Innovative Approaches to Nano-Endodontics

Abstract

Introduction: A significant obstacle in endodontic treatment is thoroughly disinfecting the intricate root canal system, which leads to treatment failure.

Methods: Due to their superior and distinctive physical characteristics, including their huge surface area/mass ratio, enhanced chemical reactivity, and ultrasmall dimensions, nanoparticles have sparked current investigation into potential treatments and preventative measures for tooth infections. An extensive analysis of the findings of research on the application of nanoparticles in endodontics is presented in this article.

Results: It has been determined that the use of nanoparticles in irrigation, medicament, sealers and restorative materials mainly enhances the antibiofilm efficacy of root canal and restorative treatments. Furthermore, it has recently been suggested that antibiotic or photosensitizer functionalized nanoparticles would have greater antibacterial activity.

Conclusion: To emphasize the practical use of nanoparticles in endodontics in the near future, there is a growing interest in this subject, which calls for quality research based on clinical and scientific cooperation.

Keywords: Nanoparticles, Antibacterial, Chitosan, Bioactive nanoparticles, Nanoscaffold

Introduction

Nanotechnology is emerging as an interdisciplinary field that is undergoing rapid development and has become a powerful tool for various biomedical applications such as tissue regeneration, drug delivery, biosensors, gene transfection, and imaging [1-3]. When dental tissues are injured by trauma or bacterial infection, their limited capacity for self-repair makes the adoption of biocompatible synthetic materials as the only accessible alternative for treatment. Due to their exposure to the harsh oral microenvironment, the majority of synthetic restorative materials have a limited lifespan and functionality [4].

A greater variety of dental restorations with improved qualities, including increased abrasion resistance, high mechanical properties, better cellular environment control, and enhanced aesthetics, are now possible as a result of recent advancements in nanomaterials. As evidenced by the large number of publications, there is currently growing interest in nanomaterials, nanotechnology, and nanoparticles in dentistry. In fact, one-third of publications on tissue engineering deal with dental diseases [5].

A material is generally defined as a nanomaterial if it's one dimension is less than 100 nm. The European Commission's Recommendation states that 'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm [6].

Measurement is one way to classify nanomaterials, also known as nanostructures. Nanoparticles are ones that are zero-dimensional, and nanowires and nanorods are ones that are one-dimensional. Double-layered nanostructures are called thin films. Given that they are all smaller than 100 nm in a single dimension, these structures all fit the previously defined definition of a nanomaterial or nanostructure [7].

This review was designed to provide a comprehensive assessment of the state of the art when it came to the use of nanotechnology in endodontics.

Nanoparticulate

The various procedures that produce the various particle types have generally been examined. Here, we provide a quick summary of such procedures [8].

Polymeric Nanoparticles

- **Milling**

To prepare polymeric nanoparticles, milling—basically a grinding process—in combination with filtration has been employed. Particles produced by milling are typically not spherical, although from the perspective of medication administration, this is acceptable.

- **Emulsion Methods**

This is the method of choice for producing polymeric nanocarriers with drugs integrated in them. Drugs that are hydrophobic are emulsified into water, typically containing surfactants, after being

co-dissolved with polymers in a common solvent. To obtain drug-containing polymeric particles, lyophilization is usually followed by solvent evaporation.

A hydrophilic drug is dissolved in water first, then it is emulsified into a solution of an organic polymer. The result is a water/oil/water (w/o/w) emulsion, which is then created by emulsifying this mixture into water that contains surfactant. In general, lyophilization and solvent drying result in micron-sized particles.

Polymeric Nanomicelles

The production of polymeric nanomicelles is carried out totally differently. The process begins with an amphoteric molecule, which is dissolved in water at progressively higher concentrations until its critical micellar concentration (CMC) is reached. When the CMC is determined, the drug and polymer are dialyzed against water after the polymer and drug have first been dissolved in an organic solvent (if the drug is hydrophobic). The polymer concentration is adjusted to be significantly higher than the CMC in the final volume of water. The "particles" can be separated after dialysis using centrifugation and/or freeze-drying. As long as the micelles remain stable in an ionic medium, reconstitution in water or saline should regenerate the micellar structure.

