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LITERATURE REVIEW: SYSTEMATIC REVIEW

Uses of Chitosan-Based Hydrogels in Dentistry: A Systematic Review

Usos de hidrogeles a base de quitosano en odontología: una revisión sistemática

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ABSTRACT: The objective of this article was to carry out a systematic review of the literature to determine the different therapeutic uses of chitosan-based hydrogels and their uses in dental therapy, as well as the modification and improvement of dental materials to promote research related to chitosan and its incorporation into dentistry as an adjunct or replacement in some dental treatments. Chitosan is a natural polymer obtained from the deacetylation of chitin, a polysaccharide abundant in nature, which, due to its biocompatibility, high biodegradability, non-antigenicity, and its ease of acquisition, has attracted biomedical interest, including in dentistry. Recent studies have shown that chitosan can be integrated into dental materials to obtain remineralizing effects, such as for antimicrobial agents, osteogenic agents, and pulp regeneration treatment. A bibliographic search was carried out in PubMed from 2018 to 2023. The results showed a wide range of uses for chitosan in the dental field, particularly its use as a remineralizing agent for tooth enamel; It has also been used in tissue regeneration mainly because of its osteogenic activity, as an antimicrobial agent, and as a vehicle for the application of medications. The use of chitosan as a nanobiomaterial is an interesting topic, since chitosan shows potential for new dental materials, either as an active ingredient or as an adjuvant vehicle for other materials.

KEYWORDS: Hydrogel; Chitosan; Xylitol; Remineralization, Tooth enamel.

RESUMEN: El objetivo de este artículo fue realizar una revisión sistemática de la literatura para determinar los diferentes usos terapéuticos de los hidrogeles de quitosano y su enfoque en la terapia odontológica, así como la modificación y mejoramiento de materiales dentales para promover investigaciones relacionadas con el quitosano y su incorporación a el área dental como coadyuvante o sustituto en algunos tratamientos odontológicos. El quitosano es un polímero natural obtenido de la desacetilación de la quitina, un polisacárido abundante en la naturaleza, que por sus características ha despertado el interés de la biomedicina. La odontología no es ajena a este interés, pues estudios recientes han demostrado que el quitosano puede integrarse a materiales dentales para obtener efectos remineralizantes, como agentes antimicrobianos, agentes osteogénicos, en tratamientos de regeneración pulpar, entre otros. Se realizó una búsqueda bibliográfica en PubMed, Scopus y Google Scholar desde 2018 hasta 2023. Los resultados mostraron una amplia gama de usos del quitosano en el ámbito odontológico. Lo que más destaca es el uso como agente remineralizante del esmalte dental; también fue utilizado en la regeneración de tejidos principalmente por su actividad osteogénica, como agente antimicrobiano, como vehículo para la aplicación de medicamentos, entre otros. El uso del quitosano como nanobiomaterial es un tema interesante, ya que por sus características, el quitosano muestra potencial para nuevos materiales dentales ya sea como ingrediente activo o como vehículo coadyuvante de otros materiales.

PALABRAS CLAVE: Hidrogel; Quitosano; Xilitol; Remineralización; Esmalte dental.

INTRODUCTION

Chitosan is a product of the deacetylation of chitin, which is a polysaccharide that is widely distributed in nature, mainly in the exoskeleton of crustaceans. Chitosan has been approved as safe for use by the United States Food and Drug Administration (FDA) because of its biocompatibility, biodegradability, non-toxicity, and ability to adhere to the mucosa (1). Given its specific physicochemical and biological characteristics, chitosan is used in the food, medical, cosmetics, water treatment, metal extraction and recycling industries (2) and also biomedicine. Chitosan has bactericidal, antibacterial, antiviral, and antitumor characteristics, and has been studied for applications in biomedical sciences (3).

Development in biomedical sciences and technology is increasing, and the study of new compounds is a priority in the production of treatment alternatives for various ailments and diseases. In biomedicine, the development of nanotechnological materials-nanomaterials such as nanoparticles, microspheres, micelles and hydrogels-has been trending (4).

