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Research Progress on Silver Nanoparticles in the Prevention and Treatment of Oral Diseases

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Abstract: Silver compounds and silver nanomaterials have shown excellent antimicrobial effects on microorganisms and have been used commonly in the clinic in recent years for the prevention and treatment of a variety of oral diseases, such as caries, gingivitis, pulpitis, dentin hypersensitivity and oral cancer. Since conventional silver and silver compounds lead to tooth staining, studies have indicated that silver nanoparticles can alleviate this problem and exhibit outstanding antimicrobial effects. Nowadays, nanomedicines have become a research topic as an emerging potential anticancer therapeutic drug. These nanomedicine carriers are characterized by intelligent response to the tumor microenvironment, which can deliver the drugs precisely to the tumor site and improve the therapeutic effect. Nanomedicine can also decrease the distribution of drugs in normal tissues, reduce side effects, and improve patient tolerance to treatment. The application of environmentally responsive nanomedicine in the treatment of oral squamous carcinoma demonstrates great potential and may become a novel strategy for the treatment of cancer. Consequently, the article provides a comprehensive overview of the advances in the application of silver materials in the prevention and treatment of oral diseases, as well as describes the possibility of nano-targeted therapy as an innovative strategy for the treatment of oral squamous carcinoma, which provides a new way of thought in tumor therapy and brings new expectation for enhancing the effectiveness of cancer treatment.

Keywords: Silver Nanoparticles; Antibacterial; Dental Caries; Oral Squamous Carcinoma; Nanomedicine.

1. Introduction

Silver is extremely antimicrobial and is a widespread metallic element in nature. The oral cavity contains a large number of microorganisms that cause a wide variety of infections. The progress and pathogenesis of many systemic diseases are affected by oral infections. Silver is commonly used clinically in the prevention and treatment of various oral diseases, such as caries, gingivitis, periodontitis and periapical disease, dentin sensitivity. However, conventional silver metals and their compounds cause tooth discoloration, and these side effects depend on the amount and frequency of application. Recent studies have found that silver-containing nanomaterials can ameliorate the problem of tooth discoloration and exhibit excellent antimicrobial effects. In addition, nanomedicines are seen as an emerging potential anticancer therapeutic agent [1], It has attracted wide attention in the field of oral squamous cancer treatment. Therefore, this review outlines the progress of the application of silver nanomaterials in the prevention and treatment of oral diseases, explores their mechanisms, and emphasizes that nano-targeted therapies have opened up new avenues for the treatment of oral squamous carcinoma.

Nanomaterials are capable of continuously releasing substances with bactericidal or bacteriostatic effects under certain conditions, which can penetrate the cytoplasmic membrane of cells and lead to cell lysis. Nanomaterials whose antibacterial activity acts by inactivating cellular enzymes and DNA, thereby inactivating electron donor groups such as carboxylates, amides, thiols, indoles, and hydroxyls. They act by creating pores in the bacterial cell wall, leading to increased permeability and cell death. Some of the possibilities raised in this regard include free metal ion toxicity due to dissolution of metals from the nanoparticle surface, or oxidative stress due to the generation of reactive oxygen species (ROS) on the nanoparticle surface[2]. Furthermore, the antimicrobial effect depends on the type of material used to prepare the nanoparticles and their particle size. Therefore, reducing the particle size is an effective means to improve biocompatibility. The smaller size of nanoparticles provides better penetration into cells and tissues and shows strong bactericidal effect [3]. Recently, it has been reported that silver nanomaterials have been extensively studied and used in different areas of dentistry and in various dental materials.

2. Application of Silver Nanomaterials in Caries

silver nanoparticles (AgNPs) is a highly effective antimicrobial agent. AgNPs carries a large number of hydroxyl groups (- OH) on its surface, resulting in strong antioxidant properties. Oxidative stress leads to the formation of an oxide film (mainly composed of iron oxide) on the surface of enamel, which leads to adhesion of the dentin surface to the enamel. As a result of the chemical reaction that occurs between hydroxyl groups (- OH) and metal ions (Ag^+), hydroxyl silver ions are produced and the complex has strong antimicrobial properties. Nano-silver is effective against cariogenic bacteria such as Streptococcus mutans and Lactobacillus, which are the main bacteria that promote the caries process [4]. Silver nanoparticles combined with fluoride and sodium trimetaphosphate (TMP) to form multifunctional nanocomposites have been shown to protect demineralized enamel and significantly inhibit the growth of Streptococcus pyogenes and Candida albicans biofilms [5]. The addition of bio-silver nanoparticles to adhesive systems enhances the antimicrobial effect by maintaining the bond