It is difficult to incorporate hydrophilic drugs into basic spherical micellar structures. To do this, we must employ liposomes, another kind of self-assembling system.

Liposomes

Rehydration can be used to create nano-sized liposomes, which can then be extruded.

Typically, known concentrations of lipids—both cholesterol-free and with—are dissolved at 60 °C in an organic solvent with a low boiling point, like ethanol. The organic solvent is removed with a rotary evaporator to create a thin film. After that, this is hydrated using an aqueous solution that contains the protein or medication. Upon rehydration, multilamellar vesicles (MLV) typically form, with sizes ranging from 0.5 to 5 μm. To create liposomes with integrated medications, these are extruded through membrane filters at high pressure, resulting in a unilamellar vesicle, or ULV, that is between 70 and 500 nm in size.

Dendrimers

In basic terms, dendrimers are hyperbranched polymer structures with the ability to "encapsulate" proteins or medications. Diffusion and, occasionally, degradation are the main ways that release is regulated. An amine-terminated molecule is typically the first step in the highly specific reaction sequence that creates these hyperbranched structures (polymers).

Such a molecule reacts first with an acrylate ester and then with ethylene diamine to produce a dendrimer that is considered "full-generation."

Nanoparticles for Endodontic Disinfection

The successful completion of root canal therapy may depend on the total eradication of bacteria, related inflammation, and injured tissues from the root canal, which serve as an environment for the reconstitution of microorganisms [9]. Even so, if bacteria enter the root canal after it has been

obturated, the therapy is likely to be unsuccessful [10]. Despite cleaning, shaping, and applying highly effective antimicrobial agents, clinical studies have demonstrated the persistence of bacteria within the root canal system [11].

Due to their novel and beneficial characteristics, nanoparticles (NPs) have garnered significant attention in recent decades as one of the novel strategies. These systems can produce more favorable drug bioavailability, serum stability, and pharmacokinetics, which can significantly increase the therapeutic efficacy of pharmaceutical products. As per existing literature, formulations based on nanotechnology offer enhanced penetration and facilitate the gradual and regulated release of active ingredients at specific target sites [12–15].

Chitosan Nanoparticles

The second most common natural biopolymer is chitosan (poly[1,4-b-D-glucopyranosamine]), a deacetylated derivative of chitin. Because of its ability to be used in a variety of forms, including powder (micro- and nanoparticles), capsules, films, scaffolds, hydrogels, beads, and bandages, chitosan has attracted a lot of interest in biomedicine [16-18].

Chitosan exhibits remarkable antimicrobial, antiviral, and antifungal characteristics [19].Gram-positive bacteria exhibited greater susceptibility in comparison to gram-negative bacteria. Inhibitory concentrations were found to be as low as 18–5000 ppm, contingent upon the type of organism, pH, level of deacetylation (DD), molecular weight, chemical modifications, and existence of proteins as well as fats [20]. There is evidence that DD affects the antibacterial efficacy. The number of amine groups rises per unit of higher DD glucosamine unit, indicating that chitosan exhibited increased antibacterial effectiveness [21]. Because of their charge, and size chitosan nanoparticles (CS-NPs) ought to possess stronger antibacterial properties.

Mechanism Of Action

The electrostatic attraction of positively charged chitosan to negatively charged bacterial cell membranes is the suggested mechanism of action, which is known as contact-mediated killing. This could result in changed permeability of the cell wall, which could ultimately cause cells to burst and release proteinaceous and other intracellular components [22]. The bacterial cells were observed to be fully encased in the chitosan under transmission electron microscopy, generating an impermeable layer [23]. This might stop vital solutes from being transported, which would kill cells. Chitosan was thought to bind with DNA in the nucleus of fungal cells, preventing the synthesis of RNA and proteins.