The production and use of biodegradable polymers is of great interest in the pharmaceutical industry and biomedical research. According to the "RAE", a compound is biodegradable when it can be degraded by biological action (5). For biomedical use, biodegradable is the conversion of materials into less complex intermediate compounds or final products by means of solubilization, hydrolysis or biological action (6).

Historically, biodegradable hydrogels have had important applications in controlled-release drug delivery, the advantage of which is that they eliminate the need to remove "vestiges" or "leftovers" of these drugs (7). Hydrogels are a type of three-dimensional (3D) polymeric network that accumulates many water particles that present specific physicochemical properties to satisfy specific needs. For this reason, they have been applied in the biomedical field in studies of physiological and pathological mechanisms, disease therapies and tissue regeneration (8).

USE OF CHITOSAN HYDROGELS IN DENTISTRY

Chitosan has been studied in biomedicine and especially in dentistry because of its restorative properties and its potential for replacing or improving the functions of various tissues (9). Diseases of the oral cavity, such as dental caries, gingivitis, periodontitis and fungal and endodontic infections have multifactorial etiology, making the development of materials with a "multifunctional" approach important.

CHITOSAN IN REMINERALIZATION OF DENTAL ENAMEL

The search for non-invasive treatments for the prevention and control of dental caries is of primary interest in dental research, since, because of its inorganic nature, the regeneration of tooth enamel is challenging (10). Tooth enamel is made up of 95% inorganic matrix, 1% to 2% organic matrix and 2% to 4% water and helps protect the vital tissues of the tooth (dentin and pulp) from environmental stimuli such as temperature and physical and chemical stimuli (11).

The positive charges of chitosan facilitate adherance to the enamel surface. In addition, tooth enamel has a negative charge, which improves adhesion. The ability of chitosan to penetrate the surface of the enamel and help remineralize the deeper layers of the enamel has been reported (12).

MATERIALS AND METHODS

To conduct this systematic review, we used the PRISMA guidelines and checklist for preferred reporting items for systematic reviews and meta-analyses (13).

SEARCH STRATEGY AND SELECTION OF STUDIES

A comprehensive literature search was conducted using the PubMed electronic database. The keywords used for the search were "Chitosan AND Hydrogel AND Dentistry," finding a total of 119 articles related to these keywords.

For the articles to be reviewed in this article, the following inclusion criteria were established: time interval between 2018 and 2023; articles that contain chitosan-based hydrogels focused on the dental area; articles that contain chitosan-based hydrogels in combination with some other material; and original articles.

The exclusion criteria were articles published before 2018 and literature review articles, systematic reviews and meta-analyses (Figure 1).

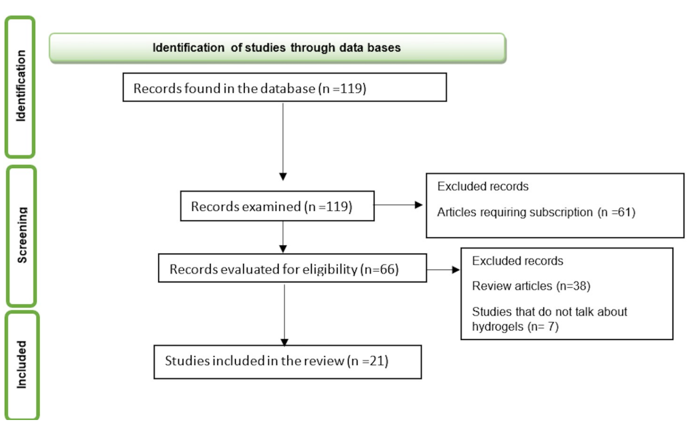

Figure 1. Flowchart of the literature search.

RESULTS

According to the bibliographic review, various dental uses of chitosan were found, mainly on the remineralization of tooth enamel, osteogenesis, antimicrobial effect, tissue regeneration and in synergy with dental materials to increase the effect of dentin adhesives (9). For this review, only chitosan-based hydrogel formulations were considered.

REMINERALIZING EFFECT

In the first study, a chitosan hydrogel was designed in combination with an amelogenin peptide derivative with the aim of creating a more clinically effective anticariogenic treatment characterized by affecting bacterial inhibition and promoting enamel remineralization. This research showed a reduction in biofilm adhesion of 95.43% and up to 100% in biofilm formation. Regarding enamel remineralization, it showed a recovery of surface microhardness of up to 50.06%, shallower carious lesions, and significantly less mineral loss (14).