strength of the adhesive. It was discovered that the antimicrobial activity of AgNPs obtained by green synthesis was lower than that obtained by chemical synthesis, without toxic effects on cells, and that they improved the microtensile bonding between the primer and the adhesive at a specific concentration [6]. Antimicrobial adhesives can prolong the life of restorations by protecting the tooth-adhesive interface[7]. In addition, novel mesoporous silica nanoparticles carrying nanosilver and chlorhexidine, which are pH-sensitive, have effective antimicrobial effects and modulate the biofilm to a non-cariogenic tendency, which reduces the cariogenic species by nearly half, and are promising for application in mouthwash or as a resin filler to prevent dental caries[8]. Nevertheless, the long-term application of silver nanoparticles as dental restorative materials can potentially cause toxic damage to the central nervous system[9].

Nanosilver Fluoride (NSF) is currently being investigated as a potential treatment for dental caries due to its ability to inhibit the adhesion and growth of cariogenic bacteria and reduce demineralization [11]. Compared to other silver compounds, NSF has the same caries preventive effect as silver diamine fluoride (SDF) without causing staining of carious tissues [12,13]. In a recent randomized clinical trial, it was demonstrated that 5% NSF was as effective as, if not superior to, 38% SDF in preventing caries progression in milky molars, without causing dentin staining [14]. Dias et al[15] exhibited in vitro experimental studies that fluoride coupled with AgNPs may improve the chemical structure and stability of collagen, but does not protect lesion surfaces from demineralization. Simultaneously, researchers have obtained comparable results with SDF and sodium fluoride for the treatment of root lesions dentin with NSF under in vitro conditions with no significant difference[16]. The application can prevent or inhibit the development of dental caries, can lead to a better aesthetic effect, and the effect of caries prevention is proportional to the concentration of the drug[17]. NSF is an excellent alternative to SDF, but its biomimetic remineralization and biofilm-forming effects require in-depth studies to prove its viability. Focusing on preventive and non-invasive dental treatments as the most effective and least costly way to improve the oral health status of populations provides valuable insights into the use of professionally applied fluoride in low- and middle-income countries and provides recommendations for its utilization[18].

3. Application of Silver Nanomaterials in the Treatment of Endodontic Diseases

Silver nanoparticles (AgNPs) have broad-spectrum anti-microbial activity and anti-biofilm formation, and are considered to be effective disinfectants for root canal irrigants, intracanal medications, and root canal sealers [19,20]. Due to their nanoscale, AgNPs penetrate deep into the root canal system and dentin tubules and enhance the antimicrobial properties of root canal rinses and sealers [21]. Use of AgNPs as a final rinse in root canal treatment increases the fracture resistance of roots after root canal treatment [22]. While AgNPs act as a carrier for intracanal medications, it progressively increases dentin hardness and promotes antimicrobial properties in endodontically treated teeth. The main bacteria isolated from cases of persistent root canal infections, reinfections and treatment failures were mostly Enterococcus faecalis, and the inhibitory effect of AgNPs on Enterococcus faecalis has been well documented [23]. Treatment with AgNPs during endodontic retreatment not only inhibited bacterial growth and biofilm formation, which in turn led to a significant reduction in postoperative pain in patients [24]. Flushing the root canal system with silver nanosolutions activated by passive ultrasonic flushing and photon induced photoacoustic flow results in better removal of Enterococcus faecalis [25]. The combination of ZnO nanocomposites with silver ions to form silver-zinc oxide complexes was found to be effective in improving antimicrobial efficacy and biological properties. The addition of ZnO/Ag nano-complexes to novel apical filling materials improves the antibacterial effect and increases the compressive strength of the materials in a specific range, but the cytotoxicity increases with increasing ZnO/Ag content [26]. The unique properties of AgNPs render them ideal additives for different endodontic biomaterials. Nevertheless, the effects of silver nanomaterials on dental pulp cells still need to be further demonstrated in a large number of studies, which opens new avenues for deeper understanding and exploration of AgNPs.

