Application of Silver in Medicine and Pharmacy

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Contributor: Dominik Żyro , Joanna Sikora , Małgorzata Iwona Szynkowska-Jóźwik , Justyn Ochocki

In the context of the growing resistance of microorganisms to available, widely used antibiotics, silver plays a key role. There is only one known case of bacterial resistance to silver—the *Pseudomonas stutzeri* strain, which naturally occurs in silver mines. The development of research in the field of coordination chemistry offers great opportunities in the design of new substances in which silver ions can be incorporated.

silver (I) silver (I) salts silver (I) complexes

1. Introduction

Pure silver is scarce in the natural environment which is probably why it attracted attention of ancient people much later than gold. According to the Greek Chronicles, its discovery around 1300 BC is attributed to Ajakos. It was Hippocrates who had observed that this remarkable element has biological properties in the treatment and prevention of diseases. The Phoenicians kept water, wine, and vinegar in silver pots to prevent them from spoilage. The antimicrobial properties of silver were scientifically confirmed as early as in the 19th century, which laid the ground for the application of metal and its compounds in medicine. During World War I, silver compounds were used to prevent infections as antibiotics were not known then. As a standard solution, silver (I) nitrate was used which was later replaced with sulfadiazine ointment. With the discovery of antibiotics and sulfonamides, the interest in silver-containing drugs has temporarily decreased, but is now gaining new momentum. It was shown that silver (I) cation has a bactericidal, antiseptic, anti-inflammatory and astringent effect. It is a natural bactericidal metal that is effective against 650 species of bacteria with low reported resistance. This is advantageous over almost all antibiotics, the use of which steadily becomes more and more vain. The growing problem of microbial resistance to antibiotics and chemotherapeutics is a challenge for modern medicine. Every year, despite the advancement of treatment methods, growing health care standards and better public awareness of pharmacotherapy, the number of deaths caused by antibiotic-resistant bacterial strains increases [1]. This substantiates the search for new compounds with potential antimicrobial activity and turns attention of researchers to the potential use of precious metals in medicine. Research on elements such as copper, zinc, titanium, nickel, magnesium, gold and silver is thought to help develop promising methods of treatment against infections [1][2][3].

2. Silver and Its Salts

Silver is a soft, malleable metal with a distinctive silver luster. It does not react with water or oxygen. Silver oxidation states [4][5][6] are presented in **Table 1**.

Table 1. Silver oxidation states.

Oxidation State	Electronic Configuration	Examples of Compounds
Ag ^{0}	**$d^{10}s^{1}$**	**rare; $Ag(CO)_3$ in 10 K**
Ag ^{I}	**d^{10}**	**Ag_2O, $[Ag(OH)_2]^-$ (aq.), $[Ag(H_2O)_4]^+$, AgF, AgCl, Ag^+ salts e.g., $AgNO_3$, Ag_2SO_4, Ag_2S. $Ag(CN)_2^-$ and other complexes**
Ag ^{II}	d^9	AgF_2, $[Ag(C_5H_5N)_2]^+$, $AgSO_4$, Ag ^{I} and Ag ^{III} are in AgO (not Ag ^{II})
Ag ^{III}	d^8	rare; $[AgF_4]^-$, $[AgF_6]^{3-}$

Most silver (I) salts, both inorganic and organic, are poorly soluble in water. Of these, only perchlorate, nitrate and fluoride have very good solubility; acetate, permanganate and sulfate have poor solubility (**Table 2**) [7].

Table 2. Solubility of silver (I) salts in water.

Silver (I) Salt	Chemical Formula	Solubility in Temp. 25 °C (g/100 g H_2O)
Perchlorate	$AgClO_4$	500.0
Nitrate	$AgNO_3$	257.0
Fluoride	AgF	100.0
Acetate	CH_3COOAg	1.11
Permanganate	$AgMnO_4$	0.9
Sulfate	Ag_2SO_4	0.83
Nitrite	$AgNO_2$	0.42
Bromate	$AgBrO_3$	0.16
Salicylate	$C_6H_4(OH)COOAg$	0.095 (in 23 °C)
Iodate	$AgIO_3$	0.044
Dichromate	$Ag_2Cr_2O_7$	0.0083 (in 15 °C)
Chromate	Ag_2CrO_4	0.0035

