

REVIEW ARTICLE

## Current Advancements and Potential Applications of Nanocomposite Hydrogels in Dentistry: A Systematic Review

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### ABSTRACT

Nanotechnology is applied in many scientific domains because it provides a variety of practical answers to scientific and medical problems. This systematic literature review using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method to analyze nanocomposite hydrogels (NCHGs) in dentistry. Based on the results of a literature review study on 40 articles, NCHGs have the potential for antibacterial agents, tissue engineering, drug delivery systems, dental materials, etc. The present review aims to provide a depth analysis of NCHGs, impart on the recent advancement in the scope of dentistry, and discuss their applications. Understanding of the principles of NCHGs, their strengths and limitations as well as their specific benefits.

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## INTRODUCTION

Nanotechnology is applied in many scientific domains because it provides a variety of practical answers to scientific and medical problems. Most research in the last few years has focused on nanoparticles. This shows that nanotechnologies and understanding of the characteristics of materials at nanoscales are in high demand. Nanotechnologies operate on dimensions less than 100 nm (1). Because of their nanoscale size, nanoparticles have a high surface area, volume-to-volume ratio, allowing them to absorb large amounts of medication and move fast through the bloodstream (2). Nanotechnology provides increased therapeutic efficacy, a larger specific surface area, more flexibility in surface functionalization, lower toxicity, better passive targeting, responsiveness to stimuli, and improved bioavailability (3).

Nanotechnology has a wide range of uses in

dentistry, including preventive dentistry, dental diagnostics, dental materials, conservative and aesthetic dentistry, endodontics, periodontics, implantology, regenerative dentistry, prosthodontics, and nanoproducts (4). Nanotechnology in dentistry has made some advancements. The increased demand for esthetic restorations has led to increased development of products that are the same color as teeth in recent years. Composite nanoparticles are one type of nanotechnology frequently utilized in dentistry. Artificial nanocomposite teeth are more abrasion-resistant and stable than acrylic and composite microfill teeth, according to research. Dental diagnostics may be more effective and of higher quality as a result of nanomedicine. Very few research and therapeutic strategies have been reported in nanotechnology on the diagnosis of dental disorders (5).

The latest breakthroughs in dental materials are biomaterials, nanoparticle drug delivery, scaffolds,

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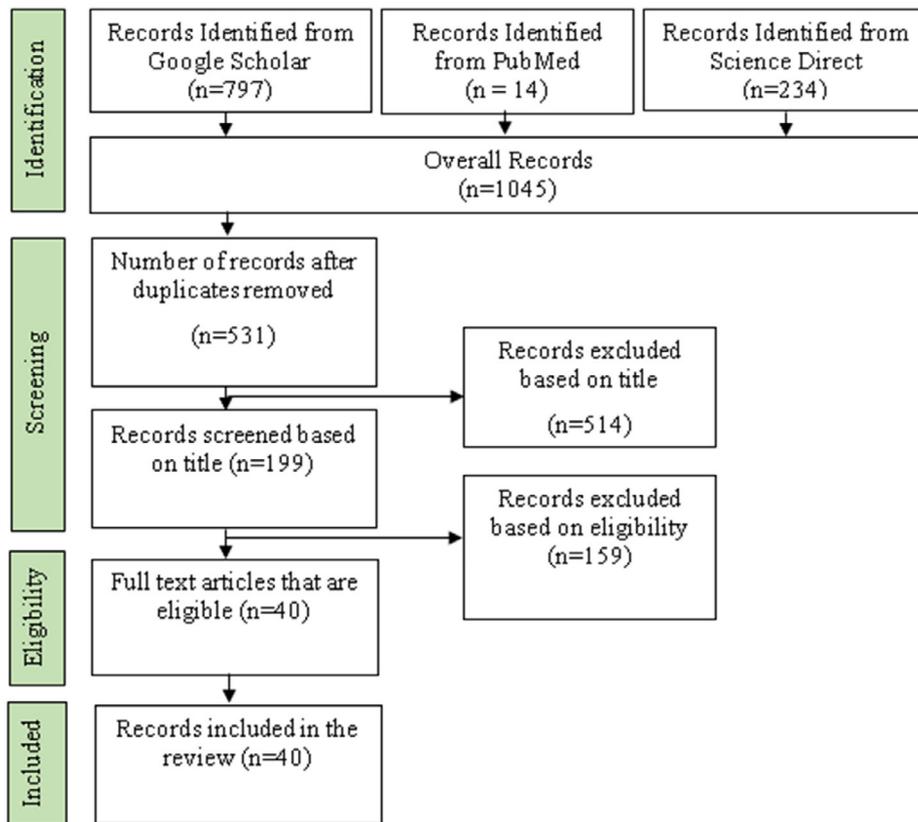


Diagram 1. PRISMA diagram flow

conductive polymers, hydrogels, polymer blends, composites and nanocomposites, nanoceramics, nanofibers, membranes, nanofilms, nanotubes, and nanorods (6). Hydrogel is a three-dimensional network structure made up of hydrophilic polymer chains that are crosslinked physically, chemically, or by polymerization (7). NCHGs are the result of the combination of existing hydrogel components and nanometer-sized fillers, which often results in improved mechanical properties or new capabilities. Recent discoveries have emphasized that this kind of hydrogel shows tremendous potential for utilization in various biomedical and engineering science due to its ease of design and synthesis. The intricate design and analysis of NCHGs, as well as their appropriate application, necessitate the collaboration of mechanics, materials, engineering, and biology. NCHGs have been employed in a wide range of biomedical and engineering science applications, including sensors, actuators, conductors, coatings, medication delivery, wound healing, tissue engineering, and antimicrobials. Many biological applications demand the usage

of NCHGs because to their superior mechanical characteristics and dynamic connection with cellular surroundings (8). The purpose of this study is to offer a thorough understanding of current NCHG knowledge, to impart on recent advancements in the field of dentistry, and to explore their applications.

