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Magnetic Nanoparticles in the Treatment of Dental and Oral Diseases: A Brief Review of Their Use as Drug Carriers

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ABSTRACT

Magnetic nanoparticles (MNPs) have attracted significant interest in the field of drug delivery, due to their unique physicochemical properties and ability to act at the molecular and cellular levels. Another property of magnetic nanoparticles that has contributed to their popularity is their ability to target specific cells, reducing the systemic toxicity of the compound. In recent years, magnetic nanoparticles and magnetic forces have been used in dentistry to deliver drugs for the prevention and treatment of dental diseases. Magnetic nanoparticle-based therapies are highly effective against bacterial and fungal pathogens that are resistant to conventional antibiotic therapy. In the field of cosmetic dentistry, magnetic nanoparticles have contributed to improving the transparency and corrosion resistance of dental materials. The use of magnetic nanoparticles in various dental drug delivery systems has also contributed to reducing the incidence of dental caries and dental diseases in the fields of root canal and periodontal treatment. The addition of magnetic nanoparticles to dental filling materials and adhesives has helped prevent the formation of biofilms. In this chapter, the applications of magnetic nanoparticles in dentistry are summarized with emphasis on their biocompatibility and safety.

Keywords: Dental Diseases, Drug Delivery, Magnetic Nanoparticles (MNPs), Nanotechnology in Dentistry

1 Introduction

ONE of the most common health issues in the world, oral and dental illnesses have a major impact on people's quality of life [1-5]. The health of the mouth and face is seriously threatened by these disorders, which include a broad variety of conditions like gingivitis, periodontal disease, tooth decay, and oral malignancies, including oral cancer [6-10]. Even while traditional diagnostic and therapy approaches for these conditions have advanced significantly, it is still difficult to achieve the best possible therapeutic results because of side effects that can harm healthy tissues and lessen the efficacy of treatments. Chemical, antibiotic, and anti-inflammatory medications are used in the conventional treatment of oral disorders; however, these medications frequently have adverse side effects that impair the healing process or the health of healthy tissues. Even if these treatments work in certain situations, they might not be accurate enough to target the faulty cells directly, which reduces their efficacy and raises the risk of consequences. Chemical, antibiotic, and anti-inflammatory medications are used in the conventional treatment of oral disorders; however, these medications frequently have adverse side effects that impair the healing process or the health of healthy tissues. Even if these treatments work in certain situations, they might not be accurate enough to target the faulty cells directly, which reduces their efficacy and raises the risk of consequences [11, 12]. In this regard, nanoparticles seem like a novel and promising way to get around a lot of these restrictions [13]. With sizes ranging from 1 to 100 nanometers, nanoparticles are incredibly tiny particles that can more precisely infiltrate cells and target damaged regions than traditional medications [14]. Drug delivery methods based on nanoparticles can be characterized as a cutting-edge way to increase treatment precision [15]. Tumor-specific antibodies, peptides, sugars, hormones, and anticancer medications can all be applied to these systems. These nanoparticles have been investigated for their ability to specifically target cancer cells and have been successfully connected to anticancer chemotherapeutic drugs. These nanoparticles are better than traditional medication delivery methods because they include nanoscale surface receptors that allow chemotherapeutic chemicals to be directed to a particular section of the body. By accurately identifying and attaching to the target tissues, these receptors aid in the exact release of drug molecules, protecting healthy cells from the harmful effects of the medication. By encasing drugs in a shell of nanoparticles, they can also be shielded against deterioration, improving therapy efficacy [16-19].