Silver (I) Salt	Chemical Formula	Solubility in Temp. 25 °C (g/100 g H_2O)
Carbonate	Ag_2CO_3	0.0033
Citrinate	$C_6H_8O_7Ag_3$	0.00284
Phosphate	Ag_3PO_4	0.000644
Chloride	AgCl	0.000193
Stearate	$CH_3(CH_2)_{16}COOAg$	0.000065
Sulphide	Ag_2S	0.000014
Bromide	AgBr	0.0000135
Iodide	AgI	0.00000026
Cyanide	AgCN	0.00000023

lectrolytic ly soluble cording to

$$AgNO_3 \rightarrow Ag^+ + NO_3^-$$

$$Ag_2SO_4 \rightarrow 2Ag^+ + SO_4^{2-}$$

$$2Ag^+ + 3H_2O \leftrightarrow Ag_2O + 2H_3O^+$$

Aqueous solutions of readily soluble silver (I) salts are therefore acidic. This is particularly important in the context of drug formulation. For instance, eye drops marked by too low pH may cause conjunctival irritation. Pharmacopoeic monographs indicate pH of the drops ranging from 3.5 to 8.5 [8][9].

3. Application of Silver and Silver (I) Salts in Medicine

Today's scientists pay great attention to silver, although its preparations have been used for wound healing ever since ancient times [10]. Among metals, silver is particularly widely used in medicine and has a well-documented antimicrobial effect against Gram-positive and Gram-negative bacteria, fungi, protozoa and viruses [11][12]. The most common compounds of silver used as medicines are: silver (I) nitrate [13], silver sulfadiazine and silver sulfathiazole. Silver preparations containing colloidal silver are also frequently employed and include colargole, protargole and targezine. Solid state silver (I) nitrate or in the form of concentrated (10–50%) aqueous solutions is used to cauterize tissues or to impregnate dentine. Silver (I) ions have also been shown to exert cytotoxic and genotoxic effects on various human cells by generating oxidative stress [14][15].

The usage of preparations containing silver has vastly changed over the years. Polish pharmacopoeias, starting with the first post-war edition as the second edition, which is a reprint of the pre-war edition from 1946, up until the most recent 12th edition, all contain monographs of silver preparations used in medicine and in pharmacy.

The Polish Pharmacopoeia 3rd (FP III, published in 1954) no longer contains the monographs *Argentum colloidale*, *Argentum gelatinosum* or *Argentum nitricum fusum* [16]. Subsequent editions of the pharmacopoeia introduce a monograph on *Argentum colloidale*, a substance that is also used today. The Polish Pharmacopoeia 12th (FP XII, published in 2020) contains the Polish version of all materials published in the basic part of the European Pharmacopoeia 10.0 and in Supplements 10.1 and 10.2, as well as national sections, i.e., without equivalents in Ph. Eur. It presents the colloidal silver monograph as follows [13]:

ARGENTUM COLLOIDALE AD USUM EXTERNUM

Srebro koloidalne do użytku zewnętrznego

Silver, colloidal, for external use; Argent colloïdal pour usage externe

- DEFINITION: Colloidal, metallic silver containing protein. Content: from 70.0% to 80.0% Ag (calculated on the dried substance).

- PROPERTIES: Appearance: green or bluish-black, metallic flakes or powder, hygroscopic.

- Solubility: easily soluble or soluble in water, practically insoluble in ethanol (96%) and in methylene chloride.

In FP XII, the silver (I) nitrate monograph is still present despite the passage of nearly 70 years from the publication of the second edition of the Polish Pharmacopoeia. In the pharmacopoeias of other countries, researchers can find monographs of other silver preparations. In addition to silver nitrate and silver proteinate, Japanese Pharmacopoeia (JP XVII, published in 2016) contains an interesting monograph of silver proteinate solution composed of 0.22–0.26% silver alongside mint water and glycerin, the two of which are considered as *corrigens* [17]. The described pharmacopoeial medicinal product is used as an antiseptic mouthwash in the course of diseases associated with pharyngitis.

A silver preparation whose monograph has never been included in any of the FP editions is targetezine (*Argentum diacetyltanninoalbuminatum*, colloidal diacetyltanine-silver complex). However, the Therapeutic Guide to the Official List of Drugs (USL), an official document of the Polish People’s Republic from 1959, provides a description of the preparation [18]:

A substance with a bactericidal and astringent effect, both for oral and external application. It is used in catarrh of the conjunctiva and mucous membranes; in gonorrhea. Internally in gastric and duodenal ulcers. Externally in the form of solutions, ointments 0.5–4%. Internally, a 1–2% solution should be administered in tablespoons.

