Review Article Pol J Public Health, Vol. 134 (2024): 112-117

EMANUELA BIS[1], MARTYNA WOŹNIAK[1], PATRYCJA ZWIERZCHLEWSKA[1], ALEKSANDRA GĘBKA[1], KAROLINA THUM-TYZO[2], RENATA CHAŁAS[2]

Application of natural polymers in mucosal diseases of the oral cavity

Abstract

The mucous membrane of the oral cavity is susceptible to various pathological conditions, such as ulcers, inflammations, or tumors. Traditional methods of treating these diseases can come with limitations or trigger undesirable effects. Biopolymers, due to their biocompatibility, biodegradability, low toxicity, and ability to regulate regenerative processes, can offer alternative therapeutic approaches. Among the natural polymers used in the treatment of oral mucosal diseases are hyaluronic acid, chitosan, cellulose, and collagen. PubMed and ResearchGate databases were included for a thorough analysis of applications of biopolymers in the treatment of oral mucosal diseases. Biopolymers have a wide range of applications in dental practice. They can be used in the form of gels, creams, rinses, and patches. Natural polymers are utilized as matrices for drug creation and transport. Thanks to their antibacterial, antifungal, and antiinflammatory properties, they are employed in the treatment of conditions like recurrent aphthous stomatitis, lichen planus, and periodontal diseases. Their potential in alleviating symptoms and enhancing wound healing in ulcerative oral cavity diseases has been demonstrated. Biopolymers have also found use in the treatment of oral cancer by increasing the apoptotic index and sensitizing tumors to radiation and chemotherapy. Biopolymers, due to their advantages and multifaceted effects, can serve as alternative methods for treating oral mucosal diseases compared to traditional approaches. In order to confirm their effectiveness, safety, and practical application, further research and assessment of their long-term effects are necessary.

Keywords: biopolymers, polymers, oral mucosa diseases.

DOI: 10.12923/2083-4829/2024-0025

INTRODUCTION

The oral cavity mucous membrane is exposed to various pathological conditions, such as ulcers, inflammation, or tumors. Traditional treatments can come with limitations or induce unwanted effects. Polymers, which are an indispensable part of modern medicine, have found specific applications in the treatment of mucous membrane diseases of the oral cavity, too. Due to their environmentally friendly production and biocompatibility from natural polymers [1], as well as cheap and reproducible use from synthetic polymers [2] they are used for various applications, including tissue repairing [3], controllable drug delivery [2,4], cancer cell separators, minimally invasive surgery, etc. In general, polymers can be divided into synthetic (e.g., polyolefines, polyesters, silicones) and natural polymers (e.g., polysaccharides, polynucleotides and proteins) [2]. Materials based on natural polymers have highly desirable properties in comparison to synthetic ones. Biopolymers, because of their availability, biocompatibility, biodegradability, low toxicity, and ability to regulate regenerative processes, can serve as alternative therapies. They show promise in symptom relief, wound healing promotion for ulcerative oral diseases, and even aiding in oral cancer treatment by enhancing apoptosis and sensitizing tumours to radiation and chemotherapy. Natural polymers used in the treatment of oral mucosal diseases include hyaluronic acid, chitosan, cellulose, and collagen, among others.

MATERIALS AND METHODS

To perform an analysis of applications of biopolymers in the treatment of oral mucosal diseases, articles available in the PubMed and ResearchGate databases were used. The following keywords used to search the database were: Biopolymers, Polymers, Oral Mucosa Diseases. The paper was prepared in consideration of original research papers and reviews. Studies published between 2015-2024 were included.

RESULTS

A detailed analysis of the literature revealed synthetic and natural polymers presented in the table 1. Based on the information collected, seven biopolymers most important for oral health were selected, including chitosan, hyaluronic acid, cellulose, sodium alginatum, polynucleotides, collagen and gelatin. The role and applications of biopolymers in the treatment of oral mucosal diseases are described in the following text.

[1] Student Research Group at the Department of Oral Medicine, Medical University of Lublin, Poland
[2] Department of Oral Medicine, Medical University of Lublin, Poland

TABLE 1. The group of natural and synthetic polymers.

Natural polymers	Synthetic polymers
Agar	Acrylic rubber
Albumin	Epoxy resin
Alginates	Nylon
Carrageenan	Phenol-formaldehyde resin
Cellulose	Polyacetylene
Chitin & Chitosan	Polyacrylonitrile
Collagen/Gelatin	Polyamide
Dextran	Polybutadiene
DNA	Polyethylene
Fibrin	Poly(ethylene oxide)
Gellan gum	Poly(ethylene terephthalate)
Hyaluronic acid	Poly(methyl methacrylate)
RNA	Polyoxyethylene
Silks	Polypropylene
Soy, wheat gluten	Polystyrene
Starch	Polytetrafluoroethylene
Xanthan	Polyvinyl chloride

Chitosan

Chitosan, an organic polymer derived from chitin [5] which is a naturally occurring β-N-acetyl-glucosamine polymer found in the cell walls of fungi and crustacean shells, holds a significant place in medical applications. It is obtained by alkaline N-deacetylation of chitin [6]. A key attribute of chitosan that contributes to its safe medical use is its biocompatibility and biodegradability [7]. Beyond this, it possesses a range of advantageous properties, functions, and diverse biological activities that make it widely applicable, including in the treatment of oral mucosa diseases [8].