Because of their special qualities, magnetic nanoparticles—a sophisticated kind of nanoparticle—are employed in contemporary medicine. Because of their sensitivity to magnetic fields, magnetic particles can be accurately guided by external magnetic fields to specific locations within the body [20]. In the field of dentistry, these magnetic particles can play a vital role in treating dental diseases such as oral cancer, as they can be used to direct drugs to cancer cells more precisely and destroy diseased cells through magnetic heat therapy, without affecting the surrounding healthy tissue [21, 22]. A significant change in the conventional treatment of oral tumors is represented by this capacity to produce heat when subjected to magnetic fields, which aids in the efficient destruction of oral malignancies. Magnetic iron oxide particles, like magnetite, are among the most commonly utilized magnetic materials in dentistry [23, 24]. Their potent magnetic characteristics make them perfect for use in therapeutic and medical research. To enhance their performance in a variety of medical applications, including targeted heat therapy and medication delivery, these particles' size, shape, and surface characteristics can be changed. Furthermore, because permanent magnets like neodymium iron boron (NdFeB) magnets employ their magnetic force to promote tissue growth and tooth movement, they have emerged as a significant factor in enhancing the outcomes of orthodontic therapy and dental implants [25].

Although non-magnetic nanoparticles are employed in medication delivery and therapy, they do not have the exact guidance property that magnetic particles offer, despite the fact that magnetic nanoparticles are crucial in the treatment of oral and dental disorders. Non-magnetic particles cannot be guided precisely to the affected tissue by magnetic fields; instead, they rely on the physical and chemical characteristics of the material, such as the particles' size or surface charge. Compared to magnetic particles, these particles are less effective because they may have more difficulty precisely locating the target tissue, even though they are sometimes effective [26, 27].

Focusing on magnetic particles, this paper attempts to provide a brief review of the current uses of magnetic materials in dentistry in light of these developments. The potential of these materials to enhance dental health care and improve patient outcomes is investigated by examining recent studies and reviews. In addition, it is demonstrated how these materials can be used to treat a variety of dental conditions, including oral cancer, using contemporary technology such as magnetic nanoparticles for drug delivery.

2 Magnetic Nanoparticles

Magnetic nanoparticles are multifunctional materials with unique properties that make them useful in a variety of medical and industrial applications [28-32]. These particles have high magnetic properties and biocompatibility, making them ideal candidates for use in drug delivery systems, medical imaging, and magnetic therapy. One of the most common structures of magnetic nanoparticles is the spinel, which has the general chemical formula AB_2O_4 [33]. In this structure, the “A” cation is bound to the tetrahedral sites, while the “B” cation occupies the octahedral sites. Spinels are classified into two main types based on the arrangement of cations in their crystal structure. The first type is the regular spinel, where the “A” cations completely occupy the tetrahedral sites, such as magnesium-alumina oxide ($MgAl_2O_4$). The second type is the reverse spinel, where the "B" cations are distributed between the tetrahedral and octahedral sites, while the "A" cations are concentrated in the octahedral sites, such as magnetic iron oxide (Fe_3O_4). These types of spinels give nanoparticles various magnetic properties that improve their efficiency in different applications [33-35].

Within the framework of magnetic nanoparticles, ferrites stand out as one of the most important magnetic materials used. Ferrite is a metal oxide with strong magnetic properties and is written in the general formula MFe_2O_4, where "M" represents the metal cation such as manganese, cobalt, nickel, copper, magnesium, iron, or zinc.

To enhance the efficiency of these particles, they are usually coated with biocompatible materials to improve their stability and prevent their agglomeration resulting from their large surface area. Common coating materials include biopolymers, silica, carbon, or noble metals. The coating also helps improve biocompatibility and protects the particles from oxidation, making them more effective for medical applications [37-39].

In addition, by modifying their surface, magnetic nanoparticles are used as drug carriers to load pharmaceutical substances onto them. Specific surface receptors such as antibodies or sugars are added that help target the affected tissues precisely. When drugs are loaded onto the surface of the particles, they can be guided by external magnetic fields to the target site, where the drugs are released gradually or as needed. This method enhances the efficiency of treatment and reduces side effects on healthy tissues, making magnetic nanoparticles an effective tool for drug delivery and targeted therapy [40-42].