Evidence-based Research

Antibacterial properties of chitosan nanoparticle solutions have been found against E. faecalis, and they were also able to inhibit the growth of biofilms [24] Planktonic bacteria were completely eradicated while their biofilm counterparts continued to exist after 72 hours, according to a different study, which suggested that the antibacterial efficacy of the substance may vary depending on the condition of the bacteria. The 90-day aging process did not cause chitosan nanoparticles to lose their antimicrobial capabilities [25].

Its antibacterial properties are also dependent on contact, concentration, and time. The effectiveness of antibacterial agents against bacteria can be hindered by inhibitors like bovine serum albumin and pulpal remnants, but it remains unaffected by dentine, dentine matrix, or lipopolysaccharides (LPS) [26]. Pre-obturation carboxymethyl chitosan conditioning of the root canal surface has been reported to improve disinfection and prevent germs from adhering to dentine. Collagen cross-linking may nevertheless provide extra structural benefits even though surface conditioning with chitosan nanoparticle preparations did not enhance the antibiofilm properties per se, according to another research. [27]. The distribution and effects of chitosan nanoparticles within the root canal system have been proposed to be improved by a number of techniques, including electrophoresis, diode laser application, high-intensity focused ultrasound, and manual dynamic activation, which involves pumping a gutta-percha cone that is well-fitted into a prepared root canal to create microbubbles and improve fluid dynamics [28]

Chitosan can function as a chelating agent and possibly increase dentine's wettability, as shown by a number of studies [28,29]. Chitosan nanoparticles also demonstrated the ability to prevent bacterial collagenase degradation, which could stabilize dentine collagen [30]. The findings of the study showed that when one last rinse of chitosan nanoparticles alone was used instead of Qmix® or 17% EDTA, the sealer penetrated dentinal tubules almost two times as deeply at 5 mm from the apex. According to this, sealer penetration is still best achieved by traditional chelating agents. In contrast, a recent study discovered that applying a tricalcium silicate sealer after conditioning dentine with a chitosan-hydroxyapatite precursor nanocomplex greatly increased the mean sealer penetration into tubules [29]. Although it has been suggested that the long treatment time and contact-dependent nature of chitosan nanoparticle-based irrigants are limitations that require further research to overcome, chitosan nanoparticle solutions seem like promising candidates for novel irrigants when combined with its antimicrobial properties [30].

Clinical Significance

Early research indicated that there is a great deal of promise for better root canal disinfection with cationic CS-NPs. Nevertheless, two significant drawbacks for CS-NPs were the extended treatment duration needed to accomplish efficient bacterial eradication and the impact of tissue inhibitors.

This justified strategies and newer research protocols to be conducted in future aimed at CS-NP applicability.

Bioactive glass Nanoparticles

Because of its antibacterial characteristics, bioactive glass (BAG) attracted a lot of attention in the field of root canal disinfection. BAG is composed of SiO2, Na2O, CaO2, and P2O5 in varying quantities. Its antibacterial activity is dependent on physiological changes that occur locally. Multiple variables have been identified as cooperating factors in the antibacterial mechanism of BAG [31].

1. Ions released into an aqueous environment cause a high pH, which is a rise in pH.

2. The effects of osmotic pressure: many bacteria are inhibited by an increase in osmotic pressure exceeding 1%.

3. Ca/P precipitation: the bacterial surface is mineralized as a result of this.

Evidence-based Research

Obeid et al. conducted a study which revealed that the antibacterial impact of BAG when used as an intracanal medicament may be considerably enhanced by employing smaller particle diameters. Therefore, compared to their bulk counterparts, the evaluated nanoparticles in this study have stronger antibacterial activities [32].