Another study reported on a hydrogel based on chitosan and agarose to treat specimens demineralized by phosphoric acid. All specimens treated with the agarose hydrogel and agarose and chitosan showed improved microhardness values compared with that of acid-etched enamel. The main difference was between the treatments with the hydrogels at 7 days, since the treatment with the agarose hydrogel showed growth of the prism, while the specimen treated with chitosan-agarose showed an increase in the interprismatic zones (10) (Table 1).

Table 1. Remineralizing effect of chitosan hydrogels.

Article	Application	Characterization techniques	Conclusions	Citation
A chitosan-agarose polysaccharide-based hydrogel for biomimetic remineralization of dental enamel.	Remineralization of tooth enamel	SEM/EDX XRD FTIR Vickers microhardness	All samples immersed in the agarose hydrogel for 7 days showed prism growth and increased micro-hardness compared to the chitosan-agarose hydrogel.	(10)
The Presence of MMP-20 Reinforces Biomimetic Enamel Regrowth.	Remineralization of tooth enamel	SEM XRD ATR-FTIR	The study indicates that MMP-20 prevents the occlusion of pro-teins within enamel crystals, MMP-20 is added to cleave amelogenin during crystal growth.	(15)
Facile Synthesis of In Situ Formable Alginate Composite Hydrogels with Ca(2+)-Induced Healing Ability.	Remineralization of tooth enamel	SEM XRD FTIR UV-Vis RMN	It was found that the CS-MA/SA-SH hy-drogel with 50% (wt.%) inorganic matter exhibited the best self-healing properties, excellent mineralization of highly crystallized HAp, and has ideal cellular compatibility.	(16)
Chitosan hydrogel containing amelogenin-derived peptide: Inhibition of cariogenic bacteria and promotion of remineralization of initial caries lesions.	Remineralizing and anti-microbial effect	UV-Vis SMH (Micro hardness) PLM (Polarized light microscopy) TMR (Transverse microradiography)	The hydrogel showed a reduction in biofilm adhesion of 95.43% and up to 100% in biofilm formation. Regarding enamel remineralization, it showed recovery of surface microhardness of up to 50.06%, less depth of carious lesions and significantly less mineral loss.	(14)

BONE REGENERATION

For bone regeneration, a chitosan and poly(ethylene glycol) hydrogel was prepared in which acetylsalicylic acid was encapsulated to achieve a continuous and prolonged release for 14 days, promoting the proliferation of periodontal ligament stem cells and therefore osteogenic activity (17).

Another interesting article described the use of gum Arabic, chitosan and nanohydroxyapatite to create a hydrogel for bone regeneration. The hydrogel showed good resistance to compression, low allergic activity and good biodegradation when implanted subcutaneously in mice. These findings showed that hydrogel has broad possibilities for the elaboration of bioactive nanostructures to carry out tests in bone regeneration (18).

ANTICARIOGENIC POTENTIAL EFFECT

The development of polyfunctional hydrogels is an important part of the evolution of dental materials. Ren *et al*. developed a chitosan hydrogel loaded with peptide derived from amelogenin, with the aim of creating a dental biomaterial with a remineralizing effect and simultaneous antimicrobial effect, thereby developing a material with an anticariogenic effect. This hydrogel reduced the adhesion of biofilms by up to 95% and inhibited biofilm formation by up to 100%, providing an antimicrobial effect. With respect to the remineralization of enamel, it showed a recovery of microhardness by up to 50% (14) (Table 3).

Jaw bone infection is one of the most prevalent side effects after a dental extraction procedure that can lead to more serious processes such as osteomyelitis, osteoradionecrosis, and drug-related osteonecrosis (19) (Table 2).

ANTIMICROBIAL EFFECT

The antimicrobial effects of chitosan are important. Because of its polycationic nature, electrostatic interactions occur between the chitosan and the anionic groups found on the surface of the bacterial cell, subsequently causing permeability of the bacterial membrane and, therefore, loss of their vital compounds, leading to cell death.