3 The Application of Magnetic Nanoparticles as Drug Carriers Represents

The application of magnetic nanoparticles as drug carriers represents one of the advanced technologies that rely on the use of magnetic particles to transport drugs to specific sites within the body with high accuracy. This system is characterized by its ability to improve the accumulation of drugs in the target tissues, destroy the affected tissues, and release the drugs when needed, making it a valuable tool in nanotherapy. These particles can be modified to achieve biocompatibility by attaching different active biocomponents to their magnetic cores, which are surrounded by a layer of organic polymers or inorganic metals, which enhances their effectiveness in biomedical applications. The use of magnetic particles contributes to reducing the possibility of side effects and reducing the drug doses required during treatment, which improves the accuracy and effectiveness of drug delivery. These particles also have a distinct ability to provide medical imaging and controlled drug release properties, making them a multifunctional means of treatment. Drug delivery agents are often injected into the bloodstream via a catheter placed near the intended target, which reduces drug doses, reduces side effects, and improves the accuracy of drug delivery. In addition, magnetic particles can be directed toward the target tissues using an external magnetic field, allowing the drug to be directed with great accuracy towards the affected tissues [45].

When magnetic particles are modified with therapeutic agents, they can be directed to treat affected oral tissues, such as periodontal tissue or dental roots, using external magnetic fields [46]. This system provides a precise and less invasive method for treating oral diseases such as periodontitis and root canal treatment [47]. In addition to their use in conventional treatments, magnetic particles represent a promising tool for the treatment of superficial tumors, including oral tumors. When combined with chemotherapeutic drugs and external magnets, superconducting magnetic nanocarriers have shown the ability to enhance the antitumor effect, opening up new horizons in the treatment of oral cancers. In the clinical context, the precise targeting of magnetic particles is one of the most important advantages of this technology, as these particles can be coated with antibodies or biological compounds directed to target specific cells such as cancer cells [48]. Thanks to their nano-sized size, these particles can penetrate microcapillaries and be easily absorbed by the target cells, contributing to the accumulation of the drug at the desired site. The use of biodegradable nanoparticles also allows for sustained release of the drug over a long period of time, allowing for higher therapeutic efficacy with fewer side effects [47, 48].

Robert Bucki et al. [49], fabricated amino silicone-coated magnetic nanoparticles (MNP@CHX) to combat oral infections, especially those based on biofilm, such as dental plaque, periodontal and oral pathology. They synthesized magnetic nanoparticles using a modified Massart method to form an iron oxide core and then coated them with suitable materials such as alkylamine to prepare the core-shell structure. Chlorhexidine was loaded onto the surface of the nanoparticles by reacting the amino group of the particles with the chloride group of chlorhexidine. Chlorhexidine-loaded nanoparticles exhibited significantly higher antibacterial and antifungal activity than free chlorhexidine in the presence of human saliva. The study also showed that chlorhexidine bound to the nanoparticles increased the ability to reduce the growth of multi-species biofilm compared to free chlorhexidine. In addition, the researchers showed that treatment with MNP@CHX induced mitochondrial depolarization in fungal cells, suggesting that oxidative stress may be part of the pathogen elimination mechanism. Notably, chlorhexidine-loaded nanoparticles did not affect host cell proliferation or their ability to secrete the pro-inflammatory cytokine IL-8, reflecting their biocompatibility. This study also demonstrated that the use of MNPs as a carrier for chlorhexidine could represent a promising approach for the development of antibacterial systems in dental applications.

Radi Masri et al. [50], developed an innovative method based on the use of magnetically guided iron nanoparticles to deliver therapeutics to the dental pulp. These particles penetrate through the natural channels in the dentin to reach the dental pulp, reducing inflammation and improving the ability of adhesives to adhere to the dentin. The researchers used chitosan-coated nanoparticles because of their high drug-loading capacity such as steroids (e.g. prednisolone) and the excellent biocompatibility they have shown in clinical studies. The results showed that this method significantly reduced the expression of inflammatory cytokines prevented the exacerbation of pulpal inflammation, and improved the penetration of adhesives into the dentin, which enhanced the adhesion strength of composite fillings. This method is painless and less expensive compared to current treatment options, with great potential for clinical application.

