

Colloidal Silver Research Summary Document

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We at **Silverlab Healthcare** read, with much interest, the **comprehensive and informative** 'Early COVID-19 Treatment Guidelines: A Practical Approach to Home-based Care for Healthy Families' document. As an established, 20-year-old South African company, we are continually conducting **extensive medical research** on our **colloidal silver** products through accredited South African and EU **laboratories** and are furthermore working closely with **doctors** and **other health care professionals** (who are themselves on the forefront of the COVID-19 pandemic). We also passionately advocate for the **right to good health for all**. To this end, we would like to propose **colloidal silver** for your kind consideration as an addition to your list of **essential products** for **early at-home treatment of COVID-19**. Silverlab's Colloidal Silver further complies since it is also a **safe, established and patent-free product**.

Colloidal silver is unique, due in part to its **multiple and complex mechanisms of action**. This is perhaps best documented in the comprehensive peer-reviewed white paper, 'The Silver Lining: towards the responsible and limited usage of silver', which was published in the **Journal of Applied Microbiology** in **2017** and which substantiates the versatility and multimodal mechanisms of action of **ionic and nano-silver**.

Some of the key findings include the following:

- 'Silver is known to react with **nucleophilic amino acid residues in proteins, and attach to sulfhydryl, amino, imidazole, phosphate and carboxyl groups**.' ⁽¹⁾
- 'It causes **bacterial cell wall damage** and **disruption of cytoplasmic membrane** leading to leaching of metabolites, interferes with **DNA synthesis**, denatures **proteins and enzymes (dehydrogenases)**, binds to **ribosomes** and inhibits **protein synthesis**, interferes with **electron transport system** and is involved in the production of **reactive oxygen species (ROS)** (Hatchett and White **1996**; Feng *et al.* **2000**).' ⁽¹⁾
- 'The **primary mode** of silver toxicity is its potential to **release silver ions**.' ⁽¹⁾
- 'Irrespective of the form of the silver used, a major characteristic that will affect the microbicidal effect of the silver is the **concentration of silver ions** released.' ⁽¹⁾

- 'The **nano form with its large surface area to volume ratio has high potential** for release of silver ions (Sotiriou and Pratsinis 2010).'⁽¹⁾
- 'All forms of silver including silver compounds and silver salts have potential to **release silver ions**.'⁽¹⁾
- 'Even the biocidal effect of elemental silver is due to formation of silver ions at low concentration on its surface.'⁽¹⁾
- 'Nanostructured silver targets the **bacterial cell wall and cell membrane** which is a **protective barrier** and serves several functions (Sondi and Salopek-Sondi 2004).'⁽¹⁾
- 'Nanoparticles **<10 nm** in diameter can **bind to bacterial cell wall** and cause its **perforation** leading to **rapid increase in cell permeability** and ultimately **cell death**.'⁽¹⁾
- 'Silver ions can also cause the **cell membrane** to **detach** from the **cell wall** - nevertheless, the **mechanism** of this process has still been **unknown** (Feng *et al.* 2000).'⁽¹⁾
- 'Silver can attack the **respiratory chain** in **bacteria** and lead to **cell death** (Sondi and Salopek-Sondi 2004).'⁽¹⁾
- 'Respiration is the **critical point** in bacterial cell metabolism and is the **mechanism of obtaining energy** to perform all the energy-demanding life processes.'⁽¹⁾
- 'The **creation of free radicals** and **induction of oxidative stress** also contributes towards **toxicity** of AgNPs/ions (Kim *et al.* 2007; Cao and Liu 2010; Wong and Liu 2010).'⁽¹⁾
- 'Sustained release of silver ions by AgNPs inside the bacterial cells in an environment with **lower pH** may create free radicals and induce oxidative stress, thus further **enhancing the bactericidal activity** (Morones *et al.* 2005; Song *et al.* 2006)'⁽¹⁾

These and various other mechanisms of action are discussed at length in the paper, and perhaps it is their **sheer complexity** that may in part explain why **colloidal silver** is so unique in that it is **scientifically proven** to be effective in **each of the cornerstones of the product categories** found to be beneficial in the early management of Covid-19, namely:

1) Immune Support

‘The Silver Lining: towards the responsible and limited usage of silver’ paper indicates that,

- ‘In **addition to its antimicrobial effect**, colloidal silver is also known to be a **powerful immune system booster**.’ ⁽¹⁾
- Furthermore, ‘A **correlation between low silver levels in body and disease** has been observed wherein individuals with low silver levels in their hair analysis were frequently found to be sick with innumerable colds, flu, fevers, and various other sicknesses.
- It was proposed that **silver deficiency** could be the **key to the improper function of the immune system** (Becker and Selden **1985**).’ ⁽¹⁾

Considering this information, Silverlab Healthcare has submitted an **Annexure B application** to the **SAHPRA**, for **colloidal silver** to be recognised as a **trace mineral** under the **complementary medicines umbrella**.

- The paper further states that ‘Increasing evidence of **AgNPs** and their possible **immunomodulatory effects** have been reported (Edwards-Jones **2009**).
- It has been demonstrated that **silver ions** greatly **enhance** the ability of **immune cells to digest infectious agents**.
- This is facilitated by increasing the digestive aids of these immune cells, like **superoxide and hydrogen peroxide** more commonly known as **ROS** (Thurman and Gerba **1989**; Jansson and Harms-Ringdahl **1993**; Feng *et al.* **2000**).’ ⁽¹⁾
- **Silver ions activate mast cells** (a crucial component of the immune system) and thus play an important role in **allergic reactions, wound healing, and defence against pathogens**.
- Silver also plays a vital role in stimulating the **lymphatic system**, which **filters out toxins** from the **circulation**.
- Silver nanoparticles **reduce cytokine expression** and thus reduce **excessive inflammation** (which otherwise slows down the process of healing).
- Antimicrobial silver also facilitates healing by **reducing microbial burden**.

2) Antiviral

- The paper notes that, '**Antiviral activity of natural mineral silver** in a variety of forms **including colloidal silver** has been demonstrated through nearly **three decades of medical research** (Fig. [2](#)).
- It has been reported that **silver can stop different types of viruses from replicating by merely binding to them.**
- Recent research demonstrates that silver is so **powerfully effective** against **viruses** that it **even stops the deadly HIV virus from infecting human cells.**
- The vital requirement in order to exhibit such powerful antiviral activity is the **size of the silver particles.**
- Nanoparticles of size ranging from **1 to 100 nm** are efficient as **smaller size leads to more interaction and inhibition of viruses** (Galdiero *et al.* [2011](#); Khandelwal *et al.* [2014](#)).
- Silver nanoparticles undergo a **size-dependent interaction** with HIV-1 virus and nanoparticles in the size range of 1–10 nm were able to attach to the virus.
- The interaction is via preferential binding of AgNPs to the gp120 glycoprotein knobs which bear the exposed sulphur residues and inhibit the virus from binding to host cells *in vitro* (Elechiguerra *et al.* [2005](#)).