## METHOD

This systematic review was written by using electronic search in PubMed, Science Direct, and Google Scholar online library databases. The selection was carried out using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) method. Search articles using the keywords “nanocomposite”, “hydrogel” and “dentistry”, “periodontal”, “endodontic”, “oral medicine”, “alveolar bone”.

The articles were selected by using the inclusion/exclusion criteria. The inclusion criteria used for the articles in this systematic review were articles written in English, original research studies published between 2019 to 2023, articles that can be

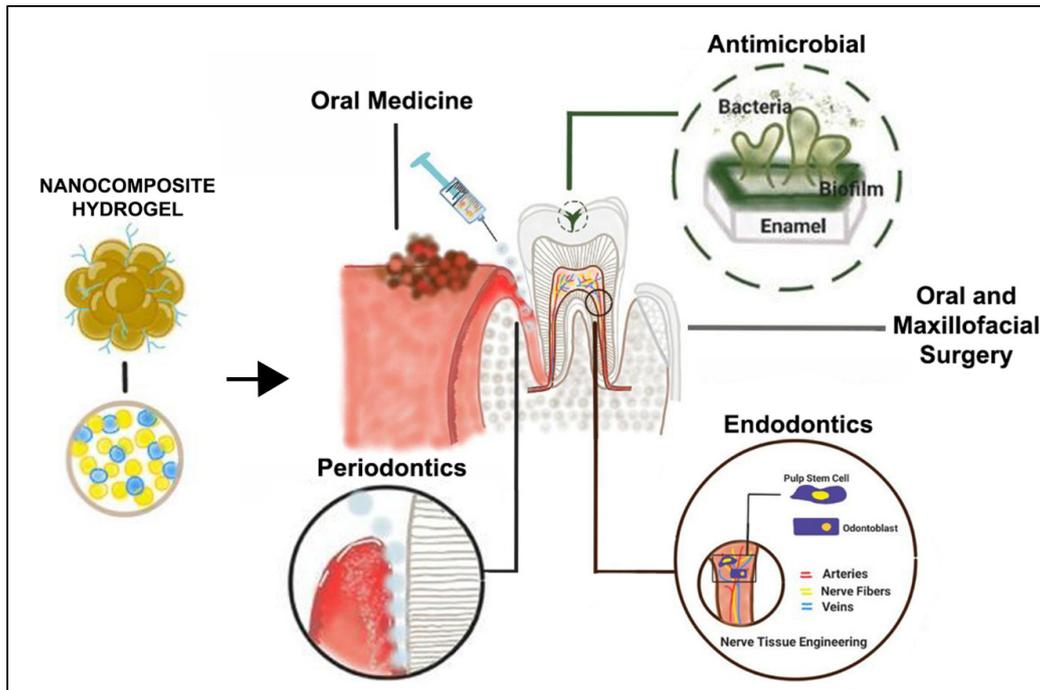


Fig. 1. Potential Application of Nanocomposite Hydrogel

accessed in full text, and articles that were related to the discussion of NCHG in dentistry. Articles written in languages other than English, articles that were published under 2019, articles can not be accessed in full text form, journals from databases that have nothing to do with research discussions, and theses, books, review articles or not original research paper were excluded from this study.

## RESULT

The initial search obtained 1045 articles. The inclusion/exclusion criteria were then applied to all of the studies found through literature search. After the selection of the articles, it gains 40 articles that were suitable within the criteria.

## DISCUSSION

### *Potential Applications of NCHGs Oral and Maxillofacial Surgery*

Hydrogels are a promising biomaterial for bone tissue engineering (BTE), ranging from naturally generated materials to synthetically derived materials (9). From the results of the systematic review, there are 26 journal articles (table 1) of various NCHG that have been used in tissue engineering and anesthesia.

Autogenous and allogenic bone grafts are

commonly used as first-line therapies for bone. But there are limitations to their usage, including donor-site morbidity, availability, and ethical issues. To overcome these, a variety of biomaterials have been developed for bone therapies, one of them is hydrogel (30). Hydrogels are frequently used as depots for targeted drug delivery and tissue engineering applications because of its biocompatibility, adjustable network property, and significant water content (9). Several studies have shown that hydrogels also can be used as scaffolds (20). Scaffold-hydrogels systems are an interesting approach because they combine the advantages and shortcomings of hydrogel and scaffolds, whereas the low mechanical properties of hydrogels can fail under heavy loads in native bone and harder porous scaffolds do not provide a native-like environment for cells to thrive in. For the purpose of the replication of hard, bone-like tissues, this scaffold-hydrogel system ought to be in the forefront of the research (20)(23). There are many articles that have incorporated various materials into hydrogel which shows increasing superiority and advantage for BTE. One of the most often utilized bioceramic materials is nHA (13)(15). Pan *et al* used a composite scaffold of hydrogel/hydroxyapatite (GH) stent for aesthetic alveolar site preservation.