Chitosan's cationic nature enables interaction with negatively charged bacterial cell walls, leading to their disruption and subsequent bacterial cell lysis [9]. This antibacterial action can help mitigate the growth and colonization of oral bacteria, potentially aiding in preventing or treating oral infections [10]. Furthermore, chitosan has the ability to permeate fungal cell membranes, initiating processes that result in their demise [11]. This property is very promising for treating fungal infections, particularly effective against oral candidiasis [12]. Saeed et al. conducted research on the activity of chitosan oligosaccharide in the growth and attachment of Candida albicans. Chitosan oligosaccharide has been incorporated into a tissue conditioner for the prevention and treatment of denture stomatitis. The study revealed a significant reduction in the number of Candida albicans colonies attached to the tissue conditioner compared with a control group [13].

The antibacterial, antifungal, and anti-inflammatory characteristics mentioned above, coupled with chitosan's coagulation properties, promotion of platelet aggregation, and ability to adhere to mucous membrane surfaces [14], pave the way for dressings or gels that extend the contact time of therapeutic agents with affected tissues. Its positive influence on wound healing and mucoadhesive attributes have led to the creation of patches for oral ulcers [15]. Furthermore, chitosan mouthwashes have significantly alleviated pain in patients with oral ulcers [9]. Epstein et al. demonstrated the effect of a non-anaesthetic chitosan-based mouth rinse (Synvaza – Synedgen Inc., Claremont, CA) on oral cavity soreness and functioning in ulcerative oral mucosal lesions. The authors observed significant reductions in oral soreness associated with talking by 67%, drinking by 62%, swallowing by 56% and eating by 50% within 72 h [16].

Chitosan demonstrates potential antitumor effects against oral cancer cells through induction of apoptosis, suppression of tumour cell growth, and reduction of tumour cell invasiveness and migration [17]. It can also act as a carrier for anticancer drugs, potentially enhancing treatment while minimizing toxicity [18]. Additionally, chitosan's potential impact on immunomodulation might prove advantageous in battling oral cancer by bolstering the immune system [19].

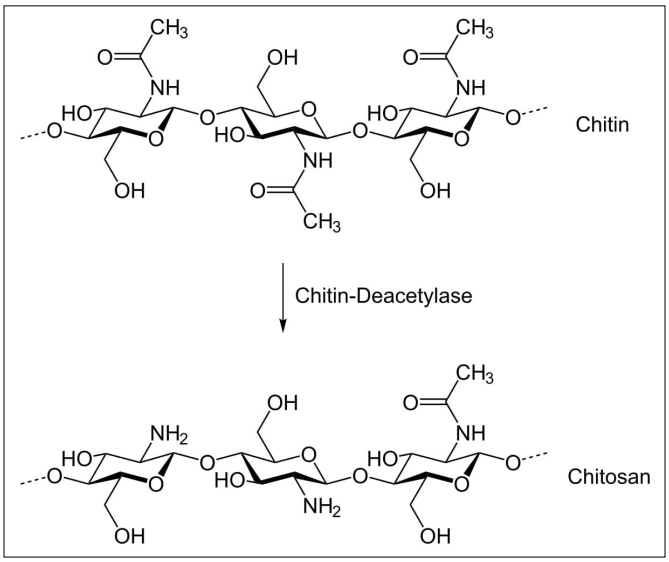

FIGURE 1. Chemical structures of chitosan.

Hyaluronic acid

Hyaluronic acid, also known as hyaluronan, is a naturally occurring polysaccharide composed of repeating units of N-acetylglucosamine and glucuronic acid [20]. It is a high molecular weight, linear molecule that is part of the glycosaminoglycan family, that are important components of the extracellular matrix in various tissues of the human body [21].

Hyaluronan is characterised by its ability to bind and retain water, giving it a gel-like consistency and lubricating properties [22]. It is biocompatible, biodegradable, and nontoxic, making it safe for various medical applications [23]. Moreover, it has the ability to form a temporary structure that facilitates the deposition of extracellular matrix (ECM) proteins. This process triggers various cellular responses, including cell proliferation, adhesion, and migration [24]. Furthermore, the hydrophilicity of hyaluronic acid, which refers to its strong affinity for water molecules, plays a crucial role in wound healing, periodontal tissue repair, and volume restoration after dental procedures [2,25].