The current, new editions of pharmacopoeias, along with the progress of pharmaceutical sciences, the development of toxicology, pharmacokinetics, pharmacodynamics and drug chemistry, provide the doses or concentrations of medicinal substances typically used and/or their maximum. This is important because over the years silver preparations have been moved to list A (very strong agents).

The first mention of the use of silver in medicine dates back to ancient times. It is probable that Hippocrates used silver preparations to treat ulcers and sores in order to accelerate wound healing. Soluble silver (I) compounds, such as silver (I) nitrate, were first used empirically as blood purifiers in 702–705 AD [19]. Later, silver (I) salts were used as antibacterial agents to treat infectious diseases, including syphilis and gonorrhea, brain infections, epilepsy, mental illness, nicotine addiction and gastroenteritis [12]. The widest use of silver in medicine was reported in the 1880s. Then, the first silver plate was implanted during cranial surgery, followed by silver eye drops being used. The nitrate solution was introduced into medicine to prevent childhood blindness and reduce the number of cases of *ophthalmia neonatorum* [20]. Obligatory ophthalmic prophylaxis in newborns with silver (I) nitrate drops, as in the Credé method, was adopted in many countries around the world until the 1970s, and in some areas it is still a routine part of the perinatal period [21][22]. Over the years, another application of silver (I) preparations appeared. Their use has been extended to treat corneal ulcers, interstitial keratitis, blepharitis and cystitis [23]. Other silver preparations that were used in medicine in the last century were registered under various trade names. Some of these include: Albargin® (*Argentum gelatinosum*), Choleval® (by Merk and Co. in New York, NY, USA), Ammargen®, Argoflavin® (a combination of tripaflavin with silver nitrate, which exhibited a synergistic effect of the two components—used as bactericide for topical applications and for intravenous injection), Poviargol® (*Protargole*) [24][25][26][27][28].

Recently, the anticancer effect of silver (I) nitrate associated with the induction of apoptosis in H-ras 5RP7 cells has been discussed [29]. The research results also prove that the anticancer effect of silver (I) compounds does not apply only to its well-dissociated salts, but also to silver (I) complex compounds [30]. Silver, which is a transition metal, has the ability to form coordination compounds. This has been the subject of research for many years, because many complex compounds where silver is coordinated can become potential therapeutic agents due to the unique biological effect of the silver (I) ion. It is also extremely desirable that the ligands, as structural parts of the silver (I) coordination linkage, show proven clinical effectiveness, such as, for example, metronidazole (MTZ) or 4-hydroxymethylpyridine derivatives. As a result of the action of the silver (I) ion and the ligand, at least a synergistic effect should be expected, however, studies indicate a hyperaddition synergism [2][31][32]. When silver comes into contact with microorganisms, there is an immediate disruption of the cell wall, which later leads to the death of these organisms. It has been proven that silver affects the metabolic behavior of bacteria, viruses and eukaryotic microorganisms. It has been suggested that silver (I) ions modify their pathogenic activity by interacting with microbial electron transport systems, cell membranes and the DNA binding mechanism. Silver has a broad spectrum of activity and is less likely to cause microbial resistance than conventional antibiotics. In addition, the antibacterial effect of silver can be enhanced by its combination with other antimicrobial agents, which should be taken into account [33][34][35]. The method of synthesizing the silver complex with 4-hydroxymethylpyridine is a patented invention [36][37].

In medicine, silver is used not only in the form of dissociating salts, but also as nanoparticles (colloidal silver) [38]. Silver owes its antibacterial and antifungal properties solely to its ionic Ag^+ form, which, however, is quite unstable and can be easily inactivated by improper complexation and precipitation, or it can be transformed into the metallic Ag (0) form lacking healing properties [39]. Pure metal continuously releases small amounts of ions that have an antibacterial effect on the metal surface [38]. The standard potential of the Ag^+/Ag system is +0.7992 V. Oxidation to the Ag+ ion is a slow process under normal conditions and leads to low effective concentrations of silver. Therefore, metallic silver is used in the alloys to coat implants or sutures [40][41]. Silver (I) salts differ in terms of their solubility and are thus capable of generating silver ions to varying degrees. The high solubility of silver (I) salts leads to a high local concentration of silver, which translates to high antibacterial activity, but also high toxicity. The solubility and toxicity of silver (I) salts depend on many external factors, e.g., they change depending on pH. Therefore, each medicinal product containing silver (I) salts requires thorough clinical studies to assess the actual concentration of silver (I) ions [21].