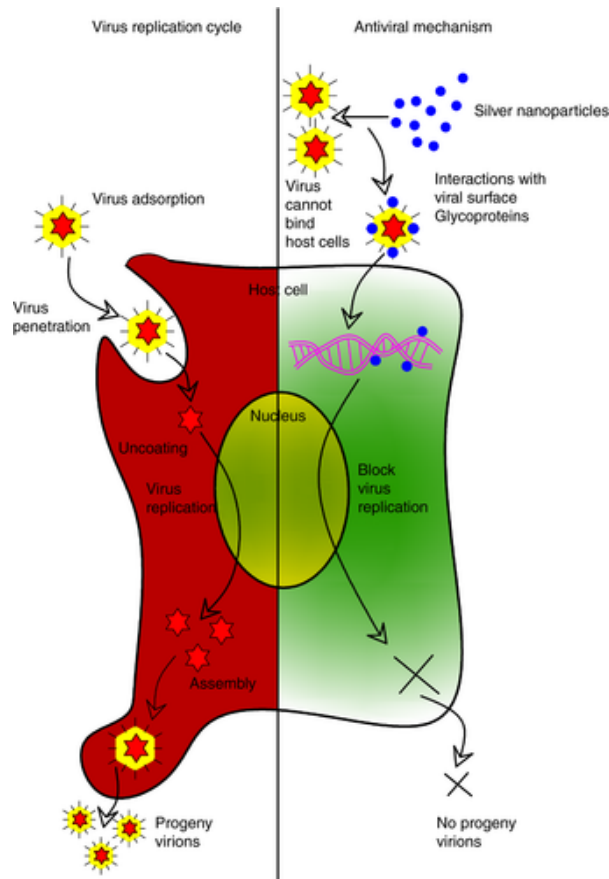


Figure 2

[Open in figure viewer PowerPoint](#)

Antiviral mechanism of action of silver nanoparticles. [Colour figure can be viewed at wileyonlinelibrary.com]

- Colloidal silver was found to show **remarkable efficacy against the smallpox virus**.
- Collargol and Protargol were the two medicinal preparations of colloidal silver used in the study.
- The reduction in concentration of viral particles was about 11 000 and 700 times for collargol and protargol respectively (Bogdanchikova *et al.* **1992**).
- **Herpes simplex virus types I and II** was reported to be inactivated by **silver nitrate** at concentrations of 30 $\mu\text{mol l}^{-1}$ or less (Shimizu *et al.* **1976**).

- **AgNPs** of approximately **10 nm** were demonstrated to inhibit **monkeypox virus** *in vitro*, supporting their potential use as an antiviral therapeutic agent (Rogers *et al.* **2008**).⁽¹⁾

This may be of **particular interest** currently due to the sporadic outbreaks of **monkeypox** which have been happening in various parts of the world recently.

- **'AgNPs** of approximately **10–50 nm** in diameter were demonstrated to interact with viral DNA of **hepatitis B virus** and prevent replication *in vitro*. In this case the antiviral mechanism was attributed to the direct interaction between the nanoparticles and HBV double-stranded DNA or viral particles (Lu *et al.* **2008**).
- The **collective authoritative medical literature reports silver to be virucidal against over 24 viruses**.
- Additionally, it has been proposed that **200 plus viral strains** known to cause **upper respiratory tract infections**, including most flu viruses, will also most likely succumb to the powerful antiviral qualities of very small particles of oligodynamic silver (Gordon and Holtorf **2006**).'⁽¹⁾

Although most studies postulate that it is the **nanoparticle** component of colloidal silver that is anti-viral, **Silverlab Healthcare's recent CSIR report** indicates that, even at half dilution, the **predominantly ionic solution is 97.1 % effective** against the **SARS-CoV-2**, as described in the conclusion, 'The IM/Q610/419-01A-18 Silverlab Healthcare sample showed activity of 97.1% and 66.6% *in vitro* at dilutions of ½ and ¼ against SARS-CoV-2, respectively. The ID50 of the sample was 5 against SARS-CoV-2. In addition, the **sample did not show cytotoxicity to 293T-ACE cells** used in the study as target cells, as shown in Figure 2. Based on this, it is possible that the sample TI is high, which is **desirable for drug candidates**. Thus, IM/Q610/419-01A-18 **Silverlab Healthcare sample tested in this study can be declared active against SARS-CoV-2 *in vitro***.'⁽²⁾

It would make for an interesting study, to determine what the exact mechanisms of action that are involved, are.

3) Anti-inflammatory

- As briefly mentioned earlier, **'Silver nanoparticles have the ability to reduce cytokine expression and thus reduce excessive inflammation that slows down the process of healing.**
- Cytokines are **signalling molecules** in the body that direct the **immune system** to send **white blood cells** and **other infection fighting agents** to the **site of infection**.
- This causes mild inflammation which is a **normal** part of healing.
- However, in case of **chronic infection or serious wound trauma**, the pro-inflammatory effects of cytokine expression can result in **excessive unwanted inflammation** which in turn **impedes the healing process**. In such cases, **antimicrobial silver has a modulating effect on cytokine expression**, resulting in both **reduced inflammation and increased healing.**' ⁽¹⁾