Table 1. NCHGs and its application in oral and maxillofacial surgery.

Material	Application	Method	Ref
Graphene Oxide, Chitosan (CS), $\beta$ -glycerophosphate (GP) thermosensitive hydrogel	Anesthesia bupivacaine hydrochloride (BH)	<i>In vitro</i> and <i>in vivo</i>	(10)
Hydrogels, graphene oxide/reduced graphene oxide (GO/rGO), aloe vera gel	Tissue engineering and antibacterial	<i>In vitro</i> and <i>in vivo</i>	(11)
Chitosan, alginate, hydroxyapatite	Craniofacial bone	<i>In vitro</i> and <i>in vivo</i>	(12)
Hyaluronic acid (HA), N-Carboxyethyl Chitosan, Aldehyde synthesized, Nano-Hydroxyapatite powder	Bone tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(13)
Titania/Hydroxyapatite-Promoted Biomimetic Alginate-Chitosan-Gelatin	Bone tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(14)
Alginate-Gelatin, Hydroxyapatite containing hDPSCs	Bone tissue engineering	<i>In vivo</i>	(15)
Hyaluronate-polyacrylamide (poly(Hya-AAm)), Carbonated hydroxyapatite (CCaHAp)	Bone tissue engineering	<i>In vitro</i>	(16)
Hydroxylapatite, laponite, alginate	Bone Augmentation	<i>In vitro</i> and <i>in vivo</i>	(17)
Dendrimer (G3)-functionalized nanoceria (G3@nCe) and Gelatin Methacryloyl (GelMA)	Bone tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(18)
Metformin-loaded mesoporous silica nanospheres (MF-MSNs)-laden gelatin methacryloyl (GelMA)	Maxillofacial defect regeneration	<i>In vitro</i>	(19)
hyaluronic acid methacryloyl (HAMA) and MXene-incorporated gelatin methacryloyl (GelMA)bioinks	Bone tissue engineering	<i>In vitro</i>	(20)
Sr-containing mesoporous bioactive glass nanoparticles (Sr-MBGNs) and gelatin methacrylate (GelMA)	Bone regeneration	<i>In vitro</i> and <i>in vivo</i>	(21)
GelMA and bioactive glass (BG)	Bone tissue engineering	<i>In vitro</i>	(22)
Soft nano silicate phase and a harder mineral-based phase made from BG	Bone tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(23)
OSA-dopamine-modified gelatin (GelDA) @amorphous calcium phosphate (ACP)/DA/Silver (Ag)	Adhesive bone repair	<i>In vitro</i>	(24)
Natural-based gelatin and synthetic-based (poly D, L (lactide-co-glycolide)-b- poly (ethylene glycol)-b-poly D, L (lactide-co-glycolide) (PLGA-PEG-PLGA) triblock copolymer was developed and loaded with transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1)	Cartilage bone tissue engineering	<i>In vitro</i>	(25)
Magnetic nanoparticles (MNPs) into polyethylene glycol (PEG)	Bone tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(26)
miRNA-activated hydrogel scaffolds (MAHSs)	Bone tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(27)
Aldehyde functionalized cellulose nanocrystals (a-CNC) and Platelet lysate (PL)	Hemostasis application	<i>In vitro</i> and <i>in vivo</i>	(28)
Gelatin, commercial microcrystalline cellulose (MCC), hydrochloride lidocaine, distilled water, buffer phosphate solution.	Anesthesia lidocaine	<i>In vivo</i>	(29)
Feather keratin-montmorillonite	Bone tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(30)
Carrageenan hydrogel Dimethylxalylglycine	Osteogenesis and angiogenesis	<i>In vitro</i>	(9)
Methylcellulose (MC), bassorin (Ba), and halloysite nanotubes (HNTs)	Bone specific gene expression	<i>In vitro</i>	(31)
3D electroconductive multi-walled carbon nanotube/cobalt composites methacryloyl hydrogel (Gel- MA-MWCNTs/Co)	Nerve tissue engineering	<i>In vitro</i>	(32)
Berberine (Ber)-loaded Cs nanoparticles (NPs), Chitosan (Cs)/Alginate (Alg), and Naringin (Nar)-loaded Cs NPs	Nerve tissue engineering	<i>In vitro</i> and <i>in vivo</i>	(33)

This study showed that nHA can improve collagen fiber strength, promote bone formation, and aid in the deposition of calcium ions (13). Chen *et al* also used HAp hydrogels scaffold and the results showed that HAp can improve scaffold mechanical properties, cell adhesion, and proliferation capacity (14). Compared to HA, Ghobashy *et al* analyzed that CcHAp has more improved osteogenic ability because it closely reflects the chemical composition of apatite (16). Furthermore, there is another way of hydrogels application that was shown by Li *et al* whereas they developed subperiosteal injectable HAp/Lap/alginate NCHGs to increase bone augmentation (17). Injectable hydrogels method shows great benefit due to their minimal invasive nature and ability to fill irregular-shaped damages. Another study that used injectable hydrogels is Varshosaz *et al* by using thermosensitive methylcellulose hydrogels containing Ba and HNTs for bone repair (31). Chitosan also has promising properties in BTE but has poor printability limits. To overcome this, Yousefiasl *et al* developed chitosan-based hydrogel combined with alginate and hydroxyapatite (12).

