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Concise Review

Silver Compounds for Caries Management

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ABSTRACT

Silver metal and compounds have antibacterial properties, although their action's mechanisms are not fully understood. Scientists generally consider that silver disrupts the bacterial cell wall. It causes a structural change in the bacterial cell membrane and cytoplasm. It also stops deoxyribonucleic acid replication, resulting in inactivating enzymatic activity and cell death. The antimicrobial effect of silver-containing compounds relies on the release of bioactive silver ions. Hence, silver metal and compounds have been used in medicine to prevent infection for hundreds of years. Silver metal and compounds are also used as antibacterial agents in dentistry. Studies have shown that silver compounds are effective in the management of dental caries. Fluoride-containing silver compounds have been found in experiments to be beneficial at remineralising dental cavities. Silver diamine fluoride (SDF) can assist in preventing and arresting tooth cavities. The World Health Organization included SDF in its Model List of Essential Medicine for both adults and children in 2021. Clinicians also use SDF to manage dentine hypersensitivity as well as to inhibit growth of periodontal pathogens. However, traditional silver compounds cause tooth discolouration because of the silver-staining effect. These side effects of their applications depend on the amount applied and the frequency of application. Researchers are developing nanosilver fluoride and silver nanoparticles to overcome the staining. This review gives an overview of the antibacterial mechanism of silver compounds, namely silver nitrate, silver fluoride, SDF, silver nanoparticles, and nano silver fluoride for caries management. The outlook for the future development of silver compounds will be discussed.

Introduction

Silver is a noble metal with high thermal and electrical conductivities, similar to platinum and gold. Silver nitrate is typically utilised in the synthesis of silver compounds. Naturally occurring silver compounds include silver sulfide, silver arsenite, silver selenide, and silver telluride.[1,2] One of the most common uses for silver compounds is as an antibacterial agent. The application of silver in medicine includes water disinfection, wound treatment, and medical equipment coating.[3] This capability results from the action of the silver ion, Ag^+, which breaks down the bacterial cell membrane and contents and prevents the normal cell processes by generating reactive oxygen species (ROS).[4] In dentistry, silver compounds, including silver nitrate, silver fluoride, and silver diamine fluoride (SDF), are commonly used for caries

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treatment. Fluoride-containing products like SDF can remineralise caries lesions with the formation of fluorapatite.[5] Additionally, nanosilver particles preserve the ability to prevent cavities whilst also avoiding undesired discolouration.[6] This review aims to illustrate their antibacterial mechanisms and application for caries management and to provide an outlook on the future development of silver compounds.

Antibacterial mechanisms of silver ions and nanosilver particles

Silver ions possess the capability to damage the cell envelope and contents of bacteria, consequently killing bacterial cells and inhibiting cell division. The outer cell layers rupture and the cytoplasm leaks into the extracellular matrix. The enzymes and proteins in the bacteria are the primary targets because of the strong binding between the silver ion and functional groups, including thiol and amino acid.[7] Exposure to silver ions also results in the generation of ROS. Figure 1 shows the antibacterial mechanism of silver ions to bacteria cell.

Destabilisation of the bacterial cell envelope

Silver ions bind to functional groups in enzymes and proteins, such as thiol groups and amino acids. This causes the cell membrane to rupture and the cytoplasmic membrane to separate. Silver ions induce the release of potassium ions and a reduction in adenosine triphosphate levels, resulting in disruption of the bacterial cell envelope.[4] Aside from their impact on bacterial enzymes, silver ions can accumulate as granules in the bacterial cell envelope, causing the cytoplasmic membrane to separate from the cell wall. The bacteria are ultimately lysed, and cytoplasm leakage is observable.[8]

Interaction with molecules inside the cell

Silver ions swiftly penetrate into bacteria cells and bind to amino acids, ribosome and deoxyribonucleic acid in cytoplasm.[7] Silver ions inactivate enzymes and inhibit bacterial action through forming a strong binding with the thiol groups in amino acids, which have the highest affinity for silver ions.[9] Silver ions bind to the S2 protein, a bacterial ribosome component, triggering denaturation of the ribosome structure and suppression of protein and enzyme biosynthesis.[10] In addition, the silver ions exhibit specific interactions with deoxyribonucleic acid because silver ions bind preferentially to natural bases rather than to the phosphate groups. They interact with nucleic acids through binding to pyrimidine bases and cause them to change from the relaxed form to the condensed form. The inhibition of deoxyribonucleic acid