Hockin H.K. Xu et al. [51] conducted a comprehensive study to develop a novel dental adhesive containing supersensitive magnetic nanoparticles (SPIONs) guided by a magnetic field to improve the bond strength to dentin. This study aims to address the poor penetration of conventional adhesives to dentin, which leads to reduced lifespan of composite fillings. The results showed that the adhesive containing 0.07 wt% SPIONs, when guided by a magnetic field, achieved a significant increase in bond strength, outperforming the decrease caused by simulated hydrostatic pulp pressure. Tests demonstrated that the use of a magnetic field during the bonding process enhanced the adhesive's ability to penetrate dentin without affecting its physical and chemical properties. In addition, the new adhesive showed high biocompatibility and antibacterial effect, making it a promising option for improving the quality and sustainability of fillings. This technology is based on the real-time movement of magnetic nanoparticles, which opens up new prospects for improving the lifespan of composite fillings and enhancing the bond strength to dentin.

In the study conducted by Fang Lan et al. [52], a novel magnetic nanomaterial (Fe_3O_4@SiO_2@DMADDM) as shown in Figure 1 was developed with antibacterial properties and is effective in controlling plaque and preventing dental caries. The chemical dimethylamino dodecyl methacrylate (DMADDM) was incorporated into these nanoparticles, and its biofilm inhibition effect was evaluated using models of conventional dental caries bacteria and models of saliva-extracted colonies. Results of FTIR, TGA, XRD, VSM, SEM, and TEM techniques demonstrated the successful loading of DMADDM onto the nanoparticles. Experiments demonstrated that the optimum concentration of nanoparticles (Fe_3O_4@SiO_2@DMADDM) of 8 mg/mL significantly reduced the biofilm of Streptococcus mutans and inhibited its lactic acid production. 16S rRNA sequencing showed that this material reduced the proportion of bacteria associated with dental caries in saliva-extracted biofilms, such as Streptococcus, Veillonella, and Neisseria while promoting the presence of beneficial bacteria such as Lactobacillus and Lactococcus at high concentrations. The results indicated that Fe_3O_4@SiO_2@DMADDM was able to mechanically remove biofilms using a magnetic field, in addition to inhibiting acid production by the positive effect of DMADDM. Moreover, the experiments demonstrated that this material had a concentration-dependent antibacterial effect, showing high performance in inhibiting biofilms and eliminating bacteria without causing significant toxic effects on human cells. Its effect was studied using a saliva-extracted biofilm model and a single-bacteria model, providing evidence for its ability to improve the stability of the oral microenvironment. The study suggests that Fe_3O_4@SiO_2@DMADDM could be used to manufacture anti-caries or dental cavity disinfectants.

In the study conducted by Joanna Mystkowska et al. [53], the effect of gold- and amino silane-coated magnetic core-shell nanoparticles (MNPs) as shown in Figure 2 on the antibacterial activity (adhesion of microorganisms, biofilm formation), rheological properties (viscosity, viscoelasticity), and physicochemical properties (pH, surface tension, electrical conductivity) of three commercially available artificial saliva formulations was evaluated. When the nanoparticles were added at a concentration of 20 μg/ml, the results showed an increase in the antibacterial activity of the artificial saliva against the tested microorganisms by 20% to 50%. The adhesion of bacterial and fungal cells (Gram-positive bacterial and fungal cells) was reduced by up to 65%, and of Gram-negative bacterial cells by 45%, especially when gold-coated nanoparticles were used. The addition of nanoparticles showed an enhancement in the antibacterial properties of the artificial saliva without affecting its rheological or physicochemical properties, which remained within the ranges of natural saliva taken from healthy subjects. In the first part of the biological tests, the ability of commercially available artificial saliva formulations to inhibit the proliferation of selected oral pathogens was evaluated. The results showed that formulation B was the most effective in reducing the proliferation of microorganisms, especially for the bacteria P. aeruginosa and the fungus C. tropicalis where the proliferation was rated at 30% compared to the control group, while 50% inhibition was observed after treatment of the bacteria S. aureus, E. coli and the fungus C. albicans with formulation B. In the next step, the protective activity of the artificial formulations against biofilm formation was evaluated, where formulation B showed the best inhibitory properties against biofilm formation. For the bacteria S. mutans, a 75% reduction in biofilm biomass was observed when formula B was used, compared to 50% in the case of formulas A and C. The effect of these formulations on the viability of cells embedded in the biofilm matrix was also evaluated, with formula B showing the only inhibitory activity against all tested oral pathogens. The study showed that the components of these synthetic formulations contain components with antibacterial properties, such as hydroxyethylcellulose and yerba santa extract, which may form a natural protective layer on mucosal surfaces, preventing the colonization of microorganisms. Also, other components such as sorbitol, lemon oil, enzymes, and fluoride ions, contributed to the control of microorganisms and the prevention of the growth of harmful flora. This study indicates that formula B, which is based on sorbitol, hydroxyethylcellulose, and the enzyme system, has the best antibacterial activity, confirming previous reports that these enzymes have been successfully used as antibacterial agents. To increase the effectiveness of the tested formulations and prevent the adhesion of microorganisms, the content of the preparation was modified by adding core-shell magnetic nanoparticles at a concentration of 20 μg/ml.