Another material that is mentioned in the table is BG. BG is a type of ceramic material that may be manipulated to produce bioactive and biocompatible conditions for BTE (23). Sadeghian *et al* stated that BG nanoparticles increased in vitro bioactivity, cell proliferation, and ALP activity (22). As mentioned before, hydrogels have poor mechanical properties, a study by Ke *et al* showed that combining montmorillonite into hydrogels can improve their mechanical characteristics and bioactivity (30).

GO/rGO nanoparticles possess unique structural features, including water dispersibility and interaction with protonated polymers like CS (10). Their robust structure enhances hydrogel properties and antibacterial activity (11). GO/rGO exhibits excellent near-infrared photothermal properties, making it a promising therapeutic approach for wound healing and drug transport (34). Eltahir *et al*, shows stimuli-responsive hydrogels transform from sols to gels, enabling injectable drug-loaded thermosensitive hydrogels to form drug depots in target tissues by mixing CS and GP (10).

GelMA hydrogels, a naturally derived gelatin-based resemble native bone extracellular matrix (ECM), have good flexibility, controllable characteristics, low-toxicity, biodegradable, and

enzymatic disintegration (18)(19). While various GelMA nanocomposites have a great role in BTE, many of them lack ROS scavenging characteristics. Kurian *et al* offer an innovative approach by developing G3@nCe/GelMA hydrogel that can promote new bone growth in vivo, modulating cellular responses, and upregulating several genes associated with osteogenesis (18). In Xu *et al* and Lee *et al* studies, GelMA is also act as a bioink as one of the primary materials used to produce three-dimensional (3D) bioprinting technology to construct BTE scaffolds (21)(20). Another study that used 3D printed technology showed that MAHSs can promote osteoblastic differentiation and cause osteogenesis in vivo due to the presence of miRNAs (27).

There are many studies of NCHG incorporating metal nanoparticles (35). Zhong *et al* used hydrogel OSA-GelDA@ACP/DA/Ag<sub>3</sub> as an adhesive bone repair (24). TiO<sub>2</sub> NPs has been shown to influence the swelling properties, increase the hydrophilicity, mechanical properties and biomineralization ability of composite hydrogels (14). Natural polymers-based hydrogels also show high potential as biomaterials for neural tissue engineering. Ebrahimi *et al*, reported that hydrogel-based biomaterials using chitosan/alginate containing both Ber- and Nar-loaded Cs NPs induce axon regeneration and extension, remyelination of nerve fiber, and cell adhesion, (33). Study by Liu *et al* stated that 3D electroconductive multi-walled Gel-MA-MWCNTs/Co are suitable for enhancing the neural differentiation of the Stem Cell Apical Papilla (SCAP) by releasing  $Co^{2+}$  indefinitely, greatly increasing HIF-1 and VEGF expression, and boosting angiogenic ability (32). Ghandforoushan *et al* stated that gelatin/PLGA-PEG-PLGA combination that contains TGF-1 were viable functional choice for in vitro cartilage regeneration (25).

Fillipi *et al* stated that tissue engineering often fails because of the lack of vascularization. To solve these issues, Fillipi *et al* generated unique magnetized NCHGs. This study shows that magnetic actuation can stimulate the osteoblastic and vasculogenic potentials of engineered bone tissue grafts, possibly at least in part by mechanically stimulating the function of progenitor cells (26). Another study showed that an injectable carrageenan NCHG containing whitlockite nanoparticles and DMOG have both angiogenic and osteogenic properties (9). Another ability of

Table 2. NCHGs and its application in periodontics.

Material	Application	Methods	Ref
Gold nanoparticle-loaded hydrogel with NIR-activated tea polyphenol modification	Reduced periodontal inflammation	<i>In vitro and in vivo</i>	(37)
Injectable NCHG by integrating dexamethasone-loaded zeolitic imidazolate frameworks-8 (DZIF) nanoparticles into the photocrosslinking matrix of methacrylic poly-phosphoester (PPEMA) and GelMA	Reduced periodontal inflammation	<i>In vitro and in vivo</i>	(38)
Poly- $\gamma$ -glutamic acid (PGA, MW = $1.2 \times 10^6$ Da, from GPC), water-soluble 1-[3-(dimethylamino) propyl]-3-ethyl carbodiimide hydrochloride (EDC), 2,2'-(Ethylenedioxy) bis(ethylamine) (98%) (EDA) & 2-aminoethyl methacrylate hydrochloride (95%) (AEM), metronidazole (Metr) (98%) & chlorhexidine digluconate solution (CHX) (20%).	Periodontitis treatment	<i>In vitro</i>	(39)
Carbonated hydroxyapatite (CHA)-agarose- $\epsilon$ -poly-lysine ( $\epsilon$ -PLL) to create asymmetric barrier membranes from polysaccharides	Periodontal tissue engineering	<i>In vitro and in vivo</i>	(40)

NCHG material is for hemostasis application. This is shown by Mendes *et al* who show an intrinsically bioactive hemostatic cryogel based on PL-CNC as a source of signaling biological components and as a hemostatic biomaterial (28). The other material, namely Graphene oxide, also takes part as a hemostatic biomaterial (36).