Silverlab Healthcare conducted studies in 2007 with Synexa on the **anti-inflammatory action** of its **18-ppm ionic colloidal silver liquid**: 'The results obtained clearly show the anti-inflammatory action of ionized Ag *in vitro*. At a final concentration of **4.503 ppm (25%) ionized Ag** was able to inhibit the production of IL-6 and TNF- α around 5 times compared to the stimulated control. This anti-inflammatory activity was **still demonstrated** at a final Ag concentration of **1.126 ppm (6.25%)** and inhibited the release of the cytokines by a factor of 3. These results indicate a **potential clinical use of the product to control tissue damage in chronic inflammatory conditions**. Obviously, we cannot conclude whether the oral intake of the product will demonstrate the same anti-inflammatory activity because the *in vitro* results cannot be extrapolated to *in vivo* situations: metabolic transformation of the product, oral uptake, etc. However, it remains an **interesting product** to consider for topical applications.' ⁽³⁾

4) Anticoagulant

The Silver Lining paper states that

- **'Anticoagulant therapies** are associated with **serious bleeding complications as exact dosing can be a challenge.**
- Excessive amounts of an anticoagulant can cause **blood loss**, whereas too little of an anticoagulant may clog patient's arteries.

- Researchers have tested the **effectiveness of nanosilver particles as an anticoagulant** and demonstrated that nanosilver has an **innate antiplatelet property**.
- It **effectively prevents integrin-mediated platelet responses**, both *in vivo* and *in vitro*, in a **concentration-dependent manner**.⁽¹⁾
- Furthermore 'In another study, **nanosilver prevented platelet adhesion without conferring any lytic effect on them** and **effectively prevented integrin-mediated platelet responses in a concentration-dependent manner** (Bandyopadhyay *et al.* **2012**)'.⁽¹⁾

The authors conclude that **more in-depth studies are required before silver can be proposed as a potential antiplatelet agent**. However, whether ingested or inhaled, colloidal silver may well play an important role in **helping to prevent the formation of blood clots**.

5) System support

Due to its **multimodal mechanism of action**, colloidal silver would seem to be a **valuable adjunct** to provide **overall system support**, mainly because of its **anti-inflammatory and anti-microbial activity**.

- As a **nasal spray**, it assists in **reducing nasal congestion** as well as **the local microbial burden**. It may further play an **important preventative role**, as the virus tends to become **firmly established first in the nasal cavity**.
- As an **oral spray or mouthwash**, it similarly **assists to reduce the pathogenic burden in the mouth**, thus potentially **soothing a sore throat** and other **painful oral conditions**, including **thrush**. It would stand to reason that colloidal silver would play a significant **preventative** role.
- Notable beneficial effects have also been experienced when colloidal silver is **nebulized**, with **oxygen saturation levels normalising relatively quickly** and, anecdotally, **similar rapid relief has been reported even for the gastro-intestinal form of COVID-19**.
- This has led to some doctors describing it as a '**pseudo-haemoglobin**' effect.

- Although the exact mechanism of action is yet to be established, perhaps a clue can be found in the '**Antimicrobial Silver in Medicinal and Consumer Applications: A Patent Review of the Past Decade (2007-2017)**', which finds that 'Silver is known to be **biologically active** when it is **dispersed into its monoatomic ionic state (Ag^+)**, when it is **soluble in aqueous environments**'.⁽⁵⁾ Furthermore, 'The **metallic (Ag^0) and ionic forms** can appear **loosely associated** with other **elements such as oxygen** or other metals and can form **covalent bonds or coordination complexes**.'⁽⁴⁾
- This would seem to be a very **promising avenue for future study**.
- It also **appears to speed up the recovery rate** and **may** therefore also assist with **long COVID**.
- Due to its **antiviral and general antimicrobial efficacy**, as well as its **favourable safety profile especially when applied topically**, colloidal silver makes an effective **sanitizer as well as a versatile general disinfectant**.

Silverlab Healthcare has recently received the results of its Sanitizer Efficacy tests, which show that 'The Silverlab Healthcare disinfectant showed effectiveness of **~ 99.9% and 99.99% against SARS-CoV-2 virus at 30- and 60-seconds exposure time, respectively**, in the infectivity assay conducted. Thus, the **disinfectant can be declared active against this virus**.'

