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REVIEW ARTICLE

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Silver in Wound and Trophic Ulcer Treatment: A Modern View of the Problem

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Abstract

This review presents published data on the history of use, mechanism of action, and effectiveness of silver and silver-based drugs in surgical practice. A literature search was carried out using PubMed, EMBASE, Google Scholar, and E-Library databases. Analysis of available literature data convincingly demonstrates the effectiveness of silver nanocomposites as antibacterial and anti-inflammatory agents. The demonstrated antimicrobial property of silver nanoparticles (AgNPs) against various antibiotic-resistant bacteria is especially significant for clinical use. Silver nanoparticles have clinically proven effective in treating wounds and trophic ulcers.**(International Journal of Biomedicine. 2024;14(2):240-245.)**

Keywords: silver • silver nanoparticles • wound • trophic ulcer

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Abbreviations

Ag, silver; **AgNPs**, silver nanoparticles; **DNA**, deoxyribonucleic acid; **GSH**, reduced glutathione; **ROS**, reactive oxygen species.

Introduction

Silver (Ag) is one of the metals most intensively used by humanity for medical purposes since ancient civilizations. The use of silver in medicine is based primarily on its disinfectant properties since silver has the most potent bactericidal effect among metals.[1] The bactericidal effect of Ag-based compounds is 1750 times more powerful than the effect of the same concentration of carbolic acid, 1500 times higher than the effect of the same concentration of phenol, and 3.5 times stronger than the effect of sublimate. Silver, having a powerful antimicrobial effect, is detrimental to antibiotic-resistant strains of more than 500 species of bacteria.[2] It has been established that Ag has the most powerful bactericidal effect among heavy metals.[3]

Hippocrates, the father of modern medicine, believed that silver powder has healing properties and is recommended for treating trophic ulcers.[1,4] One of the first silver compounds used in medical practice was silver nitrate. It was originally used in a solid form known as lapis, or hellstone.[1] In the 19th century, lapis became widespread for cauterizing excessive granulations in wounds and treating burns, and Ag-based compounds became one of the main means for the treatment and prevention of wound infections before the invention of antibiotics.[5] It was in the 19th century that active scientific study of silver and its compounds began, which led to the discovery of its antiviral, antibacterial, and immunomodulatory activities.[6] From the end of the 19th to the beginning of the 20th century, several Ag-based compounds and drugs were developed: collargol, protargol, elargol, silargel, argosulfan, and others. Some of them are still successfully used today.[1]

After the discovery of penicillin, the first antibiotic, in 1941, interest in silver as an antimicrobial drug disappeared for almost 40 years. Some experts believe that before the discovery of antibiotics, silver salts were one of the most widely used agents with antimicrobial activity.[7] However, the emergence of antibiotic-resistant strains of microorganisms has led to the search for new silver-based antibacterial drugs. In 1968, silver

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sulfadiazine was introduced into clinical practice and began one of the most successful silver-containing antimicrobials. Since that time, topical silver sulfadiazine ointment has been the standard antibacterial treatment for major burns and is widely used in their therapy.[8] The therapeutic effect of silver sulfadiazine in the local treatment of wounds and wound infections is associated with its anti-inflammatory and antiseptic effects, as well as stimulation of the proliferation and differentiation of keratinocytes.[9]

Currently, one of the most effective topical Ag-based drugs for the local treatment of wounds and wound infections is silver sulfathiazole. According to immunohistochemical analysis, when using silver sulfathiazole for local therapy in the complex treatment of complicated diabetic foot syndrome, there is a decreased expression of CD68+ macrophages in the studied tissues of trophic ulcers and wounds. In a study by Kalinichenko et al.,[10] a gradual increase in the coefficient of macrophage activity in biopsy specimens, with the systematic achievement of a threshold level of 1.0, was a reliable sign of a better regenerative response and indicated the optimal nature of the course of the wound process. The use of silver sulfathiazole in the complex treatment of patients with diabetic foot syndrome reduced the intensity of inflammatory reactions and the content of C-reactive protein and neopterin,[11] and it had a protective effect on the vascular endothelium.[12]

In recent years, various silver-based dressings have been proposed for treating wounds (Silversel, Silverlon, Silvasorb, Contreet-H, Arglaes, Aquacel-Ag, Acticoat, Nucryst, and others). Such dressings have a more practical application than metallic silver or silver salts.[13] Several studies have noted a significant reduction in the time of wound cleansing and healing, in elimination of systemic manifestations of the infectious process, in duration of required antibacterial therapy, and in hospitalization in patients using silver-based dressings. Using silver-based dressings in a moist microenvironment creates optimal conditions for epithelization during the wound process.[14]

It is now generally accepted that silver is a broad-spectrum antimicrobial agent. Because of the broad spectrum of antibacterial action, from bacteriostatic to bactericidal, Ag-based compounds have found wide applications in medicine.[15,16] In 2009, approximately 15 tons of silver were included in medical products worldwide.[17]

New prospects for the medical use of silver are opening in connection with the production of its most unique form—silver nanoparticles (AgNPs), which have more outstanding physiochemical and biological properties beyond bulk silver.[18] AgNPs can destroy multiple drug-resistant strains and prevent biofilm formation, indicating significant potential in antibacterial application.[19]

The antibacterial mechanisms of AgNPs have been discussed extensively, but the exact effect of AgNPs on bacteria is still undefined.[20] However, two mechanisms attract attention, namely contact killing and ion-mediated killing.