Dental treatments often require multiple doses of local anesthesia, leading to pain and discomfort. Gelatin and cellulose biopolymers have been studied for biomedical applications. A thawing-freezing approach was used to create gelatin-based hydrogels with gum Arabic as a crosslinking agent. The integration of cellulose nanowhiskers (NC) was investigated to control hydrogel solubility, swelling properties, and loading anesthetic medicines. The hydrogels loaded with lidocaine (LID) could be used as raw materials for buccal patches to reduce the use of injectable anesthetics during dental treatments (29).

The studies on NCHG in BTE shown in Table 1 have good compatibility with tissue and cells, osteoconductive activity, and osteoinductive activity. However, the majority of the study on hydrogels in BTE is still in the experimental stage, but there is great potential that these materials may be used in clinical treatment in the future with further research and development.

#### Periodontics

Current research explains a novel multifunctional NCHG, which can reduce and treat inflammation in the periodontal tissues. Research by Dong *et al*, Li *et al*, and Bako *et al* explained that NCHG can

remove biofilm plaques that cause inflammation thereby helping bone regeneration and treating periodontal inflammation (37)(38)(39). He, *et al*, study used NCHG as a barrier membrane which has advantages in osteoconductivity and antibacterial properties, showing its potential for periodontal tissue engineering (40).

As a result of E-Au@H's strong photothermal capability, by suppressing bacteria, decreasing inflammation in periodontal tissues by local heating, and encouraging the discharge of EGCG, E-Au@H under NIR irradiation stimulates alveolar bone repair (37). DZIF hydrogels can reduce the production of inflammatory factors in cells and shield BMSCs from an inflammatory microenvironment. The healing of alveolar bone defects has also been observed to be moderately aided by GelMA and PPE. Due to the combination of its antibacterial and anti-inflammatory factors, the NCHGs are promised to be useful for resolving complex periodontal disorders (38). NCHGs prepared by photopolymerizable MPGA and PGA-MNP represent an alternative route of administration for drugs used for dental treatment. Periodontal inflammation caused by bacterial colonies can be opposed with the use of biocompatible and biodegradable materials and their pH-dependent release properties along with short-term blue light activation (39). The barrier membrane exhibits improved biocompatibility and enhanced mechanical qualities with the addition of a higher dose of CHA. The osteoconductivity and antibacterial qualities of the membrane were established in vitro and in vivo by He *et al* in 2021

Table 3. NCHGs and its application in Oral Medicine

Material	Application	Methods	Ref
Fe <sub>3</sub> O <sub>4</sub> magnetic nanoparticles (MNPs) containing (3-amino propyl) triethoxy silane (APTES) coated with Chitosan (CS) & Tragacanth Gum (TG) to encapsulate curcumin.	Drug delivery of Chemotherapeutic drugs	<i>In vitro</i>	(41)
Tragacanth Gum (TG)-lecithin (LC) nano gels with cisplatin (CP) loading	Drug delivery for anti-cancer	Not stated	(42)
Nano glass powder-injectable hydrogel	Drug delivery for anti-malignant tumor	Not stated	(43)
BGN & BGN-Fe BGN, BGN-Fe-Ag <sub>2</sub> S (BFA), PBFA	Inhibit tumor proliferation & overcome tissue bacterial infection	<i>In vitro and in vivo</i>	(44)

Table 4. NCHGs and its applications in endodontics.

Material	Application	Methods	Ref
Boron (B) modified bioactive glass nanoparticles (BG-NPs) made of cellulose acetate/oxidized pullulan/gelatin (CA/ox-PULL/GEL) three-dimensional scaffolds with tubular morphology	Dentin regeneration	<i>In vitro</i>	(45)
Human endometrial stem cells (EnSCs) & titanium oxide nanoparticles (TiO <sub>2</sub> NPs)	Dentin regeneration, dental pulp repair	<i>In vivo</i>	(46)
Clindamycin (CLIN)-loaded Poly (D,L) Lactic Acid (PLA) nanoparticles (NPs)	Dentin-pulp reconstruction/regeneration	<i>In vitro</i>	(47)
Dentin extracellular matrix, GelMA, BG	Pulp regeneration	<i>In vitro</i>	(48)

(40). Overall, the research on NCHGs suggests that they have promising potential in treating periodontal inflammation and promoting bone regeneration. Further studies are needed to explore their efficacy and safety in clinical settings.

#### Oral Medicine

The four experiments have the same goal in the use of NCHG as a drug delivery system in the treatment of malignant cases. Shafiee *et al* and Verma *et al* considering the pH conditions (41) (42). Wu *et al* in the manufacture of NCHG-based materials has not reached the *in vitro* and *in vivo* stages so further research is needed (43). According to research by Huang *et al* PBFA hydrogel + NIR could suppress the growth of the tumor (44).