Hyaluronic acid has been investigated as a potential treatment for oral mucositis, which is inflammation and ulceration of the oral mucosa that can occur as a side effect of head and neck radiation therapy [26]. It can be applied topically as a gel or mouthwash to soothe and protect the oral mucous membrane. Local administration of hyaluronan may play an important role and provide effective relief for patients suffering from painful erosive lesions in the oral cavity [27,28].

In a study conducted on rats by Guo et al., hyaluronic acid in the form of a composite hydrogel with bioglass was employed to treat the symptoms of Oral Submucous Fibrosis (OSF), a condition affecting the oral mucous membrane. The results of the study demonstrated that this hydrogel composite effectively alleviated OSF symptoms, including mucosal pallor and limited mouth opening. Furthermore, it exhibited biocompatibility and was readily metabolised in the rat organisms, signifying its potential utility for the treatment of oral mucous membrane conditions in humans [29,30].

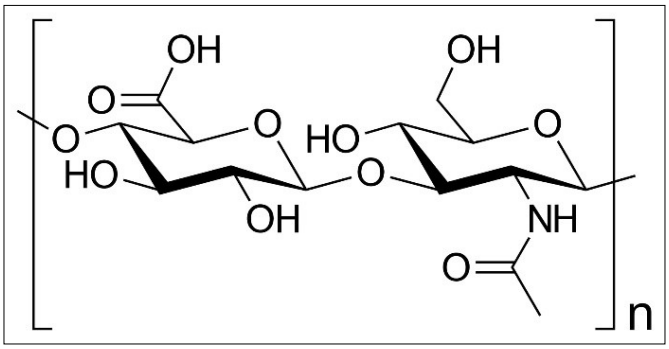

FIGURE 2. Chemical structure of hyaluronic acid.

Cellulose

Cellulose is a high molecular weight biopolymer that occurs naturally in plant cell walls or is produced by some bacteria such as Agrobacterium, Pseudomonas, Rhizobium, Escherichia spp., Komagataeibacter xylinus [2]. When it is produced by bacteria, it is called bacterial cellulose [2,31].

Bacterial cellulose is a promising material that is widely used in medicine due to its low toxicity, biocompatibility and biodegradability [32]. This means that it is well tolerated by living tissues and that the products of its degradation breakdown are neutral to the body. In addition, cellulose has a strong affinity for water molecules, making it an excellent transport medium for drugs [31].

It is used as a physical barrier in the treatment of inflammation of the skin and mucous membranes, burns, abrasions, wounds, ischemic, and diabetic wounds [33]. Horue et al. report in their study that the bacterial cellulose membrane, due to its highly hydrated state, creates an optimal moisture environment that speeds up the epithelialization process, reduces pain during dressing changes, and enhances the healing process [34]. Additionally, the membrane's absorbent capability facilitates easy removal during dressing changes, contributing to an improved healing process [35,36]. Its excellent permeability to gases further supports proper re-epithelization by allowing effective exchange between the atmosphere and the wound [34]. Thanks to its bioadhesive properties, it can be used as a scaffold for the growth of endothelial cells, chondrocytes, and smooth muscle cells, which significantly reducing healing time [37]. Martin and Nunan investigated the tissue response following the subcutaneous implantation of a cellulose membrane in mice [19]. The researchers did not observe signs of foreign body reaction throughout the study, and also noted the development of new blood vessels surrounding and within the implanted cellulose [38].

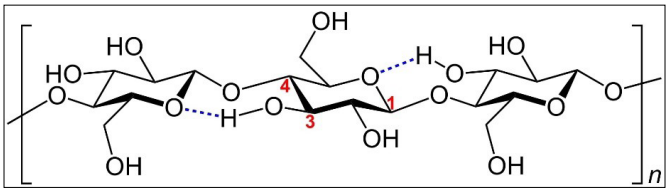

FIGURE 3. Chemical structure of cellulose.

Sodium alginatum

Alginate is a type of linear anionic polysaccharide derived from alginic acid [39]. It is composed of 1,4-linked d-mannuronate residues and 1,4-linked l-guluronates and can be extracted from various algal sources, each with a different composition [40].

Sodium alginate has numerous medical applications due to its beneficial properties such as biocompatibility, biodegradability, mucoadhesion and low-cost production [40,39]. One of these is the delivery of drugs such as 5-FU, Cur, Ibuprofen and anti-cancer microcapsules [41]. He et al. indicates that chitosan-alginate hybrid (AH) nanoparticles have been created for use as carriers in oral drug delivery for anticancer therapy [42]. The robust electrostatic interactions between the amino groups of chitosan and the carboxyl groups of alginate play a significant role in enabling the formation of stable alginate hybrid material (AHM) [43]. It can also be used in wound dressing and treatment, 3D bioprinting, cartilage regeneration and in vivo wound healing [44].