The effectiveness of nanometric bioactive glass 45S5, which has a size range of 20–60 nm, was evaluated by Waltimo et al. against clinical strains of enterococci encountered as a result of chronic root canal infections. The acquired results showed that, in comparison to its micron-sized equivalents, the nano-sized bioactive glass 45S5 allowed a ten-fold rise in silica release and solution pH elevation by more than three units. Additionally, the nano-sized material's killing power against every tested strain was noticeably higher. According to the scientists, nanoparticulate bioactive glass's enhanced antibacterial activity is directly linked to its large surface area and the consequent release of ionic components into solution [33].

Clinical Significance

Before being used in clinical settings, more research is necessary due to the inconsistent data regarding the ability of BAG microparticles and nanoparticles to produce a significant antibacterial impact.

Silver Nanoparticles

Nanoparticles of silver, gold, copper, or zinc—all of which have distinct physical characteristics and mechanisms supporting their antibacterial activities—have been utilized to treat persistent endodontic infections [34] [35,36]. Because of their extensive variety of antibacterial capabilities against different bacteria, viruses, and fungi, silver nanoparticles (AgNPs) are among the most investigated [37]. AgNPs have been studied in endodontics as irrigation solutions, root canal medications, endodontic retrofill materials, and canal sealers [38].

Mechanisms of action of AgNPs

Electron donating groups that are abundant on membranes and proteins, such as sulfhydryl, amino, imidazole, phosphate, and carbonyl groups, are very attractive to silver ions [34]. Additionally, this may cause free silver ions to enter the cell and disrupt ATP molecules, which would stop DNA replication or cause AgNPs to produce ROS [39]. AgNP uptake in Gram-negative bacteria is also facilitated by pores in their outer membrane [40]. Furthermore, AgNPs alter the effects of phosphotyrosine, which hinders organelle-to-organelle communication [41]. All of these processes lead to increased levels of free oxygen radicals and oxidative stress in the cell, as well as protein denaturation-induced cell lysis [42].

Evidence-based Research

AgNPs and NaOCl were tested against E. faecalis in an irrigation solution by Lotfi et al. The results showed that low-concentration AgNPs and 5.25% NaOCl had comparable antibacterial properties [43]. According to Hiraishi et al., biofilms were totally eradicated sixty minutes after 3.8% sodium diamine fluoride was administered [44]. In a different investigation, it was discovered that an AgNP solution dissolved more biofilm but killed fewer bacteria than a CHX solution [45]. When calcium hydroxide was applied with silver, copper, zinc, or magnesium, Yousefshahi et al. discovered that calcium hydroxide paste when combined with 1% AgNP was more successful at removing biofilms than calcium hydroxide paste used alone. [46]. Furthermore, using gutta-percha points coated with nanosilver has been found to result in less leakage [47]. Another study combined AgNPs with mineral trioxide aggregate (MTA) based on calcium disilicate, which is known to have antibacterial properties. Prevotella intermedia, Fusobacterium nucleatum, Porphyromonas gingivalis, and Aggregatibacter actinomycetemcomitans were all inhibited from growing by the AgNP-MTA formulation. [48]. Furthermore, combining 0.15% AgNPs with 5% dimethylaminohexadecyl methacrylate sealer produced a significant antibiofilm effect without compromising sealing ability, according to Baras and Melo et al. [49].

The possible discolouration of dentin and toxicity to mammalian cells are the two main problems linked to Ag-NPs. Wistar rat models were used to test two distinct Ag-NP concentrations (90 mm) by Gomes-Filho et al. [50]. There was an observed concentration-dependent in vivo tissue reaction indicative of a mild to moderate chronic inflammatory response. Following 15 days, a reaction corresponding to 2.5% sodium hypochlorite was observed with 47 ppm Ag-NPs. Ag-NPs and silver ions have toxic concentrations of 10–100 mg/L and 1–10 mg/L, respectively, for eukaryotic cells [51]. It has been the goal of research to modify and create Ag-NPs with reduced cytotoxicity to host cells and targeted antibacterial activity [52].