The combination of chitosan and zinc oxide exhibited a cytotoxic effect against *S. mutans*, but, also had more than 90% cell viability in human gingival fibroblasts; the combination of chitosan hydrogel and zinc oxide had better effectiveness than chitosan hydrogel, exhibiting an improvement of up to 33%, and zinc oxide of up to 45% (21).

Sublet and Popescu made a chitosan hydrogel in combination with poly (vinyl alcohol) (PVA) and silver nanoparticles. They reported that the chitosan/PVA hydrogels trapped with silver nanoparticles exhibited high inhibitory activity against *S. aureus* and *K. pneumonia*. Vitality tests confirmed the very low cytotoxicity of chitosan/PVA hydrogels with or without silver nanoparticles (22) (Table 4).

PERIODONTAL TREATMENT

The ability to regenerate tissues is another important characteristic of chitosan. Periodontal diseases are inflammatory processes in which destruction of the tissues that support the teeth, the bone, the periodontal ligament and the cementum occurs. Abboud *et al*. designed a chitosan hydrogel loaded with insulin for local administration in patients with periodontitis (23). Another study observed the synergistic effect of *S. baicalinase's* radix extract and chitosan, which had an inhibitory effect against hyaluronidase and an inhibitory effect on the growth of pathogens (24).

A hydrogel loaded with lyophilized platelets was made with the ability to improve the viability of platelets, demonstrating that chitosan has the potential to serve as a vehicle for the administration of biological products such as growth factors (25) (Table 5).

PULP THERAPY

Pulpal regeneration is one of the most important challenges for dentistry and for this reason, attention has been focused on chitosan which, due to its characteristics, is attractive for the development of new treatments. A chitosan hydrogel with vascular endothelial growth factor was studied to promote the odontogenic differentiation of pulp stem cells, and the results suggested that the hydrogel can continuously release vascular endothelial growth factor and contribute to odontogenic differentiation. Therefore, the hydrogel would be a perfect vehicle for bioactive molecules (26).

Another study investigated a chitosan hydrogel with fibrin, which helped decrease antigen-presenting cells, myeloid dendritic cells, T cells and B cells. NK cells decreased significantly in those treated with the fibrin-chitosan hydrogel compared with the control, indicating an improvement in the inflammatory response (27).

Moreira and Sarra created a chitosan hydrogel that, when applied with a blood clot and photomodulation therapy, induces the differentiation of pulp cells. This article provided information on improving the previous results of dental pulp regeneration through cell localization approaches (28). The creation of a chitosan hydrogel with fibroblast growth factor (bFGF-) to investigate its effects on angiogenic induction in human dental pulp stem cells was the objective of this research. The conclusions of this article show us that Poli scaffolds (ε-caprolactone)/chitosan (PCL/CS) loaded with fibroblast growth factor (bFGF-) have the potential to promote the angiogenesis of dental pulp stem cells (hDPSC), leading to new expectations for angiogenesis and a possible advance in regenerative endodontic procedures (29) (Table 6).

OTHER USES

The use of chitosan as a hydrogel has been reported in combined applications as having an antimicrobial and osteogenic effect, as in the case of this study, in which a hydrogel based on carboxymethyl-chitosan (CMCS) was created in combination with clindamycin (CDM), This hydrogel showed antimicrobial activity against streptococcus sanguinis for 14 days and had acceptable osteogenic activity, having cell viability with human mesenchymal stem cells (hMSCs) and inducing their mineralization (19).

The treatment of osteoradionecrosis is one of the most important challenges in dentistry. In this study, we created a hydrogel in which chitosan was used as a vehicle for the local administration of parathyroid hormone and which was more successful than existing treatments (30).

Another interesting study reported that a chitosan hydrogel in combination with penciclovir and lavender oil had better success than a commercial penciclovir gel for the treatment of cold sores, showing improved prolonged release, bioavailability and, therefore, improved effectiveness on the mucosa than commercial gel (31) (Table 7).

Table 2. Application of chitosan hydrogels in bone regeneration.