Ionized silver can "attack" at least three cellular components: cell membranes, cytoplasmic organelles, and DNA.[21] Silver ions interact with membrane proteins and further block the respiratory chain.[22] It has been reported that AgNPs can anchor to the bacterial cell wall, causing physical changes in the bacterial membrane followed by its damage, which can lead to leakage of cellular contents and bacterial death.[23-25] After adhesion to the bacterial wall, AgNPs can also penetrate the bacteria through the membrane. Small nanoparticles, which have a larger surface area in contact with bacterial cells, can reach the cytoplasm more often than larger nanoparticles.[24] Once inside the microbial cell, AgNPs can interact with cellular structures and biomolecules such as proteins, lipids, and DNA, thereby leading to bacterial dysfunction and, ultimately, death.[26-29] It is also speculated that AgNPs interact effectively with the carboxyl and thiol groups of β-galactosidase and inhibit intracellular biological functions, leading to cell death.[30]

In addition, the antibacterial mechanism of AgNPs is also due to their ability to produce high levels of reactive oxygen species (ROS) and free radicals,[31-33] while suppressing the expression of antioxidant enzymes (glutathione [GSH], superoxide dismutase and catalase), thereby accelerating ROS accumulation.[34,35] The released Ag^+ from AgNPs can interact with respiratory chain proteins on the membrane, interrupt intracellular O_2 reduction, and induce ROS production.[36] In turn, the accumulation of ROS leads to an apoptosis-like response, lipid peroxidation, GSH depletion, and DNA damage.[37-39]

Silver nanoparticles' unique properties make them suitable catalysts in various chemical reactions. The enhanced antimicrobial and virucidal effects of AgNPs are explained by their increased reactivity. In the range of 1–100 nm, AgNPs are tens and hundreds of times more active than other known biocidal and antibiotic drugs and are considered more promising agents as an alternative to antibiotics.[40] In the available literature, we have not found data on the formation of resistance of microorganisms to AgNPs, which, according to several authors, opens the way to overcoming resistance to antibiotics.[40,41]

At the same time, some studies have reported bacterial resistance to AgNPs. In a study by Kaweeteerawat et al.,[42] it was found that AgNPs enhanced bacterial resistance to antibiotics by promoting stress tolerance by inducing intracellular ROS. In addition, the gram-negative bacteria *Escherichia coli* 013 and *Pseudomonas aeruginosa* CCM 3955, and *E. coli* CCM 3954 can develop resistance to AgNPs after repeated exposure. This resistance was due to the production of flagellin, an adhesive protein of the bacterial flagellum, which caused the aggregation of AgNPs and thereby eliminated their antibacterial effect.[43] Genes encoding silver resistance were detected most frequently in *Enterobacter* spp. (48%), followed by *Klebsiella* spp.(41%) and *Escherichia coli* (4%).[44]

It was initially believed that AgNPs exert their activity only by releasing ions, acting as a depot. Modern research indicates that both ions and nanoparticles themselves exhibit activity.[45,46] Their pharmacological activity is based on the ability of silver to be an electron pair acceptor.[47,48] It has been demonstrated that the cellular membrane of bacteria has a negative charge due to the presence of carboxyl, phosphate, and amino groups.[49] The bactericidal efficiency of various positively and negatively charged silver nanoparticles has been extensively evaluated in the literature. The positively charged silver nanoparticles showed the highest bactericidal activity against all microorganisms tested.[50]

Thus, the interaction of Ag^+ with a bacterial cell is complex and multifactorial.[51] Since the mechanism of action of AgNPs is not specific, AgNPs act almost equally on both gram-positive and gram-negative microflora.[1] Due to the multi-component mechanism of action, microorganisms' resistance to Ag preparations rarely develops. The antifungal activity of silver preparations has also been described, with a predominantly positive mechanism of action in the form of cell membrane destruction.