Clinical Significance

For root canal disinfection, Ag-NPs with strong antibacterial activity may be employed. Still, one must take into account the extended duration of interaction that Ag-NPs need to have in order to effectively kill bacteria, and its use should ideally be restricted to ICM rather than irrigant. Furthermore, when carefully choosing a nontoxic concentration for in vivo use, one should not disregard the toxicity linked to silver ions.

Nanobubble-Enhanced Antimicrobial Agents

Nanobubbles, also known as vapor- or gas-filled cavities inside liquids, have a diameter ranging from one to two hundred nanometers. They can be created using nanobubble generators and are widely used in the chemical, fluid dynamics, industrial, agricultural, medicinal, and environmental domains [53,54]. Because of their tiny size, these bubbles will stay in the liquid and rupture there rather than exploding immediately after forming at the liquid's surface. Additionally, they are incredibly stable, retaining their size in liquid for months without suddenly exploding [53,54]. Because NB increases a medication's penetration potential without causing systemic toxicity, it has been used recently in drug delivery[55]. It is possible to combine NB water with endodontic irrigants.

Based on study conducted by Alshwali H [56], it was concluded that without altering the microhardness of dentin, NB water can facilitate the elimination of smear layers and improve medication penetration into the tubules. It seems that NB water can increase the tubular disinfection capacity of lower concentration NaOCl up to 50 µm in large canal models. In contrast to conventional needle irrigation, the application of irrigation activation (US or XP) did not further disinfect the dentinal tubules. These findings imply that NB water could be a useful addition to medications and endodontic irrigants.

Nanoparticle amendments for antimicrobial photodynamic therapy (Functionalized Nanoparticles)

When treating periradicular ailments, antimicrobial photodynamic therapy (aPDT) has the potential to be a successful adjunct to routine intracanal disinfection protocol [57-59]. This is especially true for single visit root canal treatment (RCT) and retreatment cases [60]. It makes use of a photosensitizer and light with a certain wavelength, such as toluidine blue at 600 nm[57]. The primary process that breaks down microbial cells is mediated by the production of singlet oxygen reactive species [60]. Research endeavors are in progress to enhance the antibiofilm effectiveness of aPDT by the amalgamation of photodynamic impacts and bioactive micro-and nanoparticles [58-59]. As noted in Kishen's review [61], the fusion of photosensitizers and nanoparticles (functionalized nanoparticles) could be accomplished by

1. Photosensitizers with nanoparticle enhancements

2. Nanoparticle-encapsulated photosensitizers

3. Loaded or bonded photosensitizers onto nanoparticles

4. The photosensitizer properties of nanoparticles themselves

In order to determine the antibiofilm efficiency against both monospecies and multispecies biofilms of bacteria, Shrestha and Kishen conducted an in vitro investigation to test the new association of rose bengal with chitosan nanoparticles (CSRBnps) [57-59]. High affinity for the microbial cell membrane, increased penetration into the biofilm structure, and improved antibiofilm properties have all been demonstrated by their results. In their work, Afkhami et al. [62] found that the combination of diode laser with AgNPs and indocyanine green increased the efficacy of aPDT compared to PDT alone. Indocyanine green (ICG) and nano-graphene oxide (NGO) have been shown in another study [63] to have increased activity.

In vitro tests using human dental plaque bacteria and E. faecalis biofilm in conjunction with PDT have been conducted using MB-PLGA (poly(lactic-co-glycolic) acid) loaded nanoparticles [64]. Both in the planktonic and biofilm stages, the cationic MB-PLGA nanoparticles proved to be substantially more phototoxic to bacteria. The study concluded that photosensitizer photodynamic treatment (PDT) may be delivered within root canals via cationic MB-PLGA nanoparticles.