4. Application of Silver Nanomaterials in the Treatment of Oral Squamous Carcinoma

Silver nanoparticles have effective anti-microbial, anti-viral and anti-cancer activities and have become a hotspot for cancer therapy. Silver nanoparticles can disrupt bacterial signaling, leading to reduced proliferation and apoptosis. AgNPs consistently release higher amounts of silver ions than silver particles of the same weight. The therapeutic potential of AgNPs is rather fixed and ineffective in terms of shape and capping material. AgNPs are mainly taken up by endocytosis-related mechanisms, after which the organelles are directed to lysosomal fusion. The acidic environment of the lysosome enhances the release of silver ions from AgNPs, the reactive ions of which subsequently disrupt cellular homeostasis and further lead to apoptosis[27]. In the field of oral surgery, silver nanoparticles can be used as antibacterial wound dressings for infected wound healing applications [28]. The potential application of silver nanoparticles in the rapid detection of oral cancer with 100% sensitivity was also demonstrated. The results demonstrated that Raman scattering method (SERS) with Ag-TiO2 nanoparticles as substrate showed good detection performance and could be used for rapid and accurate cancer detection[29]. The above research discoveries shed insight into the potential of silver nanoparticles for the detection and diagnosis of oral squamous cell carcinoma, and provide crucial clues for further exploration of the role of silver nanoparticles in determining the grading of tumors.

Recent studies have found that AgNPs prepared by green synthesis or chemical reduction have a significant role in decreasing the viability of head and neck cancer [30], breast cancer[31,32], prostate cancer[33] and other cancer cells and cancer stem cells. The study further revealed that AgNPs have cytotoxic effects on normal cells such as splenocytes and thymocytes. AgNPs have been reputed to regulate apoptosis and differentiation by modulating various signaling molecules in a concentration-dependent manner[34]. Cal33 responded to the lowest inhibitory concentration of silver nanoparticles in all head and neck cancer cell lines, but three times the inhibitory concentration of Cal33 was observed in

Cal33 cancer stem cells at increased resistance to AgNPs [35]. These investigations revealed the relationship between silver nanoparticles and cancer cells and cancer stem cells, which can be used as new candidates for further anticancer research, as well as providing potential therapeutic and predictive strategies, offering important clues for deeper understanding and intervention in cancer development. It is worth mentioning that silver nanoparticles as smart drug formulations can be combined with chemotherapy and thermotherapy to target different tumor sites, and exhibit high anti-tumor activity through mechanisms such as enhanced cellular uptake and silver-ion-induced cell membrane damage, which provides a novel combinatorial strategy for the complete elimination of cancer stem cells[36]. From the therapeutic point of view, nano-targeted therapies are regarded as potential anti-cancer therapeutic modalities, which afford new ideas for tumor treatment and bring new expectations for enhancing the effectiveness of cancer treatment. Consequently, further research and development of environmentally responsive nano drug carriers are of great significance for improving the therapeutic efficacy of oral squamous carcinoma.

5. Summary

Silver compounds and silver nanomaterials have a widespread application in dentistry. Topical application of ammonia silver fluoride is an efficient, straightforward, expeditious and reliable method of dental treatment. Further research continues on the broader applications of silver-containing compounds and silver nanomaterials in the dental field, especially with regard to the integration of the products into restorative protocols and methods to minimize side effects, particularly with regard to product-related staining and discoloration. There is also a requirement to investigate nanosilver for cytotoxicity and dose-related safety issues in order to avoid pulpal irritation and general adverse reactions.

Regarding the application of silver nanomedicine carriers for the treatment of oral squamous carcinoma, it is still at an early stage of research. Targeted nanotherapies provide a new framework for the treatment of cancer and offer a new research direction for the individualization and precision of cancer treatment. The future research should mainly concentrate on optimizing the nanomedicine carriers, targeting the tumor microenvironment, and exploring its clinical application in the treatment of oral diseases. This will contribute to a remarkably better therapeutic experience to further improve the survival rate and quality of life of oral cancer patients, and bring a more innovative and individualized treatment to the field of dentistry.

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