In addition to antimicrobial and antifungal effects, Ag-based drugs are characterized by local anti-inflammatory activity.[52] In contrast to the antimicrobial effect, the anti-inflammatory effect of silver at the molecular level has not been sufficiently studied.[51] The acceleration of the transition of a wound from inflammation to regeneration in experiments on animal models is associated with an increase in the concentration of epithelial growth factor after the application of silver dressing to the wound.[8] Studies on human cells have found that application of silver at concentrations of 10–20 μg/ml causes a decrease in TNF-α, IL, and IL-6.[53]

Despite significant clinical experience with the use of Ag-based compounds in medical practice, the results of scientific studies of their effectiveness and safety have been regularly subjected to critical evaluation.[54] One potential adverse reaction of using silver preparations with local exposure to wounds is the risk of developing argyria.[55] It should also be noted that there may be a deposition of silver in the cutaneous scar tissue and a change in skin color with prolonged use of the silver dressing.[56] In vitro studies have shown that there is a difference between the number of fibroblasts and the amount of collagen they produce when exposed to silver and non-silver dressings. Silver dressings reduce the number of fibroblasts by 54%–70% and collagen by 48%–68%.[57]

The study of the effectiveness of Ag^+ in antimicrobial agents has resumed. Published results of randomized clinical trials about the topical use of Ag-based preparations in the treatment of pressure ulcers,[58] microbially contaminated wounds with a high risk of infection,[59,60] acute wounds during vacuum therapy,[61] and colorectal[62-64] and plastic surgery[65,66] indicate their safety and clinical effectiveness.

A wide range of studies have focused on the use of AgNPs for wound healing. The use of AgNPs in ointments and dressings[67-70] for the purpose of preventing wound infection[71] and treating infected wounds[72] is said to be mandatory in many works. Many authors note the effectiveness of AgNPs as antibacterial agents,[73,74] as well as nanocomposites, which include silver in nanosized form[75,76] and nanofibers.[77,78] Some researchers have been able to combine the antibacterial and proliferative effects of Ag-nanocomposites. In burn wounds, they have been shown to induce the proliferation and migration of keratinocytes and fibroblasts, promoting accelerated wound healing in diabetic mice.[79,80] It was found that AgNPs stabilized with chitosan and polyvinyl alcohol not only inhibit the growth of bacteria but also can accelerate wound repair.[81,82]

In addition, AgNP targets mesenchymal stem cell proliferation and osteogenic differentiation in vitro.[83] Mouse models of burn wounds have demonstrated pronounced anti-inflammatory properties of polyamidoamine dendrimer-stabilized AgNPs.[84]

One of the most important problems is the synthesis of sufficiently stable AgNPs of a given size that retain high chemical or biological activity for a long time. In this regard, when developing methods for synthesizing AgNPs, much attention is paid to the choice of stabilizers, which determine the. stability level of AgNPs.[85] One of the possible solutions to this problem was using sodium alginate, a biopolymer of plant origin.[86] It has been shown that sodium alginate macromolecules reduce Ag^+ into small nanoparticles and simultaneously stabilize them. It has been observed that one composition not only combines the properties of two biologically active substances but also their synergy.[86]

The data analysis demonstrates the effectiveness of AgNPs as antibacterial and anti-inflammatory agents. Silver compounds have been shown to inhibit the growth and formation of bacterial biofilms.[87] In addition, it has been shown that the use of silver compounds in the treatment of wounds is also characterized by an improvement in the quality of life of patients and good cost-effectiveness. From this perspective, the development and introduction into clinical practice of new AgNP-based drugs for treating wounds and trophic ulcers, and the search for enhancing their bactericidal effect, is extremely relevant.

Competing Interests

The authors declare that they have no competing interests.

References

1. Rzheussky SE. Silver nanoparticles in medicine. Vestnik VGMU. 2022;21(2):15-24. doi: 10.22263/2312-4156.2022.2.15. (In Russ.)
2. Rzheussky SE, Kuhach VV, Valueva MA. Economic aspects of application and antimicrobial activity of silver-containing drugs. Vestnik Farmacii. 2013;2(60):25-30. (In Russ.)
3. Shrestha R, Joshi DR, Gopali J, Piya S. Oligodynamic fraction of silver, copper and brass on enteric bacteria isolated from water of Kathmandu Valley. Nepal Journal of Science and Technology. 2009;10:189-193. doi:10.3126/njst.v10i0.2959
4. Melaiye A, Youngs WJ. Silver and its application as an antimicrobial agent. Expert Opin Ther Pat. 2005;15(2):125-30. doi: 10.1517/13543776.15.2.125
5. Sattori I, Mahmudov KB, Rajabov U, Rajabali M, Nazarov F. Historical aspects of the application of silver compounds. Report of the TAAS. 2018;1:62-65. (In Russ.)
6. Marx DE, Barillo DJ. Silver in medicine: the basic science. Burns. 2014 Dec;40 Suppl 1:S9-S18. doi: 10.1016/j.burns.2014.09.010.
7. Mijnendonckx K, Leys N, Mahillon J, Silver S, Van Houdt R. Antimicrobial silver: uses, toxicity and potential for resistance. Biometals. 2013 Aug;26(4):609-21. doi: 10.1007/s10534-013-9645-z.
8. Nadworny PL, Wang J, Tredget EE, Burrell RE. Anti-inflammatory activity of nanocrystalline silver-derived solutions in porcine contact dermatitis. J Inflamm (Lond). 2010