The results show of potential Fe<sub>3</sub>O<sub>4</sub>@APTES/CS/TG nanocomposite system as a drug carrier with good controlled-release in pH and temperature sensitive environments. Shafiee, *et al.* 2019 observed that only the nanocomposite showed better release at higher temperatures and at lower pH. It is known that many pathological activities, such as inflammation or tumor experiences a local increase in temperature (by 2–5 °C) or a decrease in pH (1–2.5 pH units), as

a result, it can be used to achieve better targeting and treatment (41). The unique feature of nTG-LC nano gels containing TP can be used as reference material in drug delivery systems, especially anti-cancer therapy (42). The sol-gel approach can take advantage of lower temperatures and offer well-defined particles that open new pathways to synthesize functional biocompatible glasses that can be used in self organizing injectable hydrogel applications with well-controlled properties (43). Huang *et al*, confirmed the potency of PBFA hydrogel to inhibit tumor cell proliferation due to the CDT effect of BGN-Fe. The tumor volume of the PBFA + NIR group drastically decreased significantly during the initial 6 days. After 3 times of phototherapy, the tumors of group 4 gradually disappeared without recurrence in the next 8 days of monitoring. This indicates that the integration of PBFA hydrogel with 808 nm laser could restrain tumor growth during 14 days of treatment (44). The four experiments suggest that NCHG has potential as a drug delivery system in the treatment of malignant cases, and further research is required because there is still a small amount of data on the benefits and application of NCHG in this field to explore its full potential.

Table 5. Antimicrobial effects of NCHGs

Material	Type of Antimicrobial Test	Types of Microorganisms that were Tested	Result	Ref
Thermosensitive hydrogel loaded with biosynthesized silver nanoparticles using <i>Eucalyptus camaldulensis</i> leaf extract (bio-AgNPs)	Broth dilution method following Clinical and Laboratory Standards Institute guidelines. Antibiofilm assay by crystal violet assay followed by with confocal laser scanning microscopy.	Gram-positive bacteria (Staphylococcus aureus, Staphylococcus epidermis, Enterococcus faecalis), Gram negative bacteria (Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa), Fungi (Candida albicans), Biofilm (Candida albicans, A. baumannii, E.coli, K. pneumonia, P. aeruginosa)	The minimum inhibitory concentration (MIC) and minimum bactericidal concentration of Gram-positive and Gram-negative bacteria values ranged from 1.09 to 17.5 g/mL and 2.19->35 g/mL, respectively. The MIC and minimum fungicidal concentration of <i>Candida albicans</i> values of 4.38 and 8.75 g/mL, respectively.  The proportion of biofilm inhibition in pathogens such as <i>Candida albicans</i> , <i>A. baumannii</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , and <i>P. aeruginosa</i> at ½ MIC was as high as 83%. However, biofilm formation in methicillin-resistant <i>S. aureus</i> and <i>S. epidermidis</i> was not suppressed by the hydrogel formulation at 1/8MIC, and biofilm formation in <i>P. aeruginosa</i> was identified following treatment with 1/8MIC and 1/ 4MIC values. The CLSM showed that after 24 hours of exposure to the hydrogel formulation at 1/2MIC, the biofilm biomass fell considerably while cell death remained unaltered.	(35)
Amorphous Calcium Phosphate-Dopamine Modified gelatin-AgNP composite hydrogel	Agar plate method using LB in vitro and the bacteriostatic ring and the bacterial growth inhibition zone were evaluated.	<i>E. coli</i> and <i>S. aureus</i>	The diameter of the bacteriostatic ring grows as the ACP/DA/Ag3 particle load increases, and in comparison, there is no bacteriostatic ring around the hydrogel without ACP/DA/Ag3 particles. The diameter of the bacteriostatic ring was not specified by the authors.	(24)
NIR-triggered tea polyphenol-modified gold nanoparticles-loaded hydrogel	Agar plate method using LB in vitro and the bacteria colony were counted, each group was repeated 3 times. Scanning electron microscopy was used to examine the bacteria's morphology. <i>S. aureus</i> biofilm model was used to evaluate the anti-biofilm ability, the biofilm was stained with crystalline violet, and the absorbance was measured at 590 nm using a microplate reader.	<i>E. coli</i> , <i>S. aureus</i> , & <i>S. aureus</i> biofilm	The NIR light increased the antibacterial efficacy of the composites, with 92% and 94% antibacterial rates against <i>E. coli</i> and <i>S. aureus</i> , respectively. The E-Au@H + NIR group reduced <i>S. aureus</i> biofilm more than the other treatment groups.	(37)
Light-activated injectable hydrogel based on bioactive Ag <sub>2</sub> S nanodots conjugated Fe-doped bioactive glass nanoparticles (BGN-Fe-Ag <sub>2</sub> S) into biodegradable PEGDA and AIPH solution	Agar plate method using LB in vitro and the antibacterial performance was evaluated using turbidity and plate colony-counting techniques, followed by SEM analysis. Adult ICR female mice were used to evaluate in vivo healing of MRSA-infected lesions.	Drug-resistant <i>Staphylococcus aureus</i>	The PBFA + NIR and PA + NIR treated groups showed a great sterilizing effect, and the mice in these groups had hardly any bacterial contamination. PBFA hydrogel and NIR co-treatment effectively killed bacteria in bacteria-infected wounds.	(44)