Article	Application	Characterization techniques	Conclusions	Citation
Facile fabrication of a biocompatible composite gel with sustained release of aspirin for bone regeneration.	Bone regeneration	SEM FTIR	A prolonged release of acetylsalicylic acid was achieved for 14 days, promoting the proliferation of periodontal ligament stem cells and, therefore, osteogenic activity.	(17)
Unmodified Gum Arabic/ Chitosan/Nanohydroxyapatite Nanocomposite Hydrogels as Potential Scaffolds for Bone Regeneration.	Bone regeneration	EDX SEM FTIR XRD	The hydrogel showed good compressive strength, low allergic activity and good biodegradation when implanted subcutaneously in mice. And, due to these findings, the use of this hydrogel is recommended as a base to prepare bioactive nanostructures for testing in bone regeneration.	18)
Light-cured hyaluronic acid composite hydrogels using riboflavin as a photo-initiator for bone regeneration applications.	Bone regeneration	SEM XRD Mechanical properties (Rheometer)	The simultaneous addition of nanohydroxyapatite and chitosan increased the mechanical properties threefold and the osteogenic potential twofold, with a statistically significant difference compared to the control group.	20)
Antibacterial and osteogenic activities of clindamycin-releasing mesoporous silica/ carboxymethyl chitosan composite hydrogels.	Antimicrobial and osteogenic	BET XRD XPS	Prolonged CDM releases from both (p)-MCM-41-CDM-CMCS maintained their antibacterial effect against Streptococcus sanguinis for at least 14 days *in vitro*. *In vitro* evaluation of osteogenic activity showed that the CDM-incorporated composite hydrogel was cytocompatible with human mesenchymal stem cells (hMSCs) and induced hMSC mineralization through p38-dependent upregulated alkaline phosphatase activity.	(19)

Table 3. Application of chitosan hydrogels as anticariogenic agent.

Article	Application	Characterization techniques	Conclusions	Citation
Chitosan hydrogel containing amelogenin-derived peptide: Inhibition of cariogenic bacteria and promotion of remineralization of initial caries lesions.	Remineralizing and antimicrobial effect	UV-Vis SMH (Micro hardness) PLM (Polarized light microscopy) TMR (Transverse microradiography)	The hydrogel showed a reduction in biofilm adhesion of 95.43% and up to 100% in biofilm formation. Regarding enamel remineralization, it showed recovery of surface microhardness of up to 50.06%, less depth of carious lesions and significantly less mineral loss.	(14)

Table 4. Application of chitosan hydrogels as antimicrobial agent.

Article	Application	Characterization techniques	Conclusions	Citation
Combinatorial therapy of chitosan hydrogel-based zinc oxide nanocomposite attenuates the virulence of *Streptococcus mutans*.	Antimicrobial effect	SEM	The trial demonstrated that the combination of chitosan and zinc oxide exhibits a non-cytotoxic effect, with more than 90% cell viability in human gingival fibroblasts at different doses (78.1-625 µg/mL) within 72h. The ZnO-CS gel as an antimicrobial agent was 33% higher than that of CS and 45% than that of ZNO with a value of $p<0.05$.	(21)
Dual Cross-Linked Chitosan/PVA Hydrogels Containing Silver Nanoparticles with Antimicrobial Properties.	Antimicrobial effect	SEM FTIR Gel fraction XRD AAS	The chitosan/PVA hydrogel showed a relatively high swelling rate, reaching equilibrium within the first hour. As a result, these hydrogels are soft and highly flexible, and are ideal candidates for medical applications such as oral or wound dressings. AgNP-entrapped CS/PVA hydrogels exhibited high inhibitory activity against *S. aureus* and *K. pneumonia*. Vitality tests confirmed the lack of cytotoxicity of the CS/PVA hydrogels without and with AgNPs.	(22)

Table 5. Application of chitosan hydrogels for periodontal treatment.