Feb 19;7:13. doi: 10.1186/1476-9255-7-13.
9. Elliott C. The effects of silver dressings on chronic and burns wound healing. Br J Nurs. 2010 Aug 12-Sep 8;19(15):S32-6. doi: 10.12968/bjon.2010.19.Sup5.77707.
10. Kalinichenko AP, Hryvenko SH, Umerov EE, Uzbekova LD, Usmanova TE, Izosimov VV. The Morphological Rationality for the Expediency of Topical Application of Silver Sulfathiazole in Patients with Diabetic Foot Syndrome. International Journal of Biomedicine. 2022;12(3):404-408. doi:10.21103/Article12(3)_OA10
11. Kalinichenko A, Grivenko S, Umerov E. Features of the dynamics of inflammatory markers during local treatment of complicated forms of diabetic foot syndrome. MIA Medical Bulletin. 2022;121(6):11-14. doi:10.52341/20738080_2022_121_6_11. (In Russ.)
12. Kalinichenko AP, Grivenko SG, Umerov EE. Monitoring of molecular mechanisms of a complicated reparative process during local treatment of the diabetic foot syndrome. Tavricheskiy mediko-biologicheskiy vestnik. 2022;25(4):22-28. doi: 10.29039/2070-8092-2022-25-4-22-28. (In Russ.)
13. Lansdown AB, Sampson B, Rowe A. Sequential changes in trace metal, metallothionein and calmodulin concentrations in healing skin wounds. J Anat. 1999 Oct;195(Pt 3):375-86. doi: 10.1046/j.1469-7580.1999.19530375.x.
14. Helary C, Bataille I, Abed A, Illoul C, Anglo A, Louedec L, Letourneur D, Meddahi-Pellé A, Giraud-Guille MM. Concentrated collagen hydrogels as dermal substitutes. Biomaterials. 2010 Jan;31(3):481-90. doi: 10.1016/j.biomaterials.2009.09.073.
15. Lansdown AB. Silver in health care: antimicrobial effects and safety in use. Curr Probl Dermatol. 2006;33:17-34. doi: 10.1159/000093928.
16. Privolnev VV, Zabrosaev VS, Danilenkov NV. Silver in topical treatment of infected wounds. Vestnik of the SSMA. 2015;14(3):85-91. (In Russ.)
17. Randall CP, Oyama LB, Bostock JM, Chopra I, O'Neill AJ. The silver cation (Ag+): antistaphylococcal activity, mode of action and resistance studies. J Antimicrob Chemother. 2013 Jan;68(1):131-8. doi: 10.1093/jac/dks372.
18. Beyene HD, Werkneh AA, Bezabh HK, Ambaye TG. Synthesis paradigm and applications of silver nanoparticles (AgNPs), a review. Sustainable Materials and Technologies. 2017;13:18-23. doi:10.1016/j.susmat.2017.08.001
19. Yuan YG, Peng QL, Gurunathan S. Effects of Silver Nanoparticles on Multiple Drug-Resistant Strains of Staphylococcus aureus and Pseudomonas aeruginosa from Mastitis-Infected Goats: An Alternative Approach for Antimicrobial Therapy. Int J Mol Sci. 2017 Mar 6;18(3):569. doi: 10.3390/ijms18030569.
20. Dovnar RI, Smotrin SM. Application of silver in medicine: historical aspects and modern view on the problem. Problemy zdorov'â i èkologii. 2011;3:149-153. doi:10.51523/2708-6011.2011-8-3-30. (In Russ.)
21. Rodin AV, Golub AV, Privolnev VV. Topical administration of sulfathiazole silver in the treatment of chronic wounds. RMJ. Medical Review. 2018;12:19-23. (In Russ.)
22. Konop M, Damps T, Misicka A, Rudnicka L. Certain Aspects of Silver and Silver Nanoparticles in Wound Care: A Minireview. Journal of Nanomaterials. 2016;7614753:47. doi: 10.1155/2016/7614753
23. Seong M, Lee DG. Silver Nanoparticles Against Salmonella enterica Serotype Typhimurium: Role of Inner Membrane Dysfunction. Curr Microbiol. 2017 Jun;74(6):661-670. doi: 10.1007/s00284-017-1235-9.
24. Khalandi B, Asadi N, Milani M, Davaran S, Abadi AJ, Abasi E, Akbarzadeh A. A Review on Potential Role of Silver Nanoparticles and Possible Mechanisms of their Actions on Bacteria. Drug Res (Stuttg). 2017 Feb;67(2):70-76. doi: 10.1055/s-0042-113383.
25. Rajesha S, Dharanishanthiband V, Kanna AV. Antibacterial mechanism of biogenic silver nanoparticles of Lactobacillus acidophilus. Journal of Experimental Nanoscience. 2015;10(15):1143-1152. doi:10.1080/17458080.2014.985750
26. Qing Y, Cheng L, Li R, Liu G, Zhang Y, Tang X, Wang J, Liu H, Qin Y. Potential antibacterial mechanism of silver nanoparticles and the optimization of orthopedic implants by advanced modification technologies. Int J Nanomedicine. 2018 Jun 5;13:3311-3327. doi: 10.2147/IJN.S165125.
27. Liao C, Li Y, Tjong SC. Bactericidal and Cytotoxic Properties of Silver Nanoparticles. Int J Mol Sci. 2019 Jan 21;20(2):449. doi: 10.3390/ijms20020449.
28. Rinna A, Magdolenova Z, Hudecova A, Kruszewski M, Refsnes M, Dusinska M. Effect of silver nanoparticles on mitogen-activated protein kinases activation: role of reactive oxygen species and implication in DNA damage. Mutagenesis. 2015 Jan;30(1):59-66. doi: 10.1093/mutage/geu057.
29. López-Carballo G, Higueras L, Gavara R, Hernández-Muñoz P. Silver ions release from antibacterial chitosan films containing in situ generated silver nanoparticles. J Agric Food Chem. 2013 Jan 9;61(1):260-7. doi: 10.1021/jf304006y.
30. You C, Han C, Wang X, Zheng Y, Li Q, Hu X, Sun H. The progress of silver nanoparticles in the antibacterial mechanism, clinical application and cytotoxicity. Mol Biol Rep. 2012 Sep;39(9):9193-201. doi: 10.1007/s11033-012-1792-8.
31. Zhao R, Lv M, Li Y, Sun M, Kong W, Wang L, Song S, Fan C, Jia L, Qiu S, Sun Y, Song H, Hao R. Stable Nanocomposite Based on PEGylated and Silver Nanoparticles Loaded Graphene Oxide for Long-Term Antibacterial Activity. ACS Appl Mater Interfaces. 2017 May 10;9(18):15328-15341. doi: 10.1021/acsami.7b03987.
32. Gomaa EZ. Silver nanoparticles as an antimicrobial agent: A case study on Staphylococcus aureus and Escherichia coli as models for Gram-positive and Gram-negative bacteria. J Gen Appl Microbiol. 2017 Mar 17;63(1):36-43. doi: 10.2323/jgam.2016.07.004.
33. Siritongsuk P, Hongsing N, Thammawithan S, Daduang S, Klaynongsruang S, Tuanyok A, Patramanon R. Two-Phase Bactericidal Mechanism of Silver Nanoparticles against Burkholderia pseudomallei. PLoS One. 2016 Dec 15;11(12):e0168098. doi: 10.1371/journal.pone.0168098.
34. Yuan YG, Peng QL, Gurunathan S. Effects of Silver Nanoparticles on Multiple Drug-Resistant Strains of Staphylococcus aureus and Pseudomonas aeruginosa from Mastitis-Infected Goats: An Alternative Approach for Antimicrobial Therapy. Int J Mol Sci. 2017 Mar 6;18(3):569. doi: 10.3390/ijms18030569.
35. Ramkumar VS, Pugazhendhi A, Gopalakrishnan K, Sivagurunathan P, Saratale GD, Dung TNB, Kannapiran E. Biofabrication and characterization of silver nanoparticles using aqueous extract of seaweed *Enteromorpha compressa* and its biomedical properties. Biotechnol Rep (Amst). 2017 Feb 10;14:1-7. doi: 10.1016/j.btre.2017.02.001.
36. Long YM, Hu LG, Yan XT, Zhao XC, Zhou QF, Cai Y, Jiang GB. Surface ligand controls silver ion release of