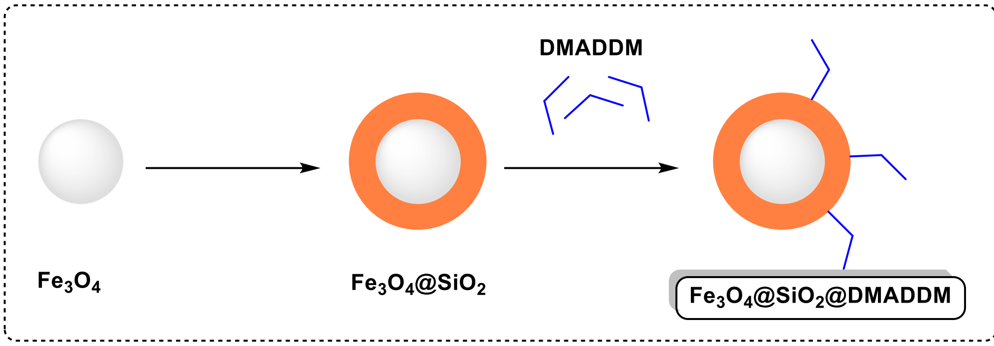

Fig. 1. The preparation of $Fe_3O_4@SiO_2@DMADDM$.

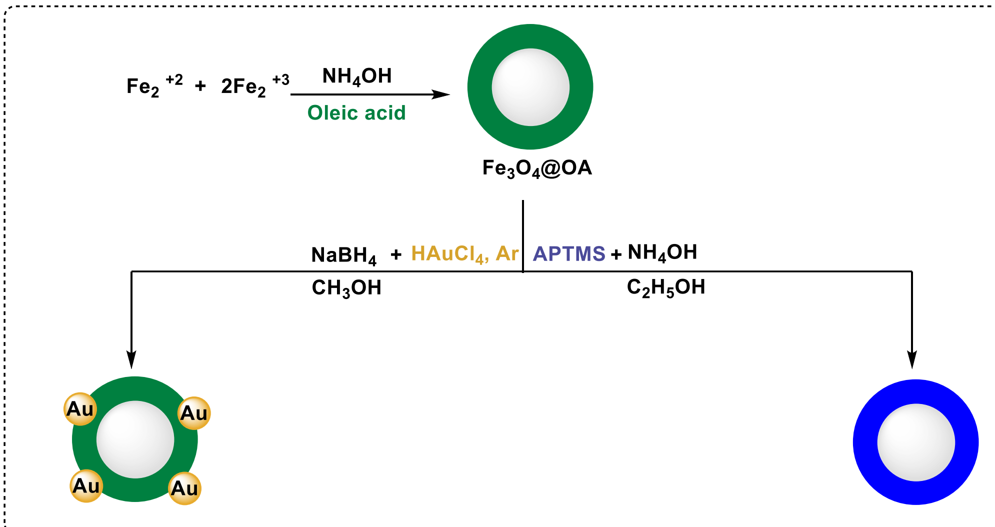

Fig. 2. Synthesis and structure of gold-coated magnetic nanoparticles (MNP@Au) with a terminal amine group (MNP@NH2) affixed to their surface.