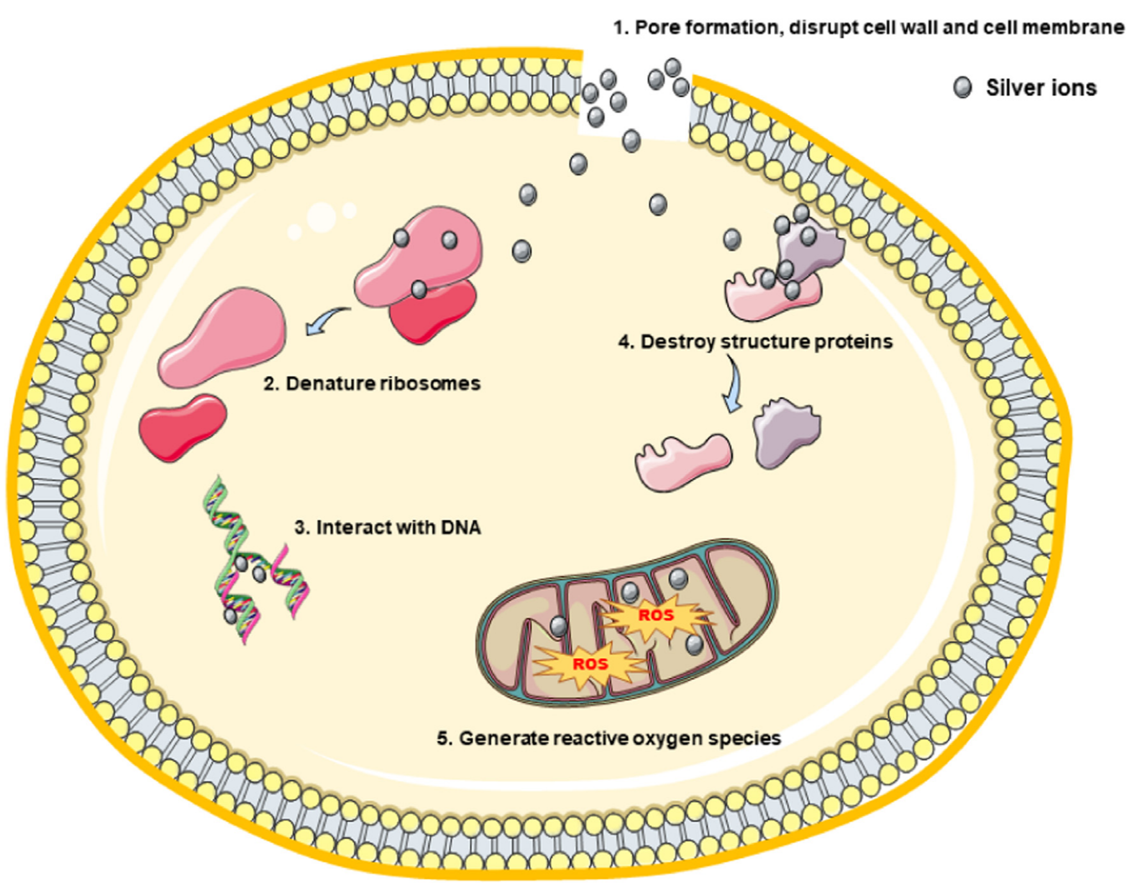

Fig. 1 – The antibacterial mechanism of silver ions to bacteria cell.

replication hinders the process of protein synthesis, cell division, and bacterial replication.[11]

ROS production

The induction of ROS production is related to the silver ion –mediated inhibition of the bacterial respiratory chain.[12] Silver ions inhibit the main respiratory proteins such as cytochrome b and increases the production of the ROS. When the ROS level exceeds the cellular antioxidant defense system's capacity, the oxidative stress process occurs, which leads to protein damage, deoxyribonucleic acid strand breakage, inhibition of cell proliferation, and cell death.[13]

Antibacterial mechanisms of silver nanoparticles

Silver nanoparticles have a higher surface-to-volume ratio and a smaller size to permeate cell membranes, making them unique antibacterial agents. Silver nanoparticles share a similar antibacterial mechanism mentioned above since they release silver ions sustainedly.[14] However, there is a debate on the efficacy of these 2 antibacterial agents.[15-17] Silver nanoparticles also have a different antibacterial mechanism over silver ions, which is the dephosphorylation of Gram-negative bacteria.[18] In addition, the morphology of the silver nanoparticles, including shape and size, have a significant impact on practical application. When compared to triangular or bigger spherical silver nanoparticles, smaller spherical silver nanoparticles were shown to be the superior antibacterial agents.[19]