Continued Tabel 5. Antimicrobial effects of NCHGs

Material	Type of Antimicrobial Test	Types of Microorganisms that were Tested	Result	Ref
NCHG using Graphene Oxide/reduced Graphene Oxide nano particle-based aloe vera	Agar Well diffusion antibiotic sensitivity assay and the antibacterial measured using zone of inhibition (mm)	<i>P. aeruginosa</i> , <i>Bacillus subtilis</i> , <i>S. aureus</i> , & <i>E. coli</i>	Aloe vera gel + rGO has the largest zone of inhibition of <i>P. aeruginosa</i> (15,75 mm), <i>E. coli</i> (13,27 mm). Hydrogel alone has the highest zone of inhibition <i>B. subtilis</i> (10,01 mm), <i>S. aureus</i> (12,56 mm). rGO conjugated in aloe vera gel showed a greater activity followed by rGO in hydrogel.	(11)
Injectable NCHG by incorporating dexamethasone-loaded zeolitic imidazolate frameworks-8 (DZIF) nanoparticles into the photocrosslinking matrix of methacrylic polyphosphoester (PPEMA) and methacrylic gelatin (GelMA)	In vitro antibacterial capacity evaluation using BHI agar plates. Biofilm disruption quantity by the crystal violet method. Live/dead bacteria analysis Visualization of biofilm formation using SEM	<i>S. mutans</i> & <i>P. gingivalis</i>	The zones of inhibition in two sets of nano-composite hydrogels were $2.1 \pm 0.2$ mm (ZIF@PGel) and $1.8 \pm 0.2$ mm, respectively. The antibacterial activity of hydrogels containing nanoparticles was superior to that of a single PGel hydrogel.	(38)
Fibrin hydrogel incorporating clindamycin (CLIN)-loaded Poly (D,L) Lactic Acid (PLA) nanoparticles (NPs)	Broth microdilution method using BHI agar plates MBIC <sub>50</sub> and MBEC <sub>50</sub> were estimated by measuring <i>E. faecalis</i> biofilm density after crystal violet staining.	<i>E. faecalis</i>	The results of the agar diffusion experiment amply shown that the hydrogel-incorporated CLIN-PLA-NPs effectively suppressed <i>E. faecalis</i> growth in a manner comparable to that of free CLIN at a concentration of $50 \text{ mgmL}^{-1}$ . The MBIC <sub>50</sub> for <i>E. faecalis</i> biofilm was found to be $4 \text{ mgmL}^{-1}$ for CLIN-PLA-NPs and free CLIN. The MBEC <sub>50</sub> was found to be $16 \text{ mgmL}^{-1}$ for CLIN-PLA-NPs and free CLIN, whereas PLA-NPs did not affect the biofilm.	(47)
Asymmetric Barrier Membranes Based on Polysaccharide using carbonated hydroxyapatite (CHA)-agarose- $\epsilon$ -poly-lysine ( $\epsilon$ -PLL) Micro-NCHG	In vitro antibacterial assay using trypticase soy broth (TSB) and Luria-Bertani (LB) medium, followed by evaluating the optical density and inhibition zone In vivo using rat subcutaneous infection model.	<i>E. coli</i> & <i>S. aureus</i>	All barrier membranes containing -PLL had effective and enduring antibacterial activities against <i>S. aureus</i> and <i>E. coli</i> . In the APC-10 groups, the number of <i>S. aureus</i> colonies was significantly lower ( $P < 0.001$ ) than in the control group.	(40)
AgNP/Alginate NCHG	Antibacterial assay using tryptic soy broth, following with evaluation of minimum bactericidal concentration (MBC) Biofilm susceptibility assays, following by SEM and CLSM techniques	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>S. mutans</i> , <i>S. mitis</i> , <i>E. faecalis</i> , & <i>S. gordonii</i>	MBC of AgNP was found $25 \text{ g g}^{-1}$ and a time-dependent death kinetic was discovered during a 180-minute period. On biofilms of Gram positive and negative bacteria, the AgNP alginate gel demonstrated considerable cell death, with the lowest level of killing being 44% for <i>S. aureus</i> and the greatest being 61% for <i>E. coli</i> .	(50)
AgNP/PEG-Based Hybrid Nanocomposite Hydrogels	Disk diffusion method using McFarland standard suspensions on the Muller-Hinton agar plates.	<i>E. coli</i> & <i>S. aureus</i>	On solid medium, bacteria were contacted with all hybrid hydrogel samples (100 mg, 5 mm in diameter). While all of the produced nanocomposites exhibit reasonable antibacterial effects on <i>S. aureus</i> and <i>E. coli</i> (range from 10 to 18 mm), they are all less effective than the control drug gentamicin (21 and 22 mm, respectively).	(51)