nanosilver and its antibacterial activity against *Escherichia coli*. Int J Nanomedicine. 2017 Apr 18;12:3193-3206. doi: 10.2147/IJN.S132327.
37. Korshed P, Li L, Liu Z, Wang T. The Molecular Mechanisms of the Antibacterial Effect of Picosecond Laser Generated Silver Nanoparticles and Their Toxicity to Human Cells. PLoS One. 2016 Aug 30;11(8):e0160078. doi: 10.1371/journal.pone.0160078. Erratum in: PLoS One. 2018 Aug 30;13(8):e0203636.
38. Lee W, Kim KJ, Lee DG. A novel mechanism for the antibacterial effect of silver nanoparticles on Escherichia coli. Biometals. 2014 Dec;27(6):1191-201. doi: 10.1007/s10534-014-9782-z.
39. Tang S, Zheng J. Antibacterial Activity of Silver Nanoparticles: Structural Effects. Adv Healthc Mater. 2018 Jul;7(13):e1701503. doi: 10.1002/adhm.201701503.
40. Gladkih PG. Effect of silver nanoparticles on biofilms of microorganisms (Review). Journal of New Medical Technologies, eEdition. 2015;1. doi:10.12737/8117. (In Russ.)
41. Gladkih PG. Effect of silver nanoparticles in combination with methyluracil on the biofilms in an experimental model of peritonitis in rats. Journal of New Medical Technologies, eEdition. 2016;2. doi: 10.12737/20408. (In Russ.)
42. Kaweeteerawat C, Na Ubol P, Sangmuang S, Aueviriyavit S, Maniratanachote R. Mechanisms of antibiotic resistance in bacteria mediated by silver nanoparticles. J Toxicol Environ Health A. 2017;80(23-24):1276-1289. doi: 10.1080/15287394.2017.1376727.
43. Panáček A, Kvítek L, Smékalová M, Večeřová R, Kolář M, Röderová M, Dyčka F, Šebela M, Prucek R, Tomanec O, Zbořil R. Bacterial resistance to silver nanoparticles and how to overcome it. Nat Nanotechnol. 2018 Jan;13(1):65-71. doi: 10.1038/s41565-017-0013-y.
44. Sütterlin S, Dahlö M, Tellgren-Roth C, Schaal W, Melhus Å. High frequency of silver resistance genes in invasive isolates of Enterobacter and Klebsiella species. J Hosp Infect. 2017 Jul;96(3):256-261. doi: 10.1016/j.jhin.2017.04.017.
45. Reidy B, Haase A, Luch A, Dawson KA, Lynch I. Mechanisms of Silver Nanoparticle Release, Transformation and Toxicity: A Critical Review of Current Knowledge and Recommendations for Future Studies and Applications. Materials (Basel). 2013 Jun 5;6(6):2295-2350. doi: 10.3390/ma6062295.
46. Liao C, Li Y, Tjong SC. Bactericidal and Cytotoxic Properties of Silver Nanoparticles. Int J Mol Sci. 2019 Jan 21;20(2):449. doi: 10.3390/ijms20020449.
47. Dakal TC, Kumar A, Majumdar RS, Yadav V. Mechanistic Basis of Antimicrobial Actions of Silver Nanoparticles. Front Microbiol. 2016 Nov 16;7:1831. doi: 10.3389/fmicb.2016.01831.
48. Ansari MA, Khan HM, Khan AA, Ahmad MK, Mahdi AA, Pal R, Cameotra SS. Interaction of silver nanoparticles with Escherichia coli and their cell envelope biomolecules. J Basic Microbiol. 2014 Sep;54(9):905-15. doi: 10.1002/jobm.201300457.
49. Van Der Wal A, Norde W, Zehnder AJB, Lyklema J. Determination of the total charge in the cell walls of Gram-positive bacteria. Colloids Surf B Biointerfaces. 1997;**9**(1–2):81–100.
50. You C, Han C, Wang X, Zheng Y, Li Q, Hu X, Sun H. The progress of silver nanoparticles in the antibacterial mechanism, clinical application and cytotoxicity. Mol Biol Rep. 2012 Sep;39(9):9193-201. doi: 10.1007/s11033-012-1792-8.