Silver compounds for caries management

The common silver compounds used for caries management are silver nitrate, silver fluoride, and SDF. The solubility of most silver compounds in water is very low and only a few silver compounds such as silver acetate, silver nitrate, and silver fluoride are soluble. The solubility of silver halides decreases from fluoride to iodide, but the silver diamine halides are soluble in water. The Table summarises the solubility of common silver compounds. Recently, novel silver nanoparticles have been studied and developed to provide alternatives for caries management. All of these silver compounds have antibacterial properties to inhibit the activity of oral bacteria. Fluoride, which promotes mineralisation, is often added or used together to manage dental caries and dentine hypersensitivity. Figure 2 summarises the synthesis of silver compounds and their applications for caries treatment.

Table – Chemical formula and solubility of common silver compounds.

Silver compound	Chemical formular	Solubility in water at 25 °C (g/L)
Silver fluoride	AgF	1.8×10^{3}
Silver nitrate	$AgNO_3$	2.2×10^{2}
Silver acetate	CH_3COOAg	11
Silver oxide	Ag_2O	2.2×10^{-2}
Silver chloride	$AgCl$	1.9×10^{-3}
Silver iodide	AgI	2.6×10^{-6}

Silver nitrate

Starting in the 1840s, silver nitrate was the first silver compound used for caries treatment.[20] Howe developed an ammoniacal silver nitrate solution (Howe's solution) in 1917 to arrest caries. The proposed reaction mechanism of silver nitrate with hydroxyapatite forms calcium nitrate, silver phosphate, and silver oxide. Both silver phosphate and silver oxide are soluble in the acidic environment; thus, alkaline ammonia is added to the solution. Howe's solution can penetrate deeper into the carious dentine. Dentists used Howe's solution for caries treatment until the 1950s.[21]

Silver nitrate possesses antibacterial properties, but it cannot remineralise carious lesions. Sodium fluoride is a common fluoride agent used to remineralise enamel and dentine. The fluoride ions can remineralise caries lesions at an early stage by forming fluoroapatite and precipitating on the demineralised enamel surface. A study reported that almost all (98%) caries lesions from a sample of 106 children were arrested for up to 4 years using this protocol.[22] A randomised controlled trial concluded that semi-annual application of 25% silver nitrate solution followed by a 5% sodium fluoride varnish was not less effective than a 38% SDF in terms of caries prevention in kindergarten children.[23,24] The trial found no significant adverse effects except for black staining of the arrested caries lesions. The same research group discovered that silver ions in the silver nitrate solution interacted with exposed collagen, which are capable of preventing dentine collagen degradation in vitro.[25] As a result, it is indicated as an alternative method for caries management, particularly in regions where SDF is unavailable.

Silver fluoride

Clinicians in Western Australia used 40% silver fluoride followed by 10% stannous fluoride to treat lesions of primary molars in young children living in a disadvantaged community in 1978, aiming to relieve the backlog of unavailable treatment needs.[26] Stannous fluoride is a reducing agent, which reduces the silver ion to silver.[27] The combination of silver fluoride and stannous fluoride can treat root caries in older adults, and the solution does not cause soft tissue irritation or chemical burn.[28] It has been established that topical administration of silver fluoride is beneficial in increasing the mineral density of demineralised enamel and dentine lesions.[29] Gotjamanos et al[30] assessed the effect of silver fluoride with restoration of glass ionomer cement to teeth with deep proximal caries and found an intact odontoblast layer as well as reparative dentine. A community trial reported that silver fluoride treatment was effective in managing caries in children in remote indigenous communities.[31] However, silver fluoride is less stable and more alkaline than SDF, which limits its clinical application considering the practical application and safety issues.[32]

SDF

SDF was first developed as a therapeutic agent for caries management by Japanese dentists in the 1970s.[32,33] The US Food and Drug Administration (FDA) approved SDF as a