These nanoparticles have clearly defined physical and chemical properties and have proven antibacterial activity. According to the published literature, the mechanism of action of magnetic nanoparticles involved in the interaction with microorganisms includes the generation of oxidative stress via the formation of reactive oxygen species (ROS), as well as interference with electron transfer in the oxidation of NADH. The nanoparticles also have the ability to disrupt the membrane of microorganisms via the formation of pores or through the cellular uptake mechanism.

In a study by Hockin H.K. Xu et al. [54], an adhesive containing magnetic nanoparticles was developed that could be controlled by magnetic forces to deliver drugs to the pulp and improve the penetration of the adhesive into the enamel. However, it did not have antibacterial properties or remineralization capabilities. The objectives of this study were to (1) develop an adhesive containing magnetic nanoparticles with dimethylaminohexadecyl methacrylate (DMAHDM), amorphous calcium phosphate (NACP) nanoparticles, and magnetic nanoparticles (MNP); and (2) investigate the effects of this adhesive on the bond strength to dentin, the secretion of calcium (Ca) and phosphate (P) ions, and the anti-biofilm properties. MNP, DMAHDM, and NACP were mixed in Scotchbond SBMP adhesive at 2%, 5%, and 20%, respectively. Two types of magnetic nanoparticles were used: acrylate-modified iron nanoparticles (AINPs) and iron oxide nanoparticles (IONPs). Each type of particle was added to the resin at 1% by mass. Magnetic forces were applied for 3 min using a commercially available cube magnet, and the shear bond strength of the dentin was measured. Streptococcus mutans* biofilms were cultured on the resin, and metabolic activity, lactic acid, and colony-forming units (CFU) were determined. Calcium and phosphate ion (Ca and P) concentrations and pH of the biofilm culture medium were also measured. The results showed that the adhesive containing magnetic nanoparticles and enhanced with magnetic force increased the shear bond strength of the dentin by 59% compared to the SBMP control ($p < 0.05$). The addition of DMAHDM and NACP did not negatively affect the bond strength of the dentin ($p > 0.05$). The addition of magnetic nanoparticles + DMAHDM + NACP reduced the colonies of S. mutans in biofilms by 4 logs. The adhesive containing NACP also transformed the biofilm medium into a reservoir of calcium and phosphate ions. The pH of the biofilm culture medium in the adhesive containing magnetic nanoparticles with NACP was safe at

6.9, while the pH of the biofilm medium in the commercial adhesive was 4.5, which promotes caries formation. The study shows that the adhesive containing magnetic nanoparticles with DMAHDM and NACP under the influence of magnetic force significantly increased the bond strength with dentin compared to the commercial control. This new adhesive also reduced the colonies of S. mutans in biofilms by 4 logs and increased the pH of biofilms from a cariogenic acidic value (4.5) to 6.9, making it promising in enhancing resin-tooth bonding, strengthening tooth structures, and inhibiting secondary caries at the edges of restorations.

In a study by Jahanfar Jahanbani et al. [55], the effect of magnetic iron oxide nanoparticles (SPIONs) on mitochondria in oral squamous cell carcinoma (OSCC) cells was investigated and their potential use as a treatment for this type of cancer. The results showed that SPIONs caused a significant increase in the level of reactive oxygen species (ROS) in OSCC mitochondria compared to normal mitochondria. This increase in ROS was due to the disruption of the electron transport chain, which led to a decrease in the activity of the enzyme succinate dehydrogenase (SDH) in OSCC mitochondria. The subsequent effects of the magnetic nanoparticles were monitored, and the researchers observed a collapse in the mitochondrial membrane potential (MMP) and mitochondrial swelling in OSCC cells, which did not occur in normal mitochondria. The nanoparticles also led to the release of cytochrome C from mitochondria into the cytosol, which enhances the apoptotic signal (cell suicide) through activation of the caspase-3 cascade. Furthermore, cell viability decreased and lipid peroxidation state (LPO) levels increased in OSCC cells, suggesting that magnetic nanoparticles induce oxidative stress in cancer cells. These changes, which include increased ROS, mitochondrial membrane breakdown, cytochrome C release, and increased caspase-3 activity, suggest selective toxic effects on OSCC mitochondria only, making magnetic nanoparticles (SPIONs) a promising candidate as a potential treatment for oral squamous cell carcinoma (OSCC). The study concluded that magnetic nanoparticles may be promising candidates for the treatment of oral squamous cell carcinoma.

