers and industry stakeholders is critical to the continued delivery of safe and effective collagen dental plugs, which achieve top notch performance standards in efficacy while maintaining same quality simultaneously globally ultimately benefitting patients from around the world across different healthcare settings (Chattopadhyay & Raines, 2014; Geckil *et al*., 2010; Gomes *et al*., 2019; Robinson *et al*., 1992).

## FUTURE DIRECTIONS AND EMERGING TRENDS

### Advances in Collagen-Based Biomaterials

Fast forward to the present day and significant innovation is occurring in the realm of collagen-based biomaterials with emerging trends including bioengineered collagen and synthetic collagens. Bioengineered collagen, which is produced by the recombinant DNA technology platform that could provide greater control over their properties and therefore may produce plugs with better mechanical integrity, biocompatibility and even tuned degradation profile than when using native collagens alone. Add to this that many of the synthetic collagen constructs can be designed with features similar to natural collagen, and you have a material for which functionality could potentially be tailored in remarkable detail (Sionkowska, 2021). The incorporation of nano- and micro-tech into the design of collagen plug is a novel progress in dental biomaterials, as nanotechnology enables precise manipulation at molecular level to enhance cell adhesion/tissue integration while micro technologies made it available to fabricate plugs mimicking complex architecture akin to dental tissues. One of the most exciting innovations is to develop "smart" collagen plugs that can sense environmental cues in oral cavity, release drugs at corresponding body fluid pH or bacteria enzyme activities so as to facilitate healing process with less infection complications. With this invention, dental care can be reinvented into real-time responsive and dynamic solutions adapted to the nature of each patient's mouth (Mannai *et al*., 1986).

### Personalized and Precision Dental Care

Collagen dental plugs are leading the revolution; and personalized and precision medicine which is trending not only in the body but also organs of mouth. Personalized medicine adapts treatments to both individual patient characteristics in terms of, for example genetic factors, lifestyle and specific clinical conditions. This autofluorescence-avoidance approach is perfect for collagen plugs, which are biocompatible and moldable. The use of digital technologies, such as 3D printing and digital imaging, is further increasing the customization of collagen plugs through patient specific design which allows one to mirror a theoretical image providing exact bite fit for socket preservation and tissue regeneration cases. Digital tools can provide rational design of collagen, however engineered plugs with controlled properties like degradation kinetics are difficult to use when cells have been incorporated into the matrix. To utilize collagen-based dental treatments in future, augmented with patient-specific data (e.g., genomics), to develop precision-designed plugs that fulfil each person's healing needs for improved outcome predictability and efficiency the minimization of complications ensuring a better comfort related satisfaction (Fauzi *et al*., 2016; Stein *et al*., 1985).

### Sustainability, Ethical, and Environmental Considerations

With the rising drive towards collagen based dental products come certain ethical and environmental implications about how collagen is sourced for and produced. Dental plugs use mostly collagen from animals such as bovine or porcine, so being humane about the sources is vital. That means striving for a carbon-negative collagen manufacturing process and sustainable by-products management. Moreover, the depletion of water and energy for collagen extraction by these methods is another pointer indicating that there should be a resolution to minimize environmental effects. Enter factors including renewable resources, waste reduction and more efficient extraction being explored by manufacturers to relieve environmental burdens. The manufacture of biodegradable and environmentally friendly collagen-based products, in turn offer an attractive answer to these same challenges and comply with the prime objective inherent in sustainable dentistry by way of reduced landfill emissions without creating further ecological pressures. Further development will be required to ensure that collagen dental plugs are useful in improving patient care and keep pace with the evolving focus on sustainability, as well advances being made with biomaterials and personalized medicine (Boyan *et al*., 1996; Chowdhury *et al*., 2018; Un *et al*., 2015).

## CONCLUSION

Collagen-containing products, especially Collagen Dental Plugs, have come a long way, providing major advantages in socket preservation and bone regeneration because of their biocompatibility and potential to facilitate natural healing while minimizing postoperative complications such as dry socket and infections. Yet, some issues remain, such as variability in patient responses and possible variability in product formulation, which must be further optimized to achieve optimal functionality. Future studies must aim at developing new collagen formulations that include bioactive agents, growth factors, or novel materials to improve the effectiveness of the treatment. Improved integration with natural tissues and more rapid healing are some of the primary potential advantages resulting from these advances. Large-scale clinical trials are also needed to determine long-term safety and efficacy in a broad range of patient populations. Lastly, interdisciplinary strategies involving materials science, regenerative medicine, and clinical dentistry can drive innovation in biomaterials, and therefore more effective collagen-based dental treatments. Collagen uses dentistry can revolutionize patient care by shortening healing times, optimizing treatment efficiency, and improving overall oral health. As material science and clinical science advance, even more sophisticated collagen products can be created, with their use extended beyond dental implants to broader applications in regenerative medicine. The vision for the future is to integrate these biomaterials into seamless comprehensive treatment protocols, satisfying both functional and aesthetic requirements. Ultimately, collagen-based solutions will continue to dictate the future trajectory of dentistry, improving patient outcomes and regenerative dental treatment.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**3D:** 3 Dimensional; **FGF:** Fibroblast Growth Factors; **DNA:** Deoxyribonucleic Acid; **GTR:** Guided Tissue Regeneration; **GBR:** Guided Bone Regeneration; **MAT:** Macromolecular Advanced Therapeutics; **ECM:** Extracellular Matrix; **IoT:** Internet of Things; **SEM:** Scanning Electron Microscopy; **FTIR:** Fourier-transform Infrared Spectroscopy; **XRD:** X-ray Diffraction; **CCG:** Complex Chronic Gingival; **CAD:** Computer-Aided Design; **SRCT:** Systematic Reviews on Clinical Trials; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **pH:** Potential of hydrogen.

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