Silver – The Science Behind the Scene

What is the active state of silver?

Silver as an unbound positively charged ion (Ag^{1+}), or charged nanoparticle ($Ag_{(n)}{}^{1+}$) as found uniquely in silver hydrosol, is the only biologically active state for work within the body. Neutral silver (Ag) or silver bound into salts and proteins is not biologically active.

- Positive silver ions (Ag^{1+}or $Ag_{(n)}{}^{1+}$) are the only active state of silver for use within the body. Acél[1] first observed that the oligodynamic (bio-active) action of silver was due to liberated Ag^{1+} as opposed to metallic (neutral) Ag.
- Chambers *et al* have shown that the activity of a specified amount of silver is related to the concentration of Ag^{1+} ion, which is in an unbound state, rather than to the chemical or physical nature of its source.[2]
- Rochart and Uzdins[3] observed that cells selectively bond only with silver that carries a positive charge.
- Eichorn *et al*[4] emphasized that the charge significantly facilitates electron displacement. The charge effectively yanks electrons away from a molecule, in essence weakening the molecular bond and rendering a microbe susceptible to membrane rupture.
- The $Ag_{(n)}{}^{1+}$ structure of silver hydrosol has been shown to have the greatest antimicrobial activity at or near the picoscalar level[5] due to the fact that it enjoys the greatest surface presentation (~6km^2 per gram Ag).[6]

[1]Acél D, Biochem Z, 1920; 112: 23-32. In: Russell, AD, Path, FR, Hugo, WB, Antimicrobial Activity and Action of Silver. *Prog Med Chem*, 1994; 31:353.
[2]Chambers CW, Proctor CM, Kahler PW. Bactericidal effect of low concentrations of silver. *J.Am.Wat.Wks.Ass*.1962; 54:208-216.
[3]Rochart C, Uzdins K. Katadyn (silver preparation): clinical application. Schweiz Med Wochenschr
1947; 77: 1100–4.
[4]Eichorn GL *et al*. Interaction of metal ions with biological systems with special reference to silver and gold. Proceedings of the First International Conference on Gold and Silver in Medicine, Bethesda, MD, 13-14 May. Washington, DC: The Silver Institute, 1987, 4.
[5]Morones JR, et al. The bactericidal effects of silver nanoparticles. *Nanotechnology*. 2005;16:2346-53.
[6]Goetz A, Tracy RL, Harris FS. Oligodyanmic Effect of Silver. Chapter 16. In: Silver in Industry, edited by L. Addicks, Reinhold Publishing Corp., NY, 1940; p.402.

Silver in the diet:

- Silver is a normal constituent of the mammalian diet.
- As a trace element it is found consistently in food and water, including whole grains, edible and medicinal mushrooms, milk[1,2,3] (whether it be cow, goat or human).
- Silver is found in spring water, sea water and even tap water.[4]

[1]Murthy GK, Rhea U. Cadmium and Silver Content of Market Milk. (Food Protection Research; National Center for Urban and Industrial Health - US Public Health Service) Journal of Dairy Science 1968;51(4):610-613.
[2]Krachler, M. "Concentrations of Selected Trace Elements in Human Milk and in Infant Formulas Determined by Magnetic Sector Field Inductively Coupled Plasma–Mass Spectrometry." *Biol Trace Elem Res. Vol. 76, pp. 97-112, 2000.*
[3]Falandysz, J, et al. "Silver content of wild-grown mushrooms from Northern Poland." Z Lebensm Unters Forsch (1994) 199:222-224.
[4]Silver in Drinking Water; Background Document for Development of WHO Guidelines for Drinking-Water Quality. Geneva 2003. (WHO/SDE/WSH/03.04/14)

Silver as an essential trace element:

In human physiology, silver plays an important role. It is literally an essential trace element for the peripheral nervous system. Science has identified receptor sites for silver in myelin neural tissue.[1,2]

[1] Gallyas, F., "Physico-Chemical Mechanism of the Argyrophil I Reaction," *Histochemistry* (1982) 74:393.
[2] Gallyas, F., "Simultaneous Determination of the Amounts of Metallic and Reducible Silver in Histologic Specimens," *Histochemistry*, (1979) 64:77-86.

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Silver's pathway of elimination:

The normal physiologic pathway in humans and animals for the metabolism and elimination of ingested silver occurs in phase II liver glutathione conjugation, which leads to normal excretion as solid waste through the colon.[3]

[3]Rentz EJ. Viral Pathogens and Severe Acute Respiratory Syndrome: Oligodynamic Ag+ for Direct Immune Intervention. *Journal of Nutritional and Environmental Medicine* (June 2003) 13(2), 109-118.