(5)

Amongst the benefits of this is that it is an overall **safe, effective, alcohol-free, and cost-effective** sanitizing solution for the pandemic and beyond.

Apart from all the above-mentioned benefits, colloidal silver may provide further support specifically as far as the treatment of COVID-19 is concerned:

6) Broad spectrum antimicrobial cover

- Apart from it being an effective **anti-viral** agent, it is also an **anti-bacterial** as well as **antifungal** agent, thereby providing **broad-spectrum antimicrobial** cover and may

- therefore be very beneficial to prevent and / or treat any secondary respiratory tract infections that may occur.
- The Silver Lining paper states that '**Anti-bacterial activity of nanosilver** (Fig. [1](#)) has been demonstrated against a wide range of Gram-positive and Gram-negative bacteria (Wijnhoven *et al.* [2009](#); Duncan [2011](#)).
- The bactericidal activity of silver has been reported to reside in its **ionic form**, and **micromolar doses** ($1-10 \mu\text{mol l}^{-1}$) of **silver ions are sufficient to kill bacteria in water** (Liu *et al.* [1994](#)).⁽¹⁾
- Furthermore, 'Nanosilver is also **effective against strains of organisms that are resistant to potent chemical antimicrobials** including **multidrug-resistant bacteria** like methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis*, vancomycin-resistant *Enterococcus*, extended spectrum β -lactamase producing *Klebsiella*, multidrug-resistant *Pseudomonas aeruginosa*, ampicillin-resistant *Escherichia coli* O157:H7 and erythromycin-resistant *Streptococcus pyogenes* (Yu [2007](#); Duncan [2011](#); Lara *et al.* [2011](#)).'⁽¹⁾
- Additionally, 'Silver has also been demonstrated to **decimate most of the well-known bacterial pathogens that cause serious secondary infections during a viral infection** such as *Streptococcus pneumonia*, *Corynebacterium diphtheria*, *Neisseria gonorrhoeae*, *Klebsiella pneumonia*, *Haemophilus influenza*, *Bordetella pertussis*, *Mycobacterium* and *Pneumococci*.
- These bacteria can cause complications including pneumonia, bronchitis, conjunctivitis, sinusitis, otitis media and other chronic illness such as asthma (Gordon and Holtorf [2006](#)).'⁽¹⁾

Silverlab Healthcare recently conducted research at NOSA, where 'The aim of the study was to determine the **minimum contact time** required to produce at least a **5-log reduction in viable bacteria**.'⁽⁴⁾ The results indicated that 'The **18ppm Ionic Silver suspension eliminated all viable cells** after a **minimum contact time in 60 seconds**, whereas the 42ppm suspension was able to achieve this in under 30 seconds'⁽⁶⁾

- Furthermore, as described in the Silver Lining paper, '**Antifungal activity of silver nanoparticles (AgNPs)** of various sizes has been demonstrated against *Candida albicans* and *Candida glabrata* which are **common causes of oral thrush and dental stomatitis**.
- Infections like these are particularly difficult to treat because the fungal micro-organisms involved form **protective biofilms** that prevent prescription antifungal drugs from functioning.
- These AgNP suspensions exhibited fungicidal activity against the tested strains at **very low concentrations** in the range of 0.4–3.3 $\mu\text{g ml}^{-1}$. Hence, AgNPs appear to be a new potential strategy to combat these infections.
- As the **nanoparticles are relatively stable in liquid medium**, their use **as mouthwash solution is proposed** (Monteiro *et al.* 2012).'⁽¹⁾

7) Antioxidant properties

- Silver also has **antioxidant properties**, as described by the Silver Lining paper: 'Antioxidants are substances that when present at **low concentrations, significantly prevent or delay** a pro-oxidant initiated **oxidation** of the substrate (Prior and Cao 1999).
- A **pro-oxidant** is a **toxic substance** that can cause **oxidative damage to lipids, proteins and nucleic acids** resulting in various pathological diseases.
- Examples of pro-oxidants include **reactive oxygen and nitrogen species (ROS and RNS)** which are **products of normal aerobic metabolic processes** (Gülçin 2012).
- It has been reported that an increased intake of **dietary antioxidants** could protect against chronic diseases such as **cancers, cardiovascular and cerebrovascular diseases** (Ramasamy *et al.* 2013).'⁽¹⁾

8) Synergistic activity of colloidal silver with antibiotics

- Furthermore, 'When **antibiotics are boosted with a small amount of silver** these **drugs can kill 10–1000 times more bacteria**.

