## Colloidal Silver

## How Silver kills bacteria finally revealed

The use of silver in medicine is as old as medicine it self but how it works has been a mystery ever since.

(BullionStreet): Silver still holds the secret of its ability to kill bacteria, thousands of years after mankind began to use the metal in medicine.

The use of silver in medicine is as old as medicine it self but how it works has been a mystery ever since.

Hippocrates is known to have used it to treat ulcers and wounds, the Romans almost certainly knew of its healing properties, its use continued through the middle ages and up to the present day.

In the antibiotic age, interest in silver may have waned a little. But with urgent need to fight antibiotic-resistant bacteria, there is resurgence in its uses

Now, a team led by James Collins, a biomedical engineer at Boston University in Massachusetts, has described how silver can disrupt bacteria, and shown that the ancient treatment could help to deal with the thoroughly modern scourge of antibiotic resistance.

The work is published in Science Translational Medicine.

Here is silver's multi-pronged approach: first, silver sticks very strongly to sulfur, found in parts of proteins. These sulfur groups normally bond to each other in proteins, holding them together and keeping the protein folded up in its correct shape.

But if silver interacts with sulfur then the protein cannot fold correctly, and thus it cannot do its job. Next silver interferes with how bacteria use iron. Iron is often held in the places it is needed by binding to sulfur. And since silver also interacts with sulfur it stops the iron doing so.

Finally, silver causes bacteria to produce extremely toxic substances called reactive oxygen species. These go on to cause damage inside the cell, harming the DNA, proteins and even the membrane that surround cells.

The net result of this silver onslaught is bacteria with severely damaged defences. Most importantly the membranes and walls that surround it are leakier after the silver treatment. Once weakened, they are much more susceptible to conventional antibiotics.

Collins and his team found that silver - in the form of dissolved ions - attacks bacterial cells in two main ways: it makes the cell membrane more permeable, and it interferes with the cell's metabolism, leading to the overproduction of reactive, and often toxic, oxygen compounds.

Both mechanisms could potentially be harnessed to make today's antibiotics more effective against resistant bacteria, Collins says.

**Colloidal silver** was used by doctors in the early 20th century, but after the development of more modern antibiotics, its use dwindled. Since the 1990s, however, there has been a resurgence of its use amid claims that it is a cure-all.

Many antibiotics are thought to kill their targets by producing reactive oxygen compounds, and Collins and his team showed that when boosted with a small amount of silver these drugs could kill between 10 and 1,000 times as many bacteria.

The increased membrane permeability also allows more antibiotics to enter the bacterial cells, which may overwhelm the resistance mechanisms that rely on shuttling the drug back out.

That disruption to the cell membrane also increased the effectiveness of vancomycin, a large-molecule antibiotic, on Gram-negative bacteria - which have a protective outer coating. Gram-negative bacterial cells can often be impenetrable to antibiotics made of larger molecules.

Collins says that he and his colleagues saw good results in mice using non-toxic amounts of silver. But, he adds,

there are ways to reduce the risk even further. "We're also encouraging people to look at what features of silver caused the helpful effects, so they can look for non-toxic versions," ⊓ he says.

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## Silver Enhances Antibiotic Activity Against Gram-Negative Bacteria

[Jose Ruben Morones-Ramirez 1,2; Jonathan A. Winkler 1,3, Catherine S. Spina 2,4 and James J. Collins 1,2,3,4]

A declining pipeline of clinically useful antibiotics has made it imperative to develop more effective antimicrobial therapies, particularly against difficult-to-treat Gram-negative pathogens. Silver has been used as an antimicrobial since antiquity, yet its mechanism of action remains unclear. We show that silver disrupts multiple bacterial cellular processes, including disulfide bond formation, metabolism, and iron homeostasis. These changes lead to increased production of reactive oxygen species and increased membrane permeability of Gram-negative bacteria that can potentiate the activity of a broad range of antibiotics against Gram-negative bacteria in different metabolic states, as well as restore antibiotic susceptibility to a resistant bacterial strain. We show both in vitro and in a mouse model of urinary tract infection that the ability of silver to induce oxidative stress can be harnessed to potentiate antibiotic activity. Additionally, we demonstrate in vitro and in two different mouse models of peritonitis that silver sensitizes Gram-negative bacteria to the Gram-positive-specific antibiotic vancomycin, thereby expanding the antibacterial spectrum of this drug. Finally, we used silver and antibiotic combinations in vitro to eradicate bacterial persister cells, and show both in vitro and in a mouse biofilm infection model that silver can enhance antibacterial action against bacteria that produce biofilms. This work shows that silver can be used to enhance the action of existing antibiotics against Gram-negative bacteria, thus strengthening the antibiotic arsenal for fighting bacterial infections.

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