Methods of Action

1. Immune Support Activity:

"Silver helps your immune system to work more efficiently. It can carry up to ten times its atomic weight in oxygen for the benefit of the immune system."[1]

- Silver enhances ROS production, facilitating the efficiency of B-lymphocyte* activity.[2]
- Oligodynamic (bio-active) silver improves the body's internal colloidal milieu (environment) by facilitating oxidative reactions central to immunity, including ROS** production.[3,4,5,6,7]
- Bio-active silver enhances White Blood Cell (WBC) activity.[8,9]

*White blood cells crucial for adaptive immune response.
**Reactive Oxygen Species are used to disrupt metabolic and respiratory pathways of pathogenic microbes.

[1]Rentz EJ. Viral Pathogens and Severe Acute Respiratory Syndrome: Oligodynamic Ag+ for Direct Immune Intervention. Journal of Nutritional and Environmental Medicine (June 2003) 13(2), 109-118.
[2]Wong KY, et al., "Further Evidence of the Anti-inflammatory Effects of Silver Nanoparticles." Chem Med Chem 2009, 4, p1129 – 1135.
[3]Park, H.J., "Silver-ion-mediated Reactive Oxygen Species generation affecting bactericidal activity." 2009 Water Research 43:1027-1032.
[4]Gan X, Liu T, Zhong J, Liu X, Li G. Effect of silver nanoparticles on the electron transfer reactivity and the catalytic activity of myoglobin. Chembiochem. 2004 Dec 3;5(12):1686-91.
[5]Samuni A, et al. On the Cytotoxicity of Vitamin C and metal ions. Eur J Biochem. 1983;99:562.
[6]Jansson, G, Harms-Ringdahl, M, "Stimulating Effects of Mercuric- and Silver Ions on the Superoxide Anion Production in Human Polymorphonuclear Leukocytes," Free Radic Res commun, 1993; 18(2):87-98.
[7]X. Chen∗, H.J. Schluesener. Nanosilver: A nanoproduct in medical application. Toxicology Letters 176 (2008) 1–12.
[8]Ellerman-Eriksen S, Rungby J, Morgensen SC. Autointerference in silver accumulation in microphages without affecting phagocytic, migratory or interferon-producing capacity. Virchows Arch 1987; 53: 243.
[9]Jansson G, Harms-Ringdahl M. Stimulating effects of mercuris and silver ions on the superoxide anion production in human polymorphonuclear leukocytes. Free Radic Res Commun 1993; 18(2):87–98.

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2. Anti-Microbial Activity:

Anti-viral, anti-bacterial, anti-fungal, anti-pathogenic: Positively charged silver nano and picoscale particles denature the protein coat of a virus (blocking replication), can penetrate the cell membrane of a bacteria and fungus and even enter the mitochondria, binding with RNA and DNA, rendering them unable to reproduce.

A. Anti-Viral Action:

"Silver is virostatic, which means that it stops a virus from replicating on contact."

- Silver nanoparticles neutralize the negatively charged Zeta-potentials of the glycoproteins within viral envelopes.[1]
- Denaturation* of protein capsid structures.[1]
- Permanent binding to DNA and RNA macromolecules preventing host cell injection and replication.[1]

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- “Silver nanoparticles possess high binding affinity for Hepatitis B Virus (HBV) dsDNA and extracellular virions.”[2]

  *Disruption of protein structure integrity.

[1]Rentz EJ. Viral Pathogens and Severe Acute Respiratory Syndrome: Oligodynamic Ag+ for Direct Immune Intervention. Journal of Nutritional and Environmental Medicine (June 2003) 13(2), 109-118.
[2]Lu, L., et al., “Silver nanoparticles inhibit Hepatitis B virus replication.” Oct 2007 Antiviral Therapy 13:253-262

B. Anti-Bacterial Action:

“Silver is bactericidal.”