Sodium alginate can be a biodegradable scaffold that surrounds periodontal ligament (PDLSC) and gingival mesenchymal stem cells (GMSC) and redirects stem cell differentiation into bone or adipose tissue, making it a promising polymer for tissue engineering [45,46]. In the treatment of moderate chronic periodontitis, it produces very good results due to its osteogenic properties [47]. When applied directly to the pocket, it increases mucoadhesion and controlled release [44].

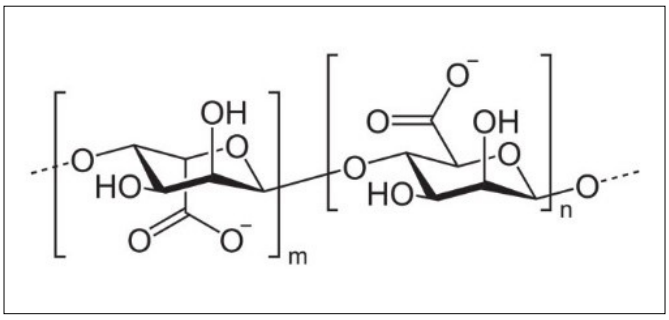

FIGURE 4. Chemical structure of sodium alginatum.

Polynucleotides

Polynucleotides are biopolymers made up of nucleotide monomers. The most common examples with distinct biological functions are DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). In living organisms, polynucleotides encode the genome. They have many advantages that make them suitable for widespread use in dentistry [48].

One of the main aims of the polynucleotide work is to develop a therapy that would inhibit the lysosomal cysteine protease, Ctsk, which is responsible for bone resorption and destruction, particularly in periodontitis. In addition, inhibition of Ctsk may have a role in the prevention of temporomandibular joint disease, as it also causes bone resorption in the joints

[49-51]. It has also been found that the use of polideoxyribonucleotide, PDRN [52], an A receptor ligand, reduces inflammatory infiltration in the gums and periodontal ligaments [53,54]. DNA/RNA, owing to its anti-inflammatory properties, is utilized as an active ingredient in formulations designed for treating oral mucosa ulcers.

It is possible to limit tumour growth by using graphene oxide and polyethyleneimine [45]. Cancer immunotherapy utilizing peptides and antisense oligonucleotides may decrease the expression of the tumor growth factor and increase apoptosis of cancer cells. This could lead to reduced tumor growth and increased sensitivity to radiotherapy and chemotherapy [49]. Moreover, oligonucleotide aptamers represent a promising therapeutic option in combating microbial infections. They demonstrate the ability to inhibit bacterial toxins, reduce pathogen invasion, and exhibit anti-biofilm activity, which allows for the replacement of conventional monoclonal antibodies [2,53]. Polypeptides, i.e. gelatin and collagen are the most commonly used polymers.

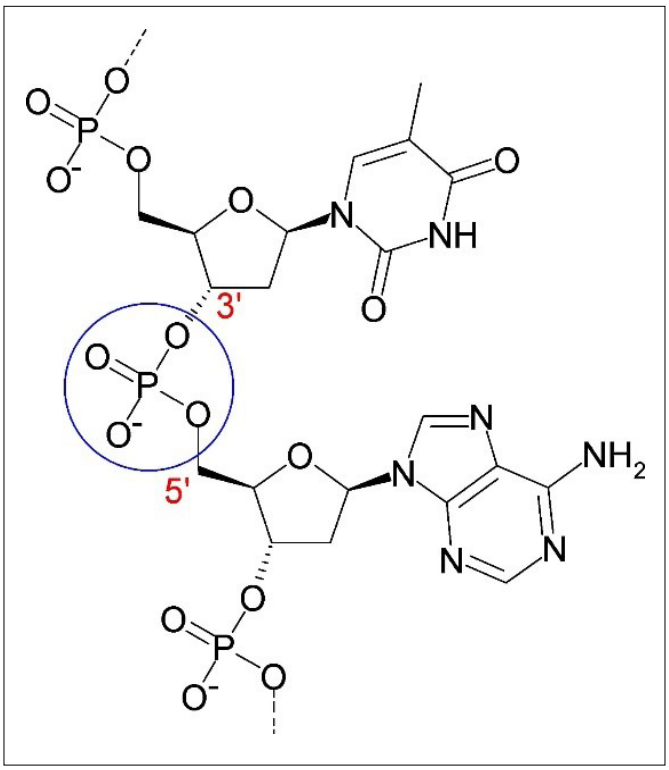

FIGURE 5. Chemical structure of polynucleotide.

Collagen

Collagen is a natural protein that constitutes the main component of the extracellular matrix in animal organisms. It exhibits strong osteoinductive properties, stimulates bone development and improves its mechanical strength. Therefore, it is most commonly used to accelerate the healing process of the tooth socket after surgical tooth extraction [55,56]. Furthermore, collagen induces the growth of the extracellular matrix, which has found application in controlled tissue regeneration during procedures performed on periodontal patients [57].