51. Rodin AV, Privolnev VV, Barsukov AN. Therapeutic potential of sulfathiazole silver for topical treatment of wound infection. Ambulatory Surgery. 2018;1–2:69-70. (In Russ.)
52. Khansa I, Schoenbrunner AR, Kraft CT, Janis JE. Silver in Wound Care-Friend or Foe?: A Comprehensive Review. Plast Reconstr Surg Glob Open. 2019 Aug 12;7(8):e2390. doi: 10.1097/GOX.0000000000002390.
53. Aparna Mani KM, Seethalakshmi S, Gopal V. Evaluation of in-vitro anti-inflammatory activity of silver nanoparticles synthesised using piper nigrum extract. Journal of Nanomedicine & Nanotechnology. 2015;6:2. doi:10.4172/2157-7439.1000268
54. Dissemond J, Böttrich JG, Braunwarth H, Hilt J, Wilken P, Münter KC. Evidence for silver in wound care - meta-analysis of clinical studies from 2000-2015. J Dtsch Dermatol Ges. 2017 May;15(5):524-535. doi: 10.1111/ddg.13233.
55. McCague A, Joe VC. A Case of Argyria and Acute Leukopenia Associated with the Use of an Antimicrobial Soft Silicone Foam Dressing. J Burn Care Res. 2016 Sep-Oct;37(5):e493-6. doi: 10.1097/BCR.0000000000000275.
56. Wang XQ, Chang HE, Francis R, Olszowy H, Liu PY, Kempf M, Cuttle L, Kravchuk O, Phillips GE, Kimble RM. Silver deposits in cutaneous burn scar tissue is a common phenomenon following application of a silver dressing. J Cutan Pathol. 2009 Jul;36(7):788-92. doi: 10.1111/j.1600-0560.2008.01141.x.
57. Zou SB, Yoon WY, Han SK, Jeong SH, Cui ZJ, Kim WK. Cytotoxicity of silver dressings on diabetic fibroblasts. Int Wound J. 2013 Jun;10(3):306-12. doi: 10.1111/j.1742-481X.2012.00977.x.
58. Chuangsuwanich A, Charnsanti O, Lohsiriwat V, Kangwanpoom C, Thong-In N. The efficacy of silver mesh dressing compared with silver sulfadiazine cream for the treatment of pressure ulcers. J Med Assoc Thai. 2011 May;94(5):559-65.
59. Beele H, Meuleneire F, Nahuys M, Percival SL. A prospective randomised open label study to evaluate the potential of a new silver alginate/carboxymethylcellulose antimicrobial wound dressing to promote wound healing. Int Wound J. 2010 Aug;7(4):262-70. doi: 10.1111/j.1742-481X.2010.00669.x.
60. Eberlein T, Haemmerle G, Signer M, Gruber Moesenbacher U, Traber J, Mittlboeck M, Abel M, Strohal R. Comparison of PHMB-containing dressing and silver dressings in patients with critically colonised or locally infected wounds. J Wound Care. 2012 Jan;21(1):12, 14-6, 18-20. doi: 10.12968/jowc.2012.21.1.12.
61. Siegel HJ, Herrera DF, Gay J. Silver negative pressure dressing with vacuum-assisted closure of massive pelvic and extremity wounds. Clin Orthop Relat Res. 2014 Mar;472(3):830-5. doi: 10.1007/s11999-013-3123-3.
62. Krieger BR, Davis DM, Sanchez JE, Mateka JJ, Nfonsam VN, Frattini JC, Marcet JE. The use of silver nylon in preventing surgical site infections following colon and rectal surgery. Dis Colon Rectum. 2011 Aug;54(8):1014-9. doi: 10.1097/DCR.0b013e31821c495d.
63. Siah CJ, Yatim J. Efficacy of a total occlusive ionic silver-containing dressing combination in decreasing risk of surgical site infection: an RCT. J Wound Care. 2011 Dec;20(12):561-8. doi: 10.12968/jowc.2011.20.12.561.
64. Tomasello G, Bellavia M, Damiani F, Damiano G, Palumbo VD, Fiorentini T, Puleio R, Spinelli G, Damiani P, Ficarella S, Bruno A, Lo Monte AI. Argentum-quarz solution in the treatment of anorectal fistulas: is it possible a conservative