In a study conducted by Jalal Pourahmad et al. [56], the effect of magnetic iron oxide nanoparticles (SPIONs) on mitochondria isolated from oral tongue squamous cell carcinoma (OTSCC) cells was investigated. The study aimed to evaluate the cytotoxicity of these nanoparticles using mitochondrial assays. Mitochondria were isolated from cancer tissues and control tongue squamous cell carcinoma cells of male Wistar rats (6 or 8 weeks old) and exposed to different concentrations of SPIONs (30, 60, 120 nM). The results showed an increase in the production of reactive oxygen species (ROS) as the main mechanism of the effect of SPIONs, followed by a collapse of the mitochondrial membrane potential, release of cytochrome C from mitochondria, and mitochondrial swelling in mitochondria isolated from OTSCC cells. The results also showed that exposure to SPIONs reduced the activity of the enzyme succinate dehydrogenase complex II in mitochondria isolated from oral tongue cancer cells. These effects were selectively toxic to the mitochondria of OTSCC cells without significant effect on mitochondria from normal tissues. Based on the results, the researchers concluded that SPIONs may be a promising therapeutic candidate for the treatment of oral tongue squamous cell carcinoma (OTSCC).

In a study by Dianbao Zhang et al. [57], a novel therapeutic strategy was developed using polyethyleneimine (PEI)-modified magnetic iron oxide (Fe_3O_4) nanoparticles to deliver inhibitory small RNAs (siRNAs) targeting BCL2 and BIRC5 genes into oral cancer cells (Ca9-22). The PEI-enhanced nanoparticles were prepared and their properties were tested using transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), and vibrating sample magnetometer (VSM). The results showed that the nanoparticles were able to inhibit siRNA in a concentration-dependent manner, and the high cell uptake capacity of the nanoparticles/siRNA was found under the influence of a magnetic field, using Pearl's blue dye and FAM labeling. The efficacy of siRNA delivery was verified by techniques such as quantitative PCR and Western blot analysis, which showed high efficiency in suppressing the target genes BCL2 and BIRC5 at the mRNA and protein levels. The results also showed that siRNA delivery using nanoparticles significantly reduced the survival and migration ability of Ca9-22 cells, reflecting an anti-cancer effect. By creating a magnetic field during the transport process, the superparamagnetic feature of the nanoparticles was used to increase the delivery efficiency, making the system more effective than conventional delivery methods like Lipofectamine 3000. According to the findings, polyethyleneimine-modified nanoparticles have a wide range of potential uses in the treatment of cancer and other illnesses as an efficient siRNA delivery system.

4 Conclusion

In conclusion, because of their distinct physicochemical characteristics, capacity to precisely target cells, and decreased systemic toxicity of medicinal chemicals, magnetic nanoparticles (MNPs) have great promise as a tool in both dental and pharmaceutical therapy. Their effectiveness against bacteria resistant to traditional antibiotics highlights the significance of this technology in the fight against infections, and their use in drug delivery for the treatment and prevention of dental diseases like caries, periodontal infections, and root canal therapy is a revolution in conventional treatment. Additionally, the application of magnetic nanoparticles helps to improve the transparency and corrosion resistance of dental materials, which improves both the functional and aesthetic elements of cosmetic dentistry. A promising alternative in the near future, magnetic nanoparticles continue to show their capacity to enhance treatment outcomes as a result of growing research and studies in this area. To assess their safety and biocompatibility in clinical settings, more research is necessary.

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