Collagen-based sponges crosslinked with glutaraldehyde and chloramphenicol are resistant to collagenases, do not absorb water, and gradually release drugs [58]. Fu et al. designed and tested antimicrobial peptide-modified polycaprolactone collagen nanosheets (APCNs). The study demonstrated that these nanosheets exhibited robust adhesion to irregular buccal mucosa surfaces under wet conditions and external force. Moreover, they displayed high antibacterial activity against both Gram-positive and Gram-negative bacteria, along with good biocompatibility [59]. Their antibacterial and antimicrobial properties have also been proven, making them useful in the therapy of oral cavity infections [60]. Gao et al. investigated the impact of marine collagen peptides (MCPs) derived from tilapia skin on the recovery of traumatic oral ulcers in rats and the associated mechanism. The researchers observed that the utilization of MCPs demonstrated an acceleration in the healing of oral mucosal ulcers and a suppression of inflammatory responses in rat and rabbits studies [61,62].

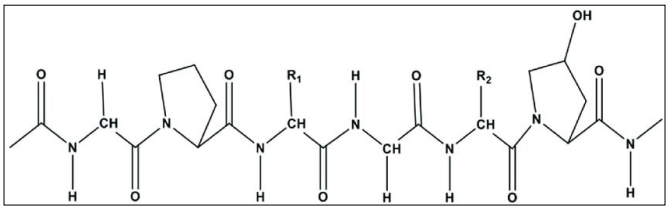

FIGURE 6. Chemical structure of collagen.

Gelatin

Gelatin is a hydrolysed form of collagen that is widely used in dentistry [63]. It belongs to biocompatible and biodegradable polymers. It has been shown to accelerate wound healing due to its mechanical support and the integrity of to the hydrofilms [64]. It makes up for tissue damage around the wound and offers a natural substrate for the extracellular matrix [65]. Therefore, it has found application in the creation of medical dressings. However, it requires cross-linking with other polymers and the administration of antimicrobial preparations [40]. Gelatin is characterised by adhesive properties and low immunogenicity [66]. It has been demonstrated that scaffolds containing gelatin and placed in periodontal pockets can contribute to a reduction in the amount of periodontal pathogens. Moreover, these scaffolds demonstrate ease of application and improve the integrity of periodontal tissues [67,68]. Furthermore, this polymer is used for cartilage regeneration and bone formation. The addition of gelatin has been shown to increase the resistance of the graft structure to fractures [69].

In addition, gelatin is used as a drug carrier [40]. However, it has several drawbacks, such as weak mechanical properties, susceptibility to protease activity, and thermal instability. Nevertheless, it has been demonstrated that drugs produced based on gelatin stimulate the process of post-extraction wound healing, which is useful in dental surgery [70]. Liu et al. prepared and employed a biomimetic hybrid scaffold, consisting of gelatin methacryloyl and decellularized human amniotic particles (GelMA-dHAP), as a tissue substitute to enhance wound healing in the oral mucosa of rabbits. They revealed that the hybrid scaffold significantly boosted fibroblast proliferation and differentiation compared to control groups. Subsequent to these initial evaluations, and to gain a deeper understanding of the underlying mechanisms of wound healing, in vivo histological and immunohistochemical studies were conducted using a rabbit oral mucosa defect model. The findings demonstrated that GelMA-dHAP has the potential to stimulate angiogenesis and collagen expression within the oral mucosa [71].

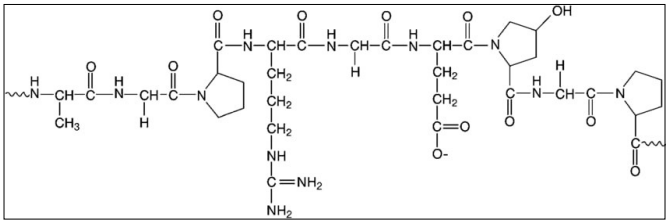

FIGURE 7. Chemical structure of gelatin.

CONCLUSIONS

In the realm of dental materials, the exploration of natural polymers has garnered significant attention for their inherent biocompatibility, widespread availability, and environmentally friendly biodegradability. However, challenges such as source variability and limited control over mechanical properties require innovative approaches. The strategic combination of natural and synthetic polymers not only enhances mechanical strength but also allows precise control over absorption rates, ensuring optimal clinical outcomes. Notable natural polymers in dentistry include chitosan, hyaluronic acid, cellulose, sodium alginate, and collagen, each contributing to diverse applications from infection prevention to tissue regeneration. Sodium alginate, with mucoadhesive properties, is of utility in drug delivery, wound dressing, and periodontal treatments. The collaborative synergy among dentists, material scientists, and researchers is pivotal in harnessing the potential of biocompatible polymers. This amalgamation of expertise and innovation positions biocompatible materials as key players in addressing oral health challenges.