Article	Application	Characterization techniques	Conclusions	Citation
Preparation and characterization of insulin-loaded injectable hydrogels as potential adjunctive periodontal treatment.	Periodontal treatment	UV-Vis	The presented design may be beneficial for local administration of insulin in patients with periodontitis.	(23)
Development and Evaluation of Thermosensitive Hydrogels with Binary Mixture of Scutellariae baicalensis radix Extract and Chitosan for Periodontal Diseases Treatment.	Periodontal treatment	ATR-FTIR Rheological analysis	The synergistic effects of lyophilized extract of *S. baicalensis* radix and chitosan toward ferrous ion chelating activity, hyaluronidase inhibition, and pathogen growth were observed.	(24)
Growth factor release and enhanced encapsulated periodontal stem cells viability by freeze-dried platelet concentrate loaded thermo-sensitive hydrogel for periodontal regeneration.	Periodontal treatment	Rheometric analysis	Freeze-dried platelet concentrate (FDPC) was incorporated into a chitosan hydrogel. Additionally, FDPC enhances the hydrogel's ability to maintain the viability of cells encapsulated within its matrix at levels comparable to the standard culture environment and to maintain the release of growth factors essential for tissue regeneration for up to two weeks.	(25)

Table 6. Application of chitosan-based hydrogels as pulp therapy.

Article	Application	Characterization techniques	Conclusions	Citation
Evaluation of Chitosan Hydrogel for Sustained Delivery of VEGF for Odontogenic Differentiation of Dental Pulp Stem Cells.	Pulp therapy	SEM	VEGF/CS/β-GP hydrogel could promote odontogenic differentiation of DPSCs better than VEGF treatment without hydrogel. The results suggested that the CS/β-GP hydrogel could continuously release VEGF and contribute to the odontogenic differentiation of DPSCs, thus it could become a potential carrier of bioactive molecules in pulp capping therapy.	(26)
Dental pulp inflammatory/ immune response to a chitosan-enriched fibrin hydrogel in the pulpotomized rat incisor.	Pulp therapy	-	Both hydrogels induced the transcription of IL-6, the percentage of leukocytes was similar in both hydrogels after one day, the proportion of granulocytes increased in both hydrogels, while antigen-presenting cells, myeloid dendritic cells, T cells and B cells decreased. NK cells decreased significantly in those treated with the fibrin-chitosan hydrogel.	(27)
Physical and Biological Properties of a Chitosan Hydrogel Scaffold Associated to Photobiomodulation Therapy for Dental Pulp Regeneration: An *In Vitro* and *In Vivo* Study.	Pulp therapy	SEM Viscosity analysis	Chitosan hydrogel when applied with blood clot and PBMT could in the future improve previous results of dental pulp regeneration through cell homing approaches.	(28)
Towards Induction of Angiogenesis in Dental Pulp Stem Cells Using Chitosan-Based Hydrogels Releasing Basic Fibroblast Growth Factor.	Pulp therapy	SEM FTIR	The conclusions of this article show us that bFGF-loaded PCL/CS scaffolds have the potential to promote hDPSC angiogenesis.	(29)

Table 7. Other uses of chitosan hydrogels.

Article	Application	Characterization techniques	Conclusions	Citation
Dual Cross-Linked Chitosan/ PVA Hydrogels Containing Silver Nanoparticles with Antimicrobial Properties.	Antimicrobial and osteogenic	BET XRD XPS	Prolonged CDM releases from both (p)-MCM-41-CDM-CMCS maintained their antibacterial effect against *Streptococcus sanguinis* for at least 14 days *in vitro*. *In vitro* evaluation of osteogenic activity showed that the CDM-incorporated composite hydrogel was cytocompatible with human mesenchymal stem cells (hMSCs) and induced hMSC mineralization through p38-dependent upregulated alkaline phosphatase activity.	(19)
The efficacy of sustained-release chitosan microspheres containing recombinant human parathyroid hormone on MRONJ.	osteonecrosis treatment	Photonic correlation spectroscopy SEM	The present study demonstrates successful attenuation of odtheoradionecrosis through a local drug delivery system combined with parathyroid hormone, unlike previously attempted treatment strategies.	(30)
Oral gel loaded with penciclovir-lavender oil nanoemulsion to enhance bioavailability and alleviate pain associated with herpes labialis.	Cold sore treatment	Rheological analysis Globule size	Compared to a marketed cream with 1% penciclovir, the oral gel formulation under study exhibited significantly greater and sustained penciclovir release, almost double the permeability of penciclovir, and a relative bioavailability of 180%. Overall, the results confirm that the oral gel formulation under study can provide an efficient delivery system for penciclovir to reach the oral mucosa and its subsequent prolonged release.	(31)

DISCUSSION

Scientific evidence has demonstrated that chitosan is a bionanomaterial with considerable potential in the biomedical sciences because it can be used as a vehicle for drug administration, tissue regeneration, and antibacterial effects (9). In the present review, 21 articles describing chitosan-based hydrogels for the dental field were analyzed.