The synthesis of silver in the nanoparticle (colloidal) form consists in the reduction of the soluble silver (I) salt by a reducing agent such as citrate, glucose, ethylene glycol or sodium borohydride [42]. The decisive role is played by the addition of stabilizing compounds that prevent the growth and aggregation of the formed silver nanoparticles [31]. Reproducible synthesis of silver nanoparticles in laboratory conditions is difficult and depends, among others, on the concentrations, reducing agent, temperature and the presence of additives. Moreover, the morphology of the obtained particles is not always stable. Often, synthesized silver nanoparticles tend to aggregate after a few hours or days if colloidal stability is insufficient [38][42].

Silver nanoparticles (Ag-NPs) are capable of creating nanostructures and are therefore used not only in medicine, but also in biotechnology, electronics, environmental remediation, biosensors, agriculture and the food industry. For technical applications on an industrial scale, Ag-NPs are produced mainly using physicochemical techniques: gamma radiation, electrochemical methods, chemical reduction and others. Alternatively, a so-called green synthesis can be used, which reduces production cost and prevents introduction of toxic residues into the natural environment. Studies suggest that biogenic Ag-NPs are even less toxic in vivo than chemically synthesized nanoparticles [43]. Ag-NPs can be synthesized biologically using microbes such as *Bacillus subtilis* and *B. licheniformis* (Gram-positive bacteria), *Escherichia coli* (Gram-negative bacteria), fungi, yeasts and viruses [39][44]. In addition, due to the richness of alkaloids, saponins, tannins, vitamins, phenols and terpenoids in organic matrix, the synthesis of Ag-NPs takes advantage of plants, plant products and algae as reducing biological agents, providing an inexpensive, one-step procedure [45]. Novel silver nanoparticles are attractive as antimicrobial agents due to their ability to function on the surface and the ability to cleave disulfide bonds. Ag-NPs act on bacteria, fungi and viruses in a shape-dependent manner. As particle size decreases, the percentage of surface atoms increases, forming many unsaturated bonds due to the absence of adjacent atoms. As a consequence, Ag-NPs possess unstable atoms with high surface energy. This type of structure provides multiple contact adsorption sites and reaction points that can be further modified [46].

Metallic silver is usually inert, but after implantation in the presence of tissues, it is ionized under the influence of oxygen, moisture and body fluids, releasing biologically active silver ions (Ag+), which bind to thiol groups (-SH), anionic protein ligands and cell membranes of bacterial cells [38]. What underlies the basis of the antimicrobial activity of silver is the ability of Ag+ to penetrate bacterial cell walls through pinocytosis, causing an increase in cellular oxidative stress in microorganisms—denaturing and inactivating proteins, as well as metabolic enzymes, which leads to growth inhibition [47][48]. Ionic silver (I) also has the ability to bind to the microbial genome (DNA or RNA), which inhibits replication of nucleic acids and prevents multiplication of microorganisms [49].

The latest discovery of Ag-NPs as biocides is related to their effectiveness as antivirals targeting infectious diseases such as: SARS-CoV, Influenza A/H5N1, Influenza A/H1N1, Herpes simplex virus types 1 and 2, Human parainfluenza virus type 3, dengue virus, HIV-1, hepatitis B virus and new encephalitis viruses. The exact mechanism of action of Ag-NPs as antivirals has not yet been fully elucidated [50]. In general, silver nanoparticles are able to reduce virus infectivity, probably by blocking virus-cell interaction, which may depend on the size and zeta potential of silver nanoparticles [51]. In vitro studies have shown the effectiveness of silver nanoparticles modified with oseltamivir in reducing influenza glycoproteins and preventing DNA fragmentation, chromatin condensation and caspase-3 function, which enabled to effectively mitigate H1N1 infection [52][53]. Recent studies have revealed suppression of human parainfluenza 3 (HPIV-3) replication through the use of Ag-NPs [54].

The anti-inflammatory effect of silver (I) nitrate or nanocrystalline silver has been experimentally confirmed in the treatment of wounds, treatment of allergic contact dermatitis and ulcerative colitis [55][56][57]. Experimental studies have shown a reduction in inflammation after the use of nanocrystalline silver, which was associated with lymphocyte apoptosis, decreased expression of pro-inflammatory cytokines and reduced gelatinase activity [19].

Research on the use of new silver preparations in combination with other active substances is also developing quite dynamically in ophthalmology. The widest and best-known example of silver used in medicine is sulfadiazine (AgSD), which became a topical antibacterial agent for the treatment of burns and fungal keratitis [58][59][60]. The profile of AgSD also shows a strong antibacterial potential against *E. coli, S. aureus, Klebsiella* spp. and *Pseudomonas* spp. [49].

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