REFERENCES

1. Tian KK, Qian ZG, Xia XX. Synthetic biology-guided design and biosynthesis of protein polymers for delivery. Adv Drug Deliv Rev. 2023;194:114728.
2. Paradowska-Stolarz A, Wieckiewicz M, Owczarek A, et al. Natural polymers for the maintenance of oral health: Review of recent advances and perspectives. Int J Mol Sci. 2021;22(19):10337.
3. Pedersen DD, Kim S, Wagner WR. Biodegradable polyurethane scaffolds in regenerative medicine: Clinical translation review. J Biomed Mater Res Part A. 2022;110(8):1460-87.
4. Samui A, Pal K, Karmakar P, et al. In situ synthesised lactobionic acid conjugated NMOFs, a smart material for imaging and targeted drug delivery in hepatocellular carcinoma. Mater Sci Eng C Mater Biol Appl. 2019;98:772-81.
5. Hong F, Qiu P, Wang Y, et al. Chitosan-based hydrogels: From preparation to applications, a review. Int J Biol Macromol. 2022;213:1223-42.
6. Valachová K, Šoltés L. Versatile use of chitosan and hyaluronan in medicine. Molecules. 2021;26(4):1195.
7. Hamedi H, Moradi S, Hudson SM, et al. Chitosan based bioadhesives for biomedical applications: A review. Carbohydr Polym. 2022;279:119100.
8. Desai N, Rana D, Salave S, et al. Chitosan: A potential biopolymer in drug delivery and biomedical applications. Pharmaceutics. 2023;15(4):1313.
9. Gao H, Wu N, Wang N, et al. Chitosan-based therapeutic systems and their potentials in treatment of oral diseases. Int J Biol Macromol. 2022;222(PB):3178-94.
10. Li J, Zhuang S. Antibacterial activity of chitosan and its derivatives and their interaction mechanism with bacteria: current state and perspectives. Eur Polym J. 2020;138:109984.
11. Verlee A, Mincke S, Stevens CV. Recent developments in antibacterial and antifungal chitosan and its derivatives. Carbohydr Polym. 2017;164:268-83.
12. Shih PY, Liao YT, Tseng YK, et al. A potential antifungal effect of chitosan against Candida albicans is mediated via the inhibition of SAGA complex component expression and the subsequent alteration of cell surface integrity. Front Microbiol. 2019;10:602.
13. Saeed A, Haider A, Zahid S, et al. In-vitro antifungal efficacy of tissue conditioner-chitosan composites as potential treatment therapy for denture stomatitis. Int J Biol Macromol. 2019 Mar;125:761-6.
14. Gheorghiță D, Moldovan H, Robu A, et al. Chitosan-based biomaterials for hemostatic applications: A review of recent advances. Int J Mol Sci. 2023;24(13):10540.
15. Shao Y, Zhou H. Clinical evaluation of an oral mucoadhesive film containing chitosan for the treatment of recurrent aphthous stomatitis: a randomized, double-blind study. J Dermatolog Treat. 2020;31(7):739-43.
16. Epstein JB, Villines DC, Baker S. Efficacy of a glycopolymer-based oral rinse upon pain associated with ulcerative and erosive lesions of the oral mucosa: A within-subject pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;126(3):240-5.
17. Adhikari HS, Yadav PN. Anticancer activity of chitosan, chitosan derivatives, and their mechanism of action. Int J Biomater. 2018;2018:27-38.
18. Herdiana Y, Wathoni N, Shamsuddin S, et al. Chitosan-based nanoparticles of targeted drug delivery system in breast cancer treatment. Polymers (Basel). 2021;13(11):1717.
19. de Jesus G, Marques L, Vale N, et al. The effects of chitosan on the healing process of oral mucosa: an observational cohort feasibility split-mouth study. Nanomater (Basel, Switzerland). 2023;13(4).
20. Bayer IS. Hyaluronic acid and controlled release: A review. Molecules. 2020;25(11):2649.
21. Iaconisi GN, Lunetti P, Gallo N, et al. Hyaluronic acid: a powerful biomolecule with wide-ranging applications-a comprehensive review. Int J Mol Sci. 2023;24(12):10296.
22. Salwowska NM, Bebenek KA, Żądło DA, et al. Physiochemical properties and application of hyaluronic acid: a systematic review. J Cosmet Dermatol. 2016;15(4):520-6.