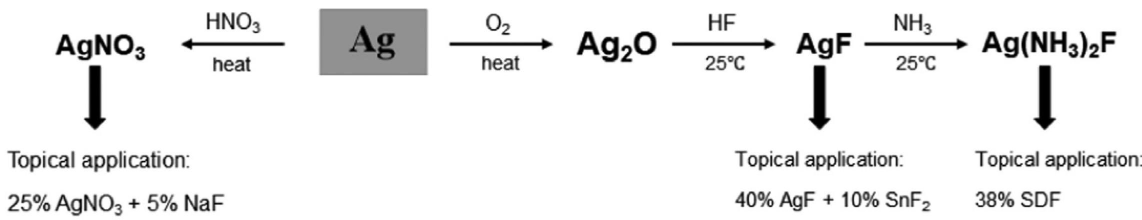

Fig. 2 – Silver compounds synthesis and their use for caries treatment.

desensitising agent in 2014, and the US FDA then approved the application of SDF for arresting caries in 2016.[34] In 2021, the World Health Organization designated SDF as an essential drug that is both effective and safe for patients. Furthermore, because it produces no aerosols and has a low risk of cross-infection, it can be utilised for caries control during the COVID-19 pandemic.[35]

Studies reported that SDF was effective in inhibiting bacterial growth and remineralising caries lesions.[36] It exhibits strong antibacterial activity and inhibits cariogenic bacteria biofilm formed by *Streptococcus mutans, Streptococcus sobrinus, Lactobacillus acidophilus, Lactobacillus rhamnosus*, and *Actinomyces naeslundii*.[37] The production of fluoroapatite and the suppression of collagen breakdown both contribute to SDF's effectiveness in remineralising caries lesions. In an in vitro study simulating the remineralisation of SDF in saliva using a buffered calcium phosphate system, the formation of fluoroapatite on the surface of carious lesions becomes hard and prevents further erosion.[38] Bacteria collagenases, matrix metalloproteinases (MMPs), and cysteine cathepsins destroy dentine type I collagen during caries formation. Research has reported that 38% SDF solution can inhibit the activity of theses enzymes, which prevents further degradation of the organic matrix in a dentine carious lesion.[39] SDF's alkaline pH neutralises the acidic environment, rendering the enzymes inactive. Silver ion inhibits MMP-2 and MMP-9, whilst fluoride ion inhibits MMP-2, MMP-8, and MMP-9.[40]

SDF is effective in arresting crown caries in children[41–43] and root caries in elderly adults.[44,45] A biannual application of 38% SDF is recommended for arresting dentin caries.[46] The in vitro study reported its efficacy in preventing secondary caries.[47]

Despite the fact that SDF has been used successfully to treat caries, the most frequently reported adverse effect is the black staining of the carious lesions.[48] The teeth staining may make some patients unsatisfied with the SDF treatment, especially in anterior teeth (Figure 3). The black stain could be due to the silver forming from the decomposition of the SDF, that is, the reduction to form silver and silver salts, such as silver chloride, formed after applying SDF on the teeth. Moreover, dark staining can form after light curing used in the later restoration period due to the photosensitivity of silver ions.[49] Researchers proposed combining SDF with potassium iodide to minimise the black staining since this combination generates tripotassium phosphate as well as silver iodide, forming white precipitate and reducing free silver ions.[27,50] The recovery of enamel microhardness was not significantly different and there were no changes in enamel porosity after SDF or SDF and potassium iodide application. However, this method was questioned due to a short-term impact and a reduction of bond strength of the resin composite to demineralised dentin.[51–53]

Silver nanoparticles and nano silver fluoride

Silver nanoparticles are particles of silver within the nanometer scale (1 nm to 100 nm). There are 3 main approaches used to synthesise silver nanoparticles: physical, chemical, and biological synthesis.[54] Owing to the high surface energy, the silver nanoparticles tend to agglomerate together.[55] Surface capping agents (also called as stabilisers), such as polyethylene glycol and polyvinyl alcohol, are added to prevent the aggregation of the nanoparticles (Figure 4).[56]

Silver nanoparticles are emerging as a new type of dental material due to their strong antimicrobial properties since they can continually release silver ions. In addition, silver nanoparticles can penetrate through the cytoplasmic