- Silver nanoparticles (primarily 1–10 nm in size) attach to the surface of the cell membrane and drastically disturb its proper function, like permeability and respiration;[1]
- Silver kills even antibiotic resistant bacteria.[1]
- With all prokaryotes (single-celled bacteria), there is a destructive translocation of silver hydrosol particles through their biological membrane or cell wall. There is a destructive translocation of silver hydrosol particles across some simple eukaryotes of various fungal species. The Zeta potential of $Ag_{(n)}^{1+}$ in the organized water molecules contributes to an electroporation event, which further destabilizes the bacterial cell wall.[2]
- Silver nanoparticles are able to penetrate inside the bacteria and cause further damage by binding with DNA in the mitochondria.[1,2,3,4]
- Silver (Ag^{1+}) ions have been tested extensively for their antibacterial efficacy on both gram negative and gram positive bacteria.[4]

[1]Singh, M. et al., “Nanotechnology in Medicine and Antibacterial Effect of Silver Nanoparticles.” Digest Journal of Nanomaterials and Biostructures Vol. 3, No.3, September 2008, p. 115–122.
[2]Rentz EJ. Viral Pathogens and Severe Acute Respiratory Syndrome: Oligodynamic Ag+ for Direct Immune Intervention. Journal of Nutritional and Environmental Medicine (June 2003) 13(2), 109-118.
[3]Clement JL, Jarrett PS. Antibacterial Silver. *Metal Based Drugs,* ed. By Frank Shaw, III, August 17th-20th, 1994; 1(5-6):472
[4]Feng *et al*. A Mechanistic Study of the Antibacterial Effect of Silver Ions on Escherichia coli and Staphylococcus aureus. *J Biomed Mater Res*, 2000 March; 52:662-8.

C. Anti-Fungal Action:

“Silver acts against fungal species in much the same way it acts against bacteria.”

Silver nanoparticles (Ag^{1+} and $Ag_{(n)}^{1+}$) exhibit powerful actions against yeast organisms, including Candida albicans.[1,2,3]

[1]Golubovich, VN, et al. “Binding of silver ions by Candida utilis cells.” Mikrobiolgiia, Jan-Feb 1976; 15(1): 119-22.
[2]Berger, TJ, et al. “Antifungal properties of electrically generated metallic ions.” Antimocrobial Oligodynamic Agents and Chemotherapy, Nov 1976; 10(5):856-60.
[3]Simonetti, N., et al. “Electrochemical Oligodynamic Ag+ for Preservative Use.” Applied and Environmental Microbiology, Dec 1992; 58(12): 3834-6.

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3. Anti-Cancer Activity:

“New study reveals silver causes damage to cancer cells.”

- Uptake of silver nanoparticles occurs mainly through clathrin mediated endocytosis and macropinocytosis.[1]
- Cancer cells appear to be susceptible to damage with lack of recovery from silver nanoparticle-induced stress.[1]

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- Silver nanoparticles are found to be acting through intracellular calcium transients and chromosomal aberrations, either directly or through activation of catabolic enzymes.[1]
- The signalling cascades are believed to play key roles in cytoskeleton deformations and ultimately to inhibit cell proliferation.[1]

[1]AshaRani, PV, et al., "Anti-proliferative activity of silver nanoparticles." BMC Cell Biology 2009, 10:65.

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4. Tissue Regeneration activity:

"Silver reduces tissue inflammation, accelerates tissue healing and prevents scar tissue formation."

- Decrease in adhesion (scar-like tissue) severity.[1]
- Silver nanoparticles may exert anti-inflammatory activities by decreasing Interferon-g* production.[1]
- Silver nanoparticles decrease TNF-a production** on LPS stimulated macrophages.[1]
- Positive silver ions (or charged silver nanoparticles) stimulate de-differentiation and re-differentiation of stem cells in vivo, accelerating healthy regenerative events wherever there is inflammation, infection or injury.[2]
- Promotes accelerated wound healing while improving cosmetic appearance on recovery (no scarring).[3]
- Positive effects exerted through antimicrobial properties, reduction in wound inflammation, and modulation of fibrogenic cytokines***.[3]

*Interferon-g production is part of the cytokine inflammatory response.
**Cytokine involved in systemic and acute phase inflammation.
***Pro-inflammatory response to tissue damage.

[1]Wong KY, et al., "Further Evidence of the Anti-inflammatory Effects of Silver Nanoparticles." Chem Med Chem 2009, 4, p1129 – 1135.
[2]Becker, RO, "Induced De-differentiation; A Possible Alternative to Embryonic Stem Cell Transplants." Neurorehabilitation 17 (2002):23-31.
[3]Jun Tian, Dr. et al. Topical Delivery of Silver Nanoparticles Promotes Wound Healing 31 Oct 2006 ChemMedChem Vol. 2 Issue 1, P. 129-136

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