23. Graça MFP, Miguel SP, Cabral CSD, et al. Hyaluronic acid-based wound dressings: A review. Carbohydr Polym. 2020;241:116364.
24. Canciani E, Sirello R, Pellegrini G, et al. Effects of vitamin and amino acid-enriched hyaluronic acid gel on the healing of oral mucosa: in vivo and in vitro study. Medicina (Kaunas). 2021;57(3):285.
25. Casale M, Moffa A, Vella P, et al. Hyaluronic acid: Perspectives in dentistry. A systematic review. Int J Immunopathol Pharmacol. 2016;29(4):572-82.
26. Agha-Hosseini F, Pourpasha M, Amanlou M, et al. Mouthwash containing Vitamin E, triamcinolon, and hyaluronic acid compared to triamcinolone mouthwash alone in patients with radiotherapy-induced oral mucositis: Randomized clinical trial. Front Oncol. 2021;11:614877.
27. Tremolati M, Farronato M, Ferrantino L, et al. Clinical performance evaluation of a hyaluronic acid dental gel for the treatment of traumatic ulcers in patients with fixed orthodontic appliances: a randomized controlled trial. Bioeng (Basel, Switzerland). 2022;9(12):761.
28. Rotaru D, Chisnoiu R, Picos AM, et al. Treatment trends in oral lichen planus and oral lichenoid lesions (Review). Exp Ther Med. 2020;20(6):198.
29. Guo Z-X, Zhang Z, Yan J-F, et al. A biomaterial-based therapy using a sodium hyaluronate/bioglass composite hydrogel for the treatment of oral submucous fibrosis. Acta Biomater. 2023;157:639-54.
30. Taskan MM, Balci Yuce H, Karatas O, et al. Hyaluronic acid with antioxidants improve wound healing in rats. Biotech Histochem. 2021;96(7):536-45.
31. Sun B, Zhang M, Shen J, et al. Applications of cellulose-based materials in sustained drug delivery systems. Curr Med Chem. 2019;26(14):2485-501.
32. Avcioglu NH. Bacterial cellulose: recent progress in production and industrial applications. World J Microbiol Biotechnol. 2022;38(5):86.
33. Alven S, Aderibigbe BA. Chitosan and cellulose-based hydrogels for wound management. Int J Mol Sci. 2020;21(24):9656.
34. Horue M, Silva JM, Berti IR, et al. Bacterial Cellulose-Based Materials as Dressings for Wound Healing. Pharmaceutics. 2023;15(2):1-26.
35. Horue M, Cacicedo ML, Fernandez MA, et al. Antimicrobial activities of bacterial cellulose – Silver montmorillonite nanocomposites for wound healing. Mater Sci Eng C Mater Biol Appl. 2020;116:111152.
36. Picheth GF, Pirich CL, Sierakowski MR, et al. Bacterial cellulose in biomedical applications: A review. Int J Biol Macromol. 2017;104(Pt A):97-106.
37. Abdelhamid HN, Mathew AP. Cellulose-based nanomaterials advance biomedicine: a review. Int J Mol Sci. 2022;23(10):5405.
38. Martin P, Nunan R. Cellular and molecular mechanisms of repair in acute and chronic wound healing. Br J Dermatol. 2015;173(2):370-8.
39. Abka-Khajouei R, Tounsi L, Shahabi N, et al. Structures, properties and applications of alginates. Mar Drugs. 2022;20(6):364.
40. Tyagi P, Agate S, Velev OD, et al. A critical review of the performance and soil biodegradability profiles of biobased natural and chemically synthesized polymers in industrial applications. Environ Sci Technol. 2022;56(4):2071-95.
41. Desai N, Jain SP. Alginate microcapsules for drug delivery. Processes. 2021;9(1):137.
42. Gamboa A, Araujo V, Caro N, et al. Spray freeze-drying as an alternative to the ionic gelation method to produce chitosan and alginate nano-particles targeted to the colon. J. Pharm. Sci. 2015;104(12):4373-85.
43. He Q, Tong T, Yu C, et al. Advances in algin and alginate-hybrid materials for drug delivery and tissue engineering. Mar Drugs. 2022;21(1):14.
44. Ahmad A, Mubarak NM, Jannat FT, et al. A critical review on the synthesis of natural sodium alginate based composite materials: An innovative biological polymer for biomedical delivery applications. Processes. 2021;9(1):1-27.