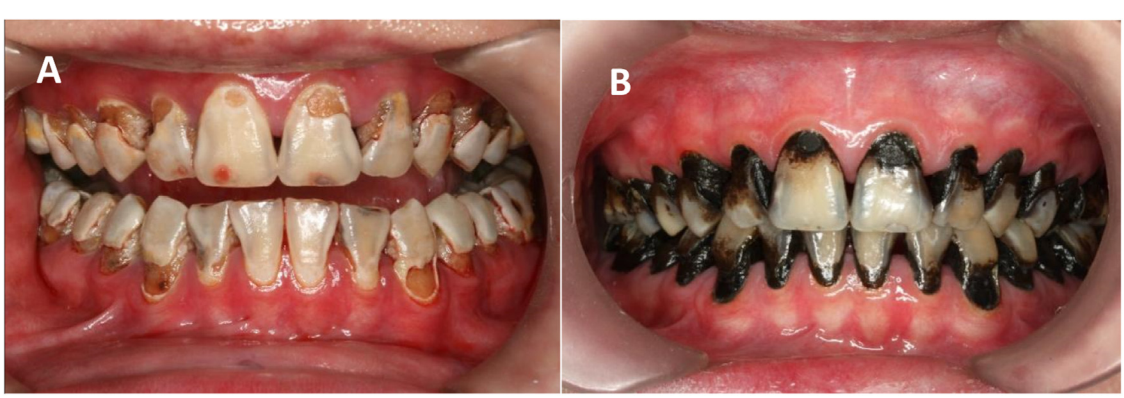

Fig. 3 – The carious teeth before and after caries arrest by silver diamine fluoride.

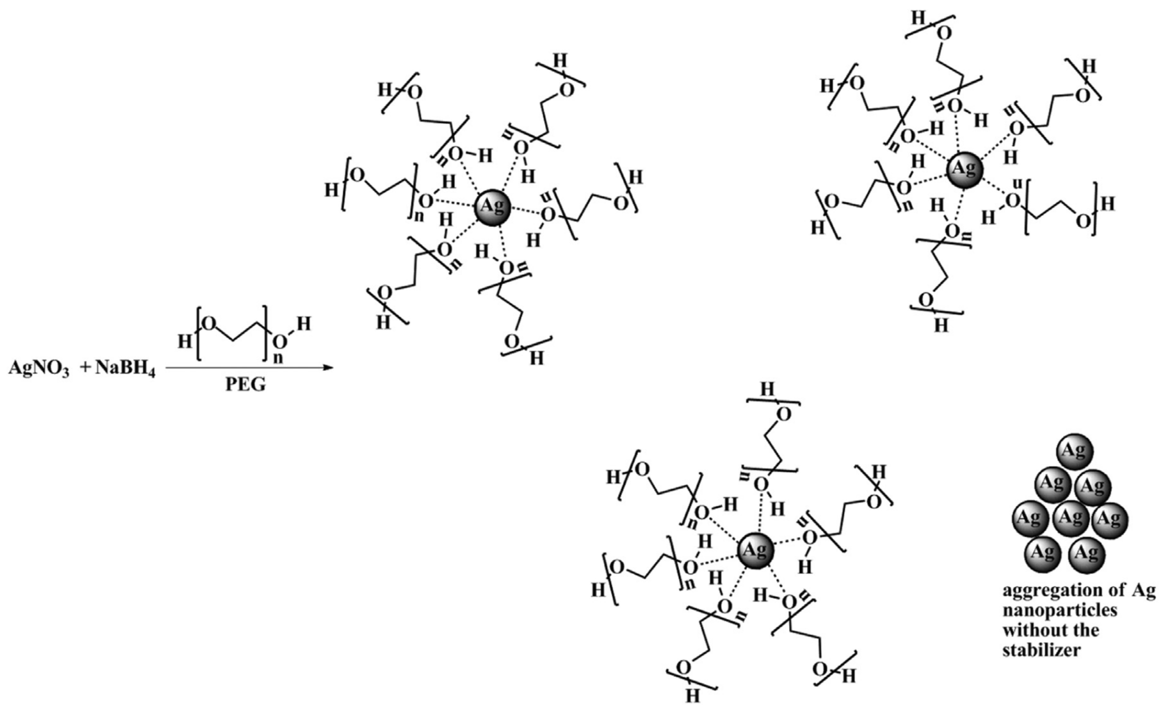

Fig. 4 – Polyethylene glycol (PEG) prevents aggregation of silver (Ag) nanoparticles.

membrane because of their nanoscale size, resulting in cell lysis. To completely comprehend these mechanisms and to improve silver nanoparticles for clinical application, more investigation is required. Silver nanoparticles can be added to acrylic resins for fabrication of removable dentures, composite resin for direct restoration, irrigating solution for root canal treatment, membrane for guided tissue regeneration, and titanium coating for implant therapy.[57] They also have the potential as a diagnostic tool for early detection of oral cancer and even as a specialized treatment.[58,59]