Continued Tabel 5. Antimicrobial effects of NCHGs

Material	Type of Antimicrobial Test	Types of Microorganisms that were Tested	Result	Ref	
AgNP/PEG-Based Hybrid Nanocomposite Hydrogels	broth, following with evaluation of minimum bactericidal concentration (MBC) - Biofilm susceptibility assays, following by SEM and CLSM techniques	- - - - - gordonii	P. aeruginosa, Strep. mutans, Strep. mitis, E. faecalis, Strep.	discovered during a 180-minute period. On biofilms of Gram positive and negative bacteria, the AgNP alginate gel demonstrated considerable cell death, with the lowest level of killing being 44% for S. aureus and the greatest being 61% for E. coli.	(51)
	- Disk diffusion method using McFarland standard suspensions on the Muller-Hinton agar plates.	- -	E. coli, S. aureus	On solid medium, bacteria were contacted with all hybrid hydrogel samples (100 mg, 5 mm in diameter). While all of the produced nanocomposites exhibit reasonable antibacterial effects on S. aureus and E. coli (range from 10 to 18 mm), they are all less effective than the control drug gentamicin (21 and 22 mm, respectively).	

### Endodontics

Rad *et al* and Hoveizi *et al*, studies demonstrated the involvement of a novel multifunctional NCHG both in scaffold form and its utility for dentin regeneration. The porosity of NCHG can create excellent mechanical strength required during endodontic treatment (45)(46). Beckhouche *et al* is also constructing a fibrin hydrogel nanocomposite scaffold equipped with CLIN-loaded PLA-NPs to provide the needed aseptic environment for DP regeneration. The hydrogels are still in process of specifying the proportion of NPs that accumulate along the dentin wall and permeate into the micrometer-sized dentinal tubules (47). One of the important features of hydrogels in tissue engineering compared to prefabricated scaffolds is their gelation ability with sufficient vigor at the expected location. This advantage was used by Sadeghian *et al* in his research to obtain the result that the characterization of the novel Gel-BG/dECM hydrogel has good mechanical performance and is useful in future dentin pulp regeneration (48). These studies highlight the potential of novel scaffolds and hydrogels for dentin regeneration, which could have significant implications for endodontic treatment and dental health. Further research is needed to fully understand the properties

and potential applications of these materials.

### Antimicrobial

Composite hydrogels can be made as antimicrobial agents. Composite hydrogels have the ability to covalently or physically bind a variety of antimicrobial compounds, including antibiotics, antimicrobial peptides, biological components, polysaccharides, AMPs, and nanoparticles (NPs). Composite hydrogel can resolve the problems generated by standard drug administration due to toxicity, repeated administration, or high dosage(49). In the last 5 years, many researchers have created new NCHG materials that have good antimicrobial effects. The following is an overview of several types of NCHG that exhibit antimicrobial actions against some microorganisms based on the findings of the systematic review.

As shown in Table 5, NCHGs show antimicrobial efficacy against certain Gram-negative and Gram-positive bacteria, fungi, and biofilms. There are many NCHGs incorporating silver nanoparticles to gain the antibacterial effect. Silver nanoparticles (AgNPs) are broad-spectrum antibacterial agents that may hold promise as antibiofilm agents (35). In this review, we found ten articles using AgNP in their NCHG for antimicrobial agents. We also

found two articles using herbal ingredients in the NCHGs, which are epigallocatechin gallate (EGCG) from green tea leaf extract combined with gold nanoparticles and aloe vera gel combined with graphene oxide/reduced graphene oxide (37) (11). There are two journals that use manufactured drugs to be incorporated into NCHG materials: fibrin hydrogel incorporating clindamycin-loaded Poly Lactic Acid nanoparticles for human dental pulp engineering and dexamethasone-loaded zeolitic imidazolate frameworks in the NCHG for periodontitis treatment (38)(47). There is also one journal that used polysaccharide-based asymmetric barrier membrane employing a carbonated hydroxyapatite-agarose-e-poly-lysine hydrogel micro-nanocomposite, which has antibacterial and osteoconductive properties (40).

Table 5 reveals that the NCHG materials have a relatively excellent antibacterial effect. NCHG materials research is currently limited to in vivo and in vitro studies. NCHG materials must be further developed to the clinical research stage before they can be used in clinical dentistry practice. Not all studies focused on evaluating oral bacteria; more research on the antimicrobial impact of oral microbes is required if the NCHGs are applied in dental practice.

## CONCLUSION

NCHG in dentistry has been applied in the field of oral and maxillofacial surgery, periodontics, endodontics, and oral medicine. NCHG can be applied in bone and neural tissue engineering. Various NCHGs have demonstrated remarkable osteogenic activity, and some of them also showed significant angiogenic activity. NCHGs are a prospective property in BTE because of these characteristics. On the other hand, NCHG is also proven to enhance anesthesia properties. In the field of periodontics, NCHG is used as a treatment for periodontitis and reduces periodontal inflammation. In some malignant situations, NCHG is also thought to be useful for medication delivery as an excellent controlled-release drug carrier. In endodontic therapy, NCHG helps dentin-pulp regeneration because it has the advantage of mechanical performance. NCHG possesses strong antibacterial properties against both gram-positive and gram-negative bacteria, biofilms, and fungi. Moreover, with the increasing interest in NCHG, we believe that a noteworthy strategy in future research, regulation, and standardization of novel

NCHGs must be developed in the field of dentistry.

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None

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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