45. Moshaverinia A, Chen C, Akiyama K, et al. Alginate hydrogel as a promising scaffold for dental-derived stem cells: an in vitro study. J Mater Sci Mater Med. 2012;23(12):3041-51.
46. Elango J, Selvaganapathy PR, Lazzari G, et al. Biomimetic collagen-sodium alginate-titanium oxide (TiO(2)) 3D matrix supports differentiated periodontal ligament fibroblasts growth for periodontal tissue regeneration. Int J Biol Macromol. 2020;163:9-18.
47. Mitrano TI, Grob MS, Carrion F, et al. Culture and characterization of mesenchymal stem cells from human gingival tissue. J Periodontol. 2010;81:917-25.
48. Regy RM, Dignon GL, Zheng W, et al. Sequence dependent phase separation of protein-polynucleotide mixtures elucidated using molecular simulations. Nucleic Acids Res. 2020;48(22):12593-603.
49. Papasotiriou I, Beis G, Iliopoulos AC, et al. Supportive Oligonucleotide Therapy (SOT) as an alternative treatment option in cancer: A preliminary study. In Vivo. 2022;36(2):898-906.
50. Chen R, Dong H, Raval D, et al. Sfrp4 is required to maintain Ctsk-lineage periosteal stem cell niche function. Proc Natl Acad Sci U S A. 2023;120(46):e2312677120.
51. Pan W, Yin W, Yang L, et al. Inhibition of Ctsk alleviates periodontitis and comorbid rheumatoid arthritis via downregulation of the TLR9 signalling pathway. J Clin Periodontol. 2019;46(3):286-96.
52. Picciolo G, Mannino F, Irrera N, et al. PDRN, a natural bioactive compound, blunts inflammation and positively reprograms healing genes in an „in vitro" model of oral mucositis. Biomed Pharmacother. 2021;138:111538.
53. Afrasiabi S, Pourhajibagher M, Raoofian R, et al. Therapeutic applications of nucleic acid aptamers in microbial infections. J Biomed Sci. 2020;27(1):6.
54. Li B, Xin Z, Gao S, et al. SIRT6-regulated macrophage efferocytosis epigenetically controls inflammation resolution of diabetic periodontitis. Theranostics. 2023;13(1):231-49.
55. Ahmed N, Gopalakrishna V, Shetty A, et al. Efficacy of PRF vs PRF + biodegradable collagen plug in post-extraction preservation of socket. J Contemp Dent Pract. 2019;20(11):1323-8.
56. Galitsyna EV, Buianova AA, Kozhukhov VI, et al. Cytocompatibility and osteoinductive properties of collagen-fibronectin hydrogel impregnated with siRNA targeting glycogen synthase kinase 3β: In vitro study. Biomedicines. 2023;11(9):2363.
57. Zhang JC, Song ZC, Xia YR, et al. Extracellular matrix derived from periodontal ligament cells maintains their stemness and enhances redifferentiation via the wnt pathway. J Biomed Mater Res A. 2018;106(1):272-84.
58. Friess W. Collagen – biomaterial for drug delivery. Eur J Pharm Biopharm. 1998;45(2):113-36.
59. Fu H, Yang J, Shen Z, et al. Antibacterial, wet adhesive, and healing-promoting nanosheets for the treatment of oral ulcers. Biomater Sci. 2023;11(9):3214-26.
60. Teodora Tihan G, Ungureanu C, Constantin Barbaresso R, et al. Chloramphenicol collagen sponges for local drug delivery in dentistry. Comptes Rendus Chim. 2015;18(9):986-92.
61. Gao Q, Shang Y, Zhou W, et al. Marine collagen peptides: A novel biomaterial for the healing of oral mucosal ulcers. Dent Mater J. 2022;41(6):850-9.
62. Hu Z, Yang P, Zhou C, et al. Marine collagen peptides from the skin of nile tilapia (Oreochromis niloticus): Characterization and wound healing evaluation. Mar Drugs. 2017;15(4):102.
63. Su K, Wang C. Recent advances in the use of gelatin in biomedical research. Biotechnol Lett. 2015;37(11):2139-45.
64. Ebhodaghe SO. A short review on chitosan and gelatin-based hydrogel composite polymers for wound healing. J Biomater Sci Polym Ed. 2022;33(12):1595-622.
65. Cao H, Wang J, Hao Z, et al. Gelatin-based biomaterials and gelatin as an additive for chronic wound repair. Front Pharmacol. 2024;15:1398939.
66. Kozłowska J, Skopińska-Wiśniewska J, Kaczmarek-Szczepańska B, et al. Gelatin and gelatin/starch-based films modified with sorbitol for wound healing. J Mech Behav Biomed Mater. 2023;148:106205.
67. Park CH, Oh J-H, Jung H-M, et al. Effects of the incorporation of ε-aminocaproic acid/chitosan particles to fibrin on cementoblast differentiation and cementum regeneration. Acta Biomater. 2017;61:134-43.
68. Sheikh Z, Hamdan N, Ikeda Y, et al. Natural graft tissues and synthetic biomaterials for periodontal and alveolar bone reconstructive applications: A review. Biomater Res. 2017;21(1):1-20.
69. Wieckiewicz M, Boening K, Wiland P, et al. Reported concepts for the treatment modalities and pain management of temporomandibular disorders. J Headache Pain. 2015;16(1):1-12.
70. Sahoo N, Sahoo RK, Biswas N, et al. Recent advancement of gelatin nanoparticles in drug and vaccine delivery. Int J Biol Macromol. 2015;81:317-31.
71. Liu M, Lin L, Shao M, et al. Decellularized human amniotic particles reinforced with gelma assist wound healing of the oral mucosa in vivo. Mater Express. 2021;11(7):1092-100.

Corresponding author
Emanuela Bis
Student Research Group at the Department of Oral Medicine,
Medical University of Lublin
e-mail: emanuelabis333@gmail.com