Nano silver fluoride is being studied as a potential therapy for tooth caries owing to its capacity to efficiently inhibit adhesion and the growth of cariogenic bacteria and reduce demineralisation.[60] They cause no significant black stains compared with other silver compounds.[61,62] Two clinical studies revealed that nano silver fluoride had the same effect on arresting caries as SDF without staining carious lesions.[63,64]

Health and safety issues of silver compounds

The major health and safety concern with silver compounds as antibacterial agents is whether they can reduce bacterial development whilst not interfering with normal cells, tissues, and organs. Although intact skin is an efficient barrier against silver, the deposition of silver is detected at mucosal surfaces and compromised skin.[65] Acute symptoms such as decreased blood pressure and stomach irritation could occur upon excessive exposure to silver ions. Chronic symptoms include fatty liver and kidney degeneration, argyria, and argyrosis, which is an irreversible pigmentation of internal organs, skin, or the eyes caused by silver compounds applied to mucosal surfaces, ingested and injected into the body, or being exposed for extended periods of time.[66]

The concentration of silver nitrate in the dental commercial product is 25%. A small amount of a single application (about 0.65 mg silver nitrate for each application using a micro-brush) is safe for treatment.[20] Side effects of SDF treatment such as gingival erythema, gingival inflammation, and mucosal or skin burns (due to its strong alkalinity) have been reported.[46] The burns are small and mildly painful in the mucosa and disappear after 48 hours without further treatment.[48]

Silver nanoparticles can accumulate in organs, especially in the liver and spleen, after a massive dose. Because of the nanoscale size, silver nanoparticles can pass through the blood–brain barrier to accumulate and increase the permeability of the barrier, which is associated with neurologic disorders.[67,68] However, there is a lack of studies relating to the long-term safety of realistic exposure doses in humans.[69] The widespread use of silver nanoparticles may contribute to the development of antibiotic resistance. As a result, it restricts their therapeutic application and necessitate careful modification of dosage.

Future outlook

The silver compounds with fluoride are effective to arrest caries and remineralise carious lesions. However, the major problem of using silver compounds like SDF is the inevitable discolouration. The design and selection of silver compounds in the future studies will be based these criteria: (1) their stability of avoiding decomposition of silver to form staining, (2) they possess stronger antibacterial activity and remineralisation capability, and (3) they are biocompatible and do not induce tissue irritation.

Silver nanotechonology has been developed as an alternative to arrest caries, as it would not stain the carious lesion surface. Nanocomposite aggregation is one popular method for meeting more advanced clinical needs. Researchers used to combine various chemicals including calcium glycerophosphate, sodium trimetaphosphate, or plant extract with silver nanoparticles together to exert more efficient antibacterial activity as well as inhibit the process of demineralisation.[70–72]

Other approaches to overcome these problems will be to search for other classes of silver compounds and develop new silver compounds. A rare class of silver compound, tetra-silver tetra-oxide (Ag_4O_4), has strong antibacterial activity. It has been used in medicine to treat diseases such as eczema, dermatitis, cancer, and diabetic foot ulcers.[73] The strong antibacterial activity of Ag_4O_4 is due to the Ag (III). A study reported that antibacterial activity of Ag (III) was much stronger than Ag (I).[74] It is less stable and would not form staining upon light irradiation. Silver carbene complexes have been reported to possess antibacterial activity, which is especially effective in inhibiting drug-resistant bacteria.[75] Nevertheless, they are still in the early stages of in vitro assessment.

Conclusion

Silver is the important starting material to synthesise the silver compounds. Silver nitrate, silver fluoride, and SDF are the most frequent antibacterial agents used in caries management, as based on their remarkable performance. The adverse effect of black staining is a main concern. Other side effects, such as gingival and mucosal irritation, can occur but can heal in a short time. Nevertheless, the treatment is effective, economic, painless, and simple to use. A future direction will be the development of new classes of silver compounds and novel silver nanoparticles to improve the performance of silver compounds currently used in dentistry.

Conflict of interest

None disclosed.

Author contributions

Grace Y. Xu and Christie Y.K. Lung conceived and drafted the manuscript; Iris X. Yin, Irene S. Zhao, Edward C.M. Lo, and Chun Hung Chu reviewed and edited the manuscript.

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