approach? Med Hypotheses. 2012 Oct;79(4):542-3. doi: 10.1016/j.mehy.2012.07.015.

65. Bailey S, Carmean M, Cinat M, Burton K, Lane C, Malinoski D. A randomized comparison study of Aquacel Ag and Glucan II as donor site dressings with regard to healing time, cosmesis, infection rate, and patient's perceived pain: a pilot study. J Burn Care Res. 2011 Nov-Dec;32(6):627-32. doi: 10.1097/BCR.0b013e31822dc409.

66. Lohsiriwat V, Chuangsuwanich A. Comparison of the ionic silver-containing hydrofiber and paraffin gauze dressing on split-thickness skin graft donor sites. Ann Plast Surg. 2009 Apr;62(4):421-2. doi: 10.1097/SAP.0b013e31818a65e9.

67. Pei Z, Sun Q, Sun X, Wang Y, Zhao P. Preparation and characterization of silver nanoparticles on silk fibroin/carboxymethylchitosan composite sponge as anti-bacterial wound dressing. Biomed Mater Eng. 2015;26 Suppl 1:S111-8. doi: 10.3233/BME-151296.

68. Fries CA, Ayalew Y, Penn-Barwell JG, Porter K, Jeffery SL, Midwinter MJ. Prospective randomised controlled trial of nanocrystalline silver dressing versus plain gauze as the initial post-debridement management of military wounds on wound microbiology and healing. Injury. 2014 Jul;45(7):1111-6. doi: 10.1016/j.injury.2013.12.005.

69. Jenwitheesuk K, Surakunprapha P, Chowchuen B. The use of nanocrystalline silver for the treatment of massive soft tissue defects with exposed bone. J Med Assoc Thai. 2013 Sep;96 Suppl 4:S177-84.

70. Guthrie KM, Agarwal A, Tackes DS, Johnson KW, Abbott NL, Murphy CJ, Czuprynski CJ, Kierski PR, Schurr MJ, McAnulty JF. Antibacterial efficacy of silver-impregnated polyelectrolyte multilayers immobilized on a biological dressing in a murine wound infection model. Ann Surg. 2012 Aug;256(2):371-7. doi: 10.1097/SLA.0b013e318256ff99.

71. Keen JS, Desai PP, Smith CS, Suk M. Efficacy of hydrosurgical debridement and nanocrystalline silver dressings for infection prevention in type II and III open injuries. Int Wound J. 2012 Feb;9(1):7-13. doi: 10.1111/j.1742-481X.2011.00822.x.

72. Asz J, Asz D, Moushey R, Seigel J, Mallory SB, Foglia RP. Treatment of toxic epidermal necrolysis in a pediatric patient with a nanocrystalline silver dressing. J Pediatr Surg. 2006 Dec;41(12):e9-12. doi: 10.1016/j.jpedsurg.2006.08.043.

73. Dhapte V, Kadam S, Moghe A, Pokharkar V. Probing the wound healing potential of biogenic silver nanoparticles. J Wound Care. 2014 Sep;23(9):431-2, 434, 436 passim. doi: 10.12968/jowc.2014.23.9.431.

74. Hebeish A, El-Rafie MH, El-Sheikh MA, Seleem AA, El-Naggar ME. Antimicrobial wound dressing and anti-inflammatory efficacy of silver nanoparticles. Int J Biol Macromol. 2014 Apr;65:509-15. doi: 10.1016/j.ijbiomac.2014.01.071.