- This is because **silver increases the membrane permeability which allows more antibiotics to enter the bacterial cells.**
- This mechanism **may overpower the resistance mechanisms that rely on shuttling the drug back out which results in making the bacteria sensitive to the antibiotic.**
- This disruption in the cell membrane is also reported to increase the effectiveness of vancomycin, a large molecule antibiotic, on Gram-negative bacteria which have a protective outer coating (Morones-Ramirez *et al.* **2013**).
- Furthermore, the drug interaction study showed **no antagonism indicating that concomitant use of colloidal silver with these antibiotics does not affect the absorption or therapeutic efficacy of either agent.**
- Hence, **use of colloidal silver in combination with antibiotics** can be an **effective strategy** due to its **low toxicity and high therapeutic activity against pathogenic micro-organisms** (Iroha *et al.* **2007**). ⁽¹⁾

This effect may be **beneficial in COVID-19** when it is further complicated by the development of a **secondary infection, and the addition of an antibiotic is necessary.**

9) Gastrointestinal diseases

- In addition, '**AgNP-impregnated *Lactobacillus fermentum* have been found to be effective against rotavirus and norovirus which cause food poisoning and winter vomiting outbreaks.**
- As AgNPs used in this study are extremely small with large surface area, it enables them to clump around the virus increasing the inhibitory effect.
- There are **concerns about using such small silver particles** in humans as they could pass into other parts of the body and cause harm.
- Hence **attaching these AgNPs to the surface of the bacterium** enables fixing of the silver onto a **larger entity** that **cannot pass** into other parts of the body.
- **Although the bacteria eventually die** as a result of the silver, they **remain intact** and the **dead cells carrying the silver particles** can then be **added to solutions** and used.'

⁽¹⁾

10) Biofilms

- According to the Silver Lining paper, 'In **the natural world, more than 99%** of all **bacteria** exist as **biofilms** (Costerton *et al.* **1987**).
- Biofilms are **the protective structures created** by the colonies of **pathogens** in order **to evade the effects of antibiotic drugs**.
- They are **protected by an extracellular matrix** held together by **proteins and polysaccharides** commonly referred to as **extracellular polymeric substance**.
- This **affects the efficiency** of the strongest of antibiotics and biofilms can be as much as a **thousand times more resistant than planktonic cells**.
- The growth of biofilms is a **major problem within the healthcare and food industries**.
- Biofilms can form on many **medical implants such as catheters, artificial hips and contact lenses**.
- According to the National Institute of Health **more than 60% of all infections are caused by biofilms**.
- These include, but are not limited to endocarditis, cystic fibrosis, otitis media, chronic prostatitis, urinary tract infections, dental plaque infections, gingivitis, periodontitis, chronic sinusitis, burn wound infections and bone infections (Kim **2001**).
- Many recent studies have demonstrated conclusively that **antimicrobial silver can penetrate through the bacterial biofilms to completely destroy them and can even prevent microbes from developing biofilms**.
- As compared to the antibiotics, **silver is proposed to be less affected** by the micro-environmental variations found in biofilms due to its **multimodal mechanism of action** (Bjarnsholt *et al.* **2007**).'⁽¹⁾

11) Facilitates tissue repair

Colloidal silver further facilitates **tissue repair**, which may also be of interest with regards to **COVID-19**, due to the **widespread and extensive** tissue damage that the infection can cause.