Due to a number of factors, it has been discovered that combining photosensitizer with nanoparticles increases the effectiveness of antimicrobial PDT [65]:

(a) Increased photosensitizer concentration per mass and subsequent ROS generation
(b) Decreased photosensitizer efflux from the target cell, which lowers the risk of medication resistance

(c)Possibility of focusing on the bacteria due to increased surface charge-related interaction

(d)Increased photosensitizer stability upon conjugation

(e)Reduced physical quenching impact as a result of the aggregate of photosensitizers

(f) ROS release under control following photoactivation is feasible.

Clinical Significance

Different nanoparticles that had been functionalized demonstrated a general increase in efficacy as well as quick action against bacteria. While functionalized BAG and AG-NPs should still only be thought of as long-term root canal medications, photosensitizer functionalized nanoparticles may be utilized as a last resort for root canal disinfection.

Continuous research is being done to optimize these functionalized nanoparticles' concentration and application technique.

Nano-Sealers

The antibacterial activity of common sealers has been shown to last up to one week, after which the majority of them exhibit a marked reduction in antibacterial activity (66–67). The main goals of incorporating NPs into sealers have been to decrease bacterial penetration, boost antibacterial activity in dentinal tubules, increase sealer substantivity, and increase antibacterial activity diffusion. The adherence of E. faecalis to dentin was significantly reduced when ZnO NPs, ZnO/CS Mix, CS-layer-ZnO, or CS NPs were applied to root dentin. A 95% reduction in bacterial adherence was produced by ZnO NPs, ZnO/CS Mix, and CS-layer-ZnO, whereas an 80% reduction was produced by CS NPs. Chlorhexidine-treated dentin that was subsequently treated with nanoparticles demonstrated the greatest reduction in bacterial adherence (97%) [68]. Better antibacterial qualities and the capacity to disperse antibacterial components were demonstrated by ZnO NP-loaded root canal sealer, which is particularly significant in a root canal environment [69]. A different study examined the effects of CS NPs added to root canal sealers both with and without dentin surface modification using chitosan modification cations [70].

Additionally, different root canal sealers and temporary restorative materials were found to have enhanced antibacterial efficacy when treated with Quaternary Ammonium Polyethylenimine (QAPEI) nanoparticles [71-74]. QAPEI nanoparticles were added to AH Plus and pulp canal sealer EWT (PCS) by Barros et al. [71]. The QAPEI nanoparticles had a positive charge of 68.5 ± 1.9 mV and a size of 58 ± 18 nm. The wettability of PCS and AH Plus was raised by adding these nanoparticles to the sealers. When nanoparticles were added, the surface charge of the set sealers also significantly increased.

Clinical Significance

For root canal disinfection, the majority of nanoparticles tested rely on contact-mediated and time-dependent antibacterial activity.

Therefore, by preventing bacterial biofilm formation on the surface and at the resin-dentin interface, the addition of different nanoparticles to sealers or root filling materials greatly increased their antibacterial efficacy. The few in vitro research on root filling materials containing nanoparticles highlights the need for comprehensive and standardized investigations into potential clinical application areas.

Nano-regenerative Endodontics

Throughout the many phases of regenerative endodontics, nanofibers have been utilized as nanoscale carriers for bioactive compounds. The flexible nanofiber matrix satisfies multiple needs when utilized as a scaffold, such as drug delivery, adhesion of bioactive molecules, growth factor attachment, and three-dimensional (3D) matrix formation, all of which promote cell homing behavior for the regenerative process [75]. Nanofibers come in a variety of architectural shapes, such as hollow tubes, ribbon-shaped, necklace-like, uniaxially aligned, biaxially orientated, porous, and nanowire-in-microtubes [76]. A nanofibrous architecture placed on a smooth-walled scaffold promotes the adsorption of the cell adhesion protein. Natural collagen fibers and poly (L) lactic acid scaffold nanofibrous layout are similar in terms of their physical structure. It provides an environment that is similar to extracellular matrix and encourages attachment and proliferation in human DPSCs [77]. Nanofibers function as a scaffold and a porous 3D surface that promotes cell attachment when regenerative cells (such as dental pulp cells, mesenchymal cells, odontoblasts, and growth factors) are implanted. Polymeric nanofibers can be made by a variety of methods, such as electrospinning, thermally induced phase separation, and self-assembly. These methodologies enable the fabrication of 3D nanofibrous scaffolds with interconnected pore topologies that promote cell infiltration, proliferation, and delivery of nutrients [78].