75. Singh D, Singh A, Singh R. Polyvinyl pyrrolidone/carrageenan blend hydrogels with nanosilver prepared by gamma radiation for use as an antimicrobial wound dressing. J Biomater Sci Polym Ed. 2015;26(17):1269-85. doi: 10.1080/09205063.2015.1087366.

76. Im AR, Kim JY, Kim HS, Cho S, Park Y, Kim YS. Wound healing and antibacterial activities of chondroitin sulfate- and acharan sulfate-reduced silver nanoparticles. Nanotechnology. 2013 Oct 4;24(39):395102. doi: 10.1088/0957-4484/24/39/395102.

77. GhavamiNejad A, Rajan Unnithan A, Ramachandra Kurup Sasikala A, Samarikhalaj M, Thomas RG, Jeong YY, Nasseri S, Murugesan P, Wu D, Hee Park C, Kim CS. Mussel-Inspired Electrospun Nanofibers Functionalized with Size-Controlled Silver Nanoparticles for Wound Dressing Application. ACS Appl Mater Interfaces. 2015 Jun 10;7(22):12176-83. doi: 10.1021/acsami.5b02542.

78. Wu J, Zheng Y, Wen X, Lin Q, Chen X, Wu Z. Silver nanoparticle/bacterial cellulose gel membranes for antibacterial wound dressing: investigation in vitro and in vivo. Biomed Mater. 2014 Jun;9(3):035005. doi: 10.1088/1748-6041/9/3/035005.

79. Rangasamy S, Tak YK, Kim S, Paul A, Song JM. Bifunctional Therapeutic High-Valence Silver-Pyridoxine Nanoparticles with Proliferative and Antibacterial Wound-Healing Activities. J Biomed Nanotechnol. 2016 Jan;12(1):182-96. doi: 10.1166/jbn.2016.2179.

80. Abdel-Mohsen AM, Jancar J, Abdel-Rahman RM, Vojtek L, Hyršl P, Dušková M, Nejezchlebová H. A novel in situ silver/hyaluronan bio-nanocomposite fabrics for wound and chronic ulcer dressing: In vitro and in vivo evaluations. Int J Pharm. 2017 Mar 30;520(1-2):241-253. doi: 10.1016/j.ijpharm.2017.02.003.

81. Li C, Fu R, Yu C, Li Z, Guan H, Hu D, Zhao D, Lu L. Silver nanoparticle/chitosan oligosaccharide/poly(vinyl alcohol) nanofibers as wound dressings: a preclinical study. Int J Nanomedicine. 2013;8:4131-45. doi: 10.2147/IJN.S51679.

82. Li CW, Wang Q, Li J, Hu M, Shi SJ, Li ZW, Wu GL, Cui HH, Li YY, Zhang Q, Yu XH, Lu LC. Silver nanoparticles/chitosan oligosaccharide/poly(vinyl alcohol) nanofiber promotes wound healing by activating TGFβ1/Smad signaling pathway. Int J Nanomedicine. 2016 Jan 21;11:373-86. doi: 10.2147/IJN.S91975.

83. Zhang R, Lee P, Lui VC, Chen Y, Liu X, Lok CN, To M, Yeung KW, Wong KK. Silver nanoparticles promote osteogenesis of mesenchymal stem cells and improve bone fracture healing in osteogenesis mechanism mouse model. Nanomedicine. 2015 Nov;11(8):1949-59. doi: 10.1016/j.nano.2015.07.016.

84. Liu X, Hao W, Lok CN, Wang YC, Zhang R, Wong KK. Dendrimer encapsulation enhances anti-inflammatory efficacy of silver nanoparticles. J Pediatr Surg. 2014 Dec;49(12):1846-51. doi: 10.1016/j.jpedsurg.2014.09.033.

85. Shulgina TA, Nechaeva OV, Glinskaya EV, Daryin NI, Torgashova AS, Teslyuk DA, Babailova AV, Panfilova EA. Antimycotic Activity of Silver Nanoparticles Depending on the Stabilizer Used. Izv. Saratov Univ. (N.S.), Ser. Chemistry. Biology. Ecology. 2017;17(4):465-468. doi: 10.18500/1816-9775-2017-17-4-465-468. (In Russ.)

86. Riabushko VI, Yurkova IM, Riabushko LI, Estrela-Lopys VR, inventors; Riabushko VI, Yurkova IM, Riabushko LI, Estrela-Lopys VR, assignees. The method of obtaining a water-soluble bactericidal composition containing silver nanoparticles. Ukraine patent UA 10539. 2005 November 15. (In Ukrainian).

87. Mohanta YK, Biswas K, Jena SK, Hashem A, Abd Allah EF, Mohanta TK. Anti-biofilm and Antibacterial Activities of Silver Nanoparticles Synthesized by the Reducing Activity of Phytoconstituents Present in the Indian Medicinal Plants. Front Microbiol. 2020 Jun 23;11:1143. doi: 10.3389/fmicb.2020.01143. Erratum in: Front Microbiol. 2020 Sep 11;11:1784.