Chitosan-based hydrogels have been shown to be an option for the remineralization of tooth enamel and provide novel anticariogenic treatments. For amelogenin-derived peptide hydrogel, a recovery of up to 50% in microhardness was shown in damaged tooth enamel (14). For chitosan hydrogel in combination with agarose, the enamel prism grew with a 7-day treatment (10).

Chitosan-based hydrogels provide active agents in bone regeneration in combination with artificial polymers. Chitosan and polyethylene glycol hydrogel was used as a capsule in which acetylsalicylic acid was introduced, which induced the proliferation of periodontal ligament stem cells and induced osteogenic activity (17). Another study used gum Arabic, chitosan and nanohydroxyapatite, which, because of its physical characteristics, has broader potential for the development of bioactive structures to make biomaterials for bone regeneration (18).

A hydrogel based on chitosan was found to have a remineralizing and antimicrobial effect and an anticariogenic effect. In this research, the authors made a chitosan hydrogel in combination with peptide derived from amelogenin, in which a reduction of biofilm adhesion on enamel of more than 95% and a 100% reduction in biofilm formation was reported (14).

Hydrogels with an antimicrobial effect have been developed, among which is a chitosan and zinc oxide hydrogel showing a cytotoxic effect against *S. mutans* and a 100% viability in human gingival fibroblasts (21). Another investigation was based on a hydrogel of chitosan/PVA/ and silver nanoparticles which exhibited inhibitory activity against *S. aureus* and *K. pneumonia*; low toxicity was also shown in viability tests (22).

Hydrogels have been reported to act as potential agents for the treatment of periodontal disease and pulp therapy since chitosan shows a potential tissue regeneration effect. In the first case, a hydrogel loaded with insulin was investigated for the treatment of periodontitis (23). Another study was based on the combination of *S. baicalensis* radix extract and chitosan, which had an inhibitory effect against hyaluronidase combined with an inhibitory effect on the growth of pathogens (24, 29).

In the case of pulp therapy, chitosan hydrogels were studied in combination with vascular endothelial growth factor, which contributes to odontogenic differentiation (26). Another study showed that a chitosan hydrogel in combination with fibrin improved the inflammatory response (27). A chitosan hydrogel was also combined with a blood clot and, with the help of photomodulatory therapy, induced the differentiation of pulp cells (28).

Other uses of chitosan hydrogels have also been found, for example, the combination of a chitosan hydrogel with clindamycin to obtain an antimicrobial and osteogenic effect (19). An alternative has also been sought in the treatment of osteoradionecrosis, in which chitosan hydrogel was combined with parathyroid hormone, revealing an improvement compared with existing treatments (30). The chitosan hydrogel in combination with penciclovir for the treatment of cold sores had a longer release and better bioavailability than the commercial chitosan gel (31).

CONCLUSION

The use of chitosan in biomedicine is a cutting-edge topic as it has potential for use in different areas. In this review, different uses of chitosan-based hydrogels in different areas of dentistry were identified. Chitosan hydrogels have different applications such as remineralization of tooth enamel, tissue regeneration, antimicrobial effects and, especially, as a vehicle for the administration of drugs. The most specific advantage of chitosan is its low cost and availability, since being a natural polymer it is found in nature and can be obtained in a straightforward way. The prospects for the use of this material are positive since the potential of this bionanomaterial is broad. Although more studies are needed in reference to the use of chitosan, either as an active ingredient or as a vehicle for drug administration, the scientific evidence shows us that it is a viable option.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Conceptualization and design: J.A.V.S. and C.B.J.
Literature review: J.A.V.S. and C.B.J.
Methodology and validation: C.G.F. and C.B.J.
Formal analysis: C.G.F., L.A.A.G. and C.B.J.
Investigation and data collection: J.A.V.S. and C.B.J.
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Supervision: C.G.F., L.A.A.G., G.A.M.C., V.Z.A. and C.B.J.
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