New generation silver-based antibacterials and antivirals

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The antibacterial activity of silver to preserve food and water quality and to heal wounds has been exploited by man since early civilizations, more than 6,000 years ago (1). Before the introduction of antibiotics in the 1940s, silver was the main antimicrobial agent available (1).

Since the early 2000s, the interest in silver as antimicrobial agent against bacteria and fungi has flourished again due the fact that silver ions (Ag^+) are able to target almost all biomolecules in the bacterial cell at the same time thereby preventing mutant strains development, the resistance mechanism observed with antibiotics (2).

Carried by porin proteins, Ag^+ and Ag nanoparticles (NPs) enter the cell membrane (3) causing its rupture and cytoplasmic leakage, driving the formation of highly oxidizing species including H_2O_2, and hydroxyl and superoxide free radicals which rapidly oxidise DNA, RNA and proteins (3). Most importantly from the viewpoint of practical application, the Ag^+ ions are not deactivated by the killing mechanism, with the dead bacteria serving as a reservoir for releasing lethal cations for further action against other live bacteria (4).

The interest in silver in medicine further surged with the more recent discovery that Ag NPs are potent and broad-scope antiviral agents against numerous viruses, including several influenza viruses, hepatitis B virus, poliovirus, respiratory syncytial virus, and most recently even African swine fever virus (5). The mechanism of action, for example against human immunodeficiency virus HIV-1, includes concomitant action as virucidal agent and inhibitor of viral entry (6), as well as inhibitor of virus replication.

Starting in the early 2000s, several companies started to commercialize silver-based antimicrobial formulations both as medications and to impart textiles, garments, consumer goods in widely different materials, surfaces of washing machines, food storage containers and water tanks with antimicrobial properties. *Silpure*, *Mepilex Ag*, *Microban*, *Sanitized AG*, *iSys AG* are just selected tradenames of commercially available silver-based antimicrobial products for medicinal and consumer applications. Only between 2007 and 2017, nearly 5000 patented products using any forms of silver for bactericidal action have been registered (20% in English, >50% of the global total in Chinese, followed by Korean and Japanese language filings) (7).

Showing the practical relevance of new generation silver-based antivirals and antimicrobials, in early 2020 a Swiss company commercialized an antiviral and antimicrobial textile treatment tested effective against human coronavirus (8). This is not trivial also because tests for antiviral effect require the involvement of highly regulated laboratories able to effectively test the antiviral activity in bodily fluids (viruses generally only survive a very short time outside the body).

Besides testing on human coronavirus, the latter treatment leads to dramatically improved reduction of virus infectivity against several influenza viruses, and the respiratory syncytial virus, by combining vesicle and silver technologies: vesicles target lipid-enveloped viruses easing rapid virus deactivation, while silver inhibits the replication of both viruses and bacteria (8).

A crucially important requirement for this and related applications is the stability of the biological activity of the original high activity. A number of new technologies aimed at improving the stability of silver-based treatments employ therefore microencapsulation of the active silver species.

For example, garments and domestic textiles treated with silver-based formulations need to retain their activity upon several washing cycles. This is often the case because Ag^+ on garments is capable to exert strong antibacterial activity up to extremely low concentration levels, as shown by >99.9%

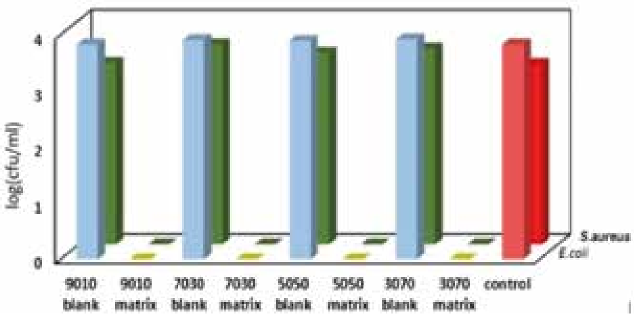

Figure 1. Antibacterial activity of different (10%, 30%, 50% and 70% methyl-modified) *SilverSil* xerogels against *S. aureus* (green bars), and *E. coli* (blue bars). The activity of different blank matrices and of the control solution is also plotted (red bars). (Reproduced from Ref.10, under the terms of the Creative Commons Attribution License).

inhibition of *Escherichia coli* growth on textiles retaining as little as 2 ppb Ag after prolonged washing (9). After that, however, activity is lost.

Dubbed *SilverSil*, the new class of antibacterial materials comprised of organically modified silica (ORMOSIL) obtained by sol-gel hydrolytic co–polycondensation of TEOS and methyltriethoxysilane (MTEOS) and physically doped with Ag nanoparticles, shows such remarkably high and stable activity against representative Gram-positive and Gram-negative pathogenic bacteria (10). In detail, *SilverSil* xerogels of different degree of organic modification show (Figure 1) very high antibacterial activity against *Staphylococcus aureus* and *E. coli* bacteria. The 70% methyl-modified xerogel, namely the glass with the highest activity against methicillin-resistant *S. aureus*, washed with different amounts of water in 7 consecutive washing cycles, leaches less than 2.5% of the entrapped silver, retaining its strong antibacterial activity.

ORMOSIL alcogels rapidly and strongly bind to most surface substrates (11). Hence, it will be enough to modify the sol-gel synthetic route via easy procedures well known in sol-gel materials chemistry to make *SilverSil* available as a nanosol paint with which to functionalize the surface of any object needing prolonged antibacterial protection, from water and food storage tanks to the healthcare built environment, from medical products such as surgical masks through aircraft passenger cabins, swimming pools, schools, bathroom and workplace environments.

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