It has been reported that low-dose simvastatin added to a poly (L) lactic acid nano scaffold enhances stem cell regenerative capacity in inflamed dental pulp tissue, thereby promoting dentin regeneration [79]. It is preferable for scaffold-mediated angiogenesis from the surrounding tissue. Furthermore, the scaffold's blood vessel structure enhances the flow of nutrients and oxygen as well as the elimination of metabolic waste, all of which contribute to the development of a favorable environment for DPSC growth. Dental pulp cells are known to promote angiogenesis because endothelial cells grown on simvastatin/nanofibrous-poly (L) lactic acid scaffolds are reported to form highly connected vascular-like structures [79].

In a different study, the use of 3D nanofibrous gelatin/magnesium phosphate scaffolds improves dentin regeneration by human pulp stem cells and causes a regulated release of metallic ions [80]. An injectable scaffold offers advantages over a bulk scaffold that can be implanted for dental regenerative procedures. Kuang et al. created injectable cell carriers in the form of nanofibrous spongy microspheres using poly (L) lactic acid-block poly (L-lysine) copolymers by using methods for thermally induced phase separation and self-assembly [81].

Various materials in nanoscale form for endodontic tissue regeneration

Chitosan

Research indicates that when recombinant keratinocyte growth factor forms a compound with mucoadhesive low-molecular-weight chitosan, both its biological activity and stability are enhanced [82]. In contrast, it has been found that a carboxymethyl chitosan-based scaffold containing transforming growth factor (TGF)-β1-loaded chitosan nanoparticles improves stem cell migration and differentiation [83]. In a different study, it was discovered that the steady and slow release of bovine serum albumin from chitosan nanoparticles increased the activity of alkaline phosphatase in SCAP, an early marker of odontoblast-like differentiation [84]. The odontogenic differentiation of SCAP is enhanced by the odontogenic stimulant dexamethasone when it is loaded onto chitosan nanoparticles, according to Shrestha et al.'s research [85]. As an endodontic irrigant, sodium hypochlorite has been found to have adverse consequences that can be mitigated by conditioning the dentin surface with chitosan nanoparticles or dexamethasone-modified chitosan nanoparticles; conditioning with chitosan nanoparticles promoted the adherence, viability, and differentiation of SCAP [86].

Hydroxyapatite

Biodegradable polymers made from synthetic materials such as polycaprolactone, polyglycolide, and polylactide exhibit poor cell adherence and propagation due to an absence of biological recognition sites. Nanohydroxyapatite enhances protein absorption, cell adhesion, and cell proliferation; it is also very soluble, which stimulates the polymer's bioactivity to increase. Three-dimensional porous biodegradable networks can be constructed from alginate. It has been demonstrated that DPSCs seeded on alginate and nanohydroxyapatite scaffolds express osteogenic differentiation-related markers and induce calcium deposition and biomineralization [87,88]. According to Kim et al. [89], apatite-mineralized polycaprolactone nanofibrous scaffolds stimulate the creation and odontogenic differentiation of human dental pulp cells via the integrin-mediated signaling pathway when compared to plain polycaprolactone fibers.

Cellulose Nanocrystals

As a result of serving as efficient junctional elements, cellulose nanocrystals incorporated into injectable hyaluronic acid hydrogels promote cell adhesion, migration, and proliferation, Silva et al. reported that these hydrogels have boosted scaffold network stiffness and stability [90]. Pulpal tissue revascularization and regeneration were enhanced by the addition of a platelet lysate rich in proangiogenic and chemotactic components into the reinforced hydrogel [90].