- As described in the Silver Lining paper, 'When **silver ions come in contact with the wound bed, they combine with proteins, peptides and other chemical species** normally present in the tissues.
- After all the available sites are saturated with binding of silver ions, the antibacterial action of silver **begins at about 20–30 min following the exposure of bacteria to the ions.**
- The next reaction is an association between the **silver ions and sensitive cells** present in the wound such as **mature fibroblast and epithelial cells**, resulting in **dedifferentiation of these cells into embryonic cell types capable of redifferentiation** into other cell types.
- Production of dedifferentiated fibroblasts requires a **continuous supply of excess silver ions for at least 48–72 h following saturation of the active chemical sites in the previous reaction.**
- **If sufficient silver ions** are made available, a **third reaction** begins to take place.
- This constitutes a **specific physical association of at least some of the silver ions with the collagen fibres present in the wound to produce a unique structure called as silver-collagen complex** having the specific properties required to **induce activation** of the **dedifferentiated fibroblast** cells previously produced.
- After this, an adequate **blastema** is formed in the tissue which **supports regeneration and wound repair** by the process of **redifferentiation of blastema** into the **required cell types** (Becker *et al.* 1998).'⁽¹⁾

12) Relieves allergic reactions

There has been an approach by several doctors to treat COVID-19 using antihistamines as an integral part of their initial response to the infection.

- As described earlier, '**Silver ions are reported to activate mast cells** which are a crucial component of the immune system and play an **important role in allergic reactions**, wound healing and defence against pathogens.'⁽¹⁾

It would therefore seem that colloidal silver acts, in part, as a **natural antihistamine**.

Colloidal silver is indeed a fascinating product, which has multiple other health benefits, apart from its potential benefits in the management of COVID -19, including the following:

1) May assist with various respiratory tract conditions:

- As described in the Silver Lining paper, 'Colloidal or nano silver owing to its **strong and broad-spectrum antimicrobial properties** could possibly have the potential to heal a **variety of upper respiratory tract infections** in an effective way.
- Some of these infections include **pneumonia, bronchitis, cystic fibrosis, chronic obstructive pulmonary disease, sinus, asthma, allergies, and other lung diseases**.
- The treatment consists of **atomizing silver** using a **nebulizer or nasal spray**.
- Although this treatment appears to be very promising, its full-fledged use is limited until the long-term safety of inhaling minute silver particles into lungs is exhibited by clinical studies.
- A **28-day inhalation toxicity** study of AgNPs in rats **did not** exhibit any significant changes in the haematology and blood biochemical values for both male and female rats, and **no distinct histopathology** findings were observed, indicating that **exposure to silver did not have any significant health effects** (Ji *et al.* 2007).
- However, a **90-day** animal study resulted in **lung function changes due to prolonged AgNP inhalation exposure** (Sung *et al.* 2008).

- Another AgNP inhalation toxicity study for 90 days indicated that **lungs and liver** were the major target tissues for prolonged AgNP accumulation.
- However, a **higher dose with prolonged exposure was needed** to induce any toxic responses (Sung *et al.* 2009).
- Inhalation exposure studies of colloidal silver have not been conducted on human subjects until now.
- **Recent human oral exposure study** demonstrated that a **14-day oral dosing** of a commercial colloidal silver product **did not produce any observable clinically important toxic effect**.
- No morphological changes were detected in the lungs, heart or abdominal organs.
- No significant changes were noted in pulmonary ROS or pro-inflammatory cytokine generation.
- **Further study** of silver-based nanomaterials over **longer human exposures** is necessary to determine the risks (Munger *et al.* 2014).
- As colloidal silver has been shown to **alleviate inflammatory symptoms in cystic fibrosis** patients (Baral *et al.* 2008), it could be developed into successful treatment for chronic lung infections associated with cystic fibrosis.
- Currently there is no evidence to support the use of silver products in the above-mentioned upper respiratory tract infections but their **potential benefits might be worthy of further exploration**.
- Nanosilver could also have potential applications in the treatment of **tuberculosis**, a serious infectious airborne bacterial disease caused by the bacterium *Mycobacterium tuberculosis*.
- The antibiotic-resistant tuberculosis pathogens were **rapidly killed when tested against nanosilver capped with bovine serum albumin** (Seth *et al.* 2011).
- AgNPs were found to inhibit ***M. tuberculosis*** by inducing **metabolic disturbances** in the **cytoplasm** of these cells at a concentration of **10 ppm** (Song *et al.* 2006).

- Silver can be used in **respiratory devices** like ventilators, inhalers and continuous positive airway pressure machines to **prevent the growth of micro-organisms in the water reservoir and breathing apparatus.**
- This acts as a **disinfectant** and helps keep the **devices clean of microbial build up and biofouling.**
- Silver when used in this apparatus also helps keep the **lungs infection free** and **prevents the chronic upper respiratory tract infections** associated with usage of such devices.’ ⁽¹⁾

2) Wound and burn healing:

As previously discussed, colloidal silver facilitates tissue repair, and it is therefore useful for a diverse variety of wounds, including burns.

- As described in the Silver Lining paper, ‘Electrically generated silver ions were reported to kill **numerous forms of infectious micro-organisms.** For example, *Providencia stuartii*, a **burn wound isolate which was resistant to all antibiotics except amikacin**, was susceptible to electrically generated silver with a minimum bactericidal concentration of 0.73 g ml⁻¹.
- **Oligodynamic Ag⁺ was found to be 10–100 times superior to silver sulfadiazine in case of both Gram-positive and Gram-negative pathogens in terms of achieving the minimal lethal dose** (Berger *et al.* **1976b**).’ ⁽¹⁾

3) Improved cosmetic appearance:

- The Silver Lining paper reports that ‘When wound healing properties of AgNPs were investigated in an animal model, **rapid healing** and **improved cosmetic appearance** was observed in a **dose-dependent manner.**
- Moreover, the study confirmed that AgNPs exerted positive effects such as **antimicrobial activity, reduction in wound inflammation and modulation of fibrogenic cytokines** (Tian *et al.* **2007**).

- It has been implied that AgNPs could one day play a **key medical role in decreasing inflammation in chronic infections, wounds and other inflammatory medical conditions** (Shin *et al.* 2007; Klippstein *et al.* 2010).’ ⁽¹⁾

4) Bone regeneration:

- Interestingly, ‘It was way back in 1970s that electrically generated silver ions were used for the first time to treat severe cases **of antibiotic-resistant osteomyelitis**, a bone infection that causes large wounds in the flesh.
- In this study, silver ions were directly generated into open infected wounds through the use of a small, battery-operated colloidal silver generator operating at 0.9 volts.
- It was observed that the **silver effectively killed the disease-causing micro-organisms and also triggered regrowth of human tissue and bone at the site of the infection.**
- Electrically generated silver ions not only **killed the pathogens and healed the infection** but also **stimulated tissue and bone regrowth** (Becker 2000).’ ⁽¹⁾

5) Anti-cancer:

- As the Silver Lining paper postulates, ‘The idea that silver could be effective against cancer has been around since a long time.
- In 1970s, **Dr. Becker** proposed that silver can **revert cancerous cells back to healthy cells** when electrochemical treatment was used to generate **silver ions directly into a cancer cell culture** (Becker and Selden 1985).
- However, there are no further studies confirming such a mechanism.
- **More recent studies** on anticancer property of silver are based on **cytotoxic effect of silver.**
- The anticancer properties of colloidal silver and AgNPs stabilized by chitosan were tested against human breast cancer cells (MCF-7) and liver cancer cells (HepG2) for development of anticancer drugs.

- It was observed that **both the forms of silver** caused the **breast and liver cancer cells to self-destruct in a dose-dependent manner**.
- The experimental results indicated that there was an **immediate induction of cellular damage in terms of loss of cell membrane integrity, oxidative stress and apoptosis postsilver treatment** (Franco-Molina *et al.* **2010**; Prema and Thangapandian **2015**).
- When biologically synthesized AgNPs were tested on tumour-bearing mice and Dalton's lymphoma ascites cell lines, they activated the caspase 3 enzyme leading to induction of apoptosis (Fig. **5**) which was further confirmed by subsequent nuclear fragmentation (Sriram *et al.* **2010**).
- Additionally, **silver ions can displace the K⁺-dependent glucose transport mechanism** which is the exclusive means by which cancerous cells obtain **nutrition**, thereby **selectively starving cancer cells without harming normal cells**.