Bioactive Glass

By electrospinning dexamethasone molecules into the biopolymer nanofiber matrix, Lim et al. discovered that the resulting nanofiber composite exhibited a continuous, controlled release of dexamethasone for a period of fourteen days (about 2 weeks). Additionally, by stimulating integrins, bone morphogenetic protein, and the signaling pathway referred to as the mammalian target of rapamycin, or mTOR, it enhances the development of odontogenic human dental pulp cells [90]. A composite nanofibrous scaffold made of polycaprolactone/gelatin and mesoporous bioactive glass nanoparticles was shown by Kim et al. [91] to be able to promote the odontogenic

differentiation of human dental pulp cells through the activation of bone morphogenic proteins (BMP), integrins, and the mitogen-activated protein kinase signaling pathway.

Calcium Silicate Nanoparticles

Huang et al. synthesized mesoporous calcium silicate nanoparticles into an injectable paste, exhibiting well-organized mesoporous channels with substantial surface areas and pore volumes. These nanoparticles may be a unique material in the field of regenerative endodontics, based on the prolonged release pattern of calcium and silicate ions that they demonstrated [92]. A distinct, ready-to-use calcium silicate-based nanoparticulate bioceramic paste has been found in another investigation to exhibit excellent apatite production, improve DPSC adhesion, migration, and attachment, and stimulate dentin bridge formation for pulp healing [93].

Antimicrobials

For canal disinfection during regenerative treatments, TAP—which comprises minocycline, ciprofloxacin, and metronidazole —has been advised. When TAP is utilized at quite high doses, the disadvantages include noticeable tooth discolouration and severe dental stem cell loss.

Triple antibiotic-eluting nanofiber constructions with a tubular shape and high concentrations of TAP have antibacterial properties against multispecies biofilm that are similar to those observed during investigations conducted by Albuquerque et al. [94]. Ciprofloxacin, minocycline, and metronidazole are present in these structures in much smaller amounts.

Comparable outcomes were also documented by Palasuk et al., who found that nanocomposite scaffolds containing polydioxanone, metronidazole, or ciprofloxacin had no harmful effects on human DPSCs while demonstrating strong antibacterial action against Enterococcus faecalis and Porphyromonas gingivalis [95]. According to a recent study, polydioxanone (PDS) polymer nanofibers treated with clindamycin and triple antibiotic-free (minocycline-free) show strong antibacterial activity and minimal cytotoxicity. Clindamycin-containing nanofibers had smaller diameters than PDS nanofibers free of antibiotics, according to scanning electron microscopy [96]. This increases the surface area available for drug release over time. Silver nanoparticles can also cause mitochondrial malfunction and oxidative stress in human cells. In contrast, low concentrations of silver nanoparticles do not appear to be toxic to mammalian cells. Moreover, an investigation conducted by Oncu et al. [97] discovered that when ambient silver nanoparticles are generated, they do not interfere with human dermal fibroblasts. However, cytotoxic effects are reported at concentrations of >50% [98]. In another work using DPSCs, carboxymethyl cellulose-silver nanoparticles demonstrate good antibacterial activities and low toxicity at a concentration of 16%.

Clinical Significance

Combining stem cells with bioactive nanostructured scaffolds creates a more favorable environment for dental pulp healing. Long-term clinical trial research is obviously needed to evaluate the therapeutic effectiveness of nanomaterials in regenerative endodontics.

Conclusion

In endodontics, nanoparticle-based therapeutic approaches may increase the effectiveness of antibacterial and antibiofilm agents. By altering their surface, functionalized nanoparticles could be able to selectively engage with bacteria and biofilm at the infection site by delivering chemicals or medications. Newer multifunctional nanoparticles are being designed in conjunction with biologists, doctors, and engineers based on therapeutic requirements. In light of current advancements, the idea of using nanoparticles in endodontics and healthcare as a whole should be embraced cautiously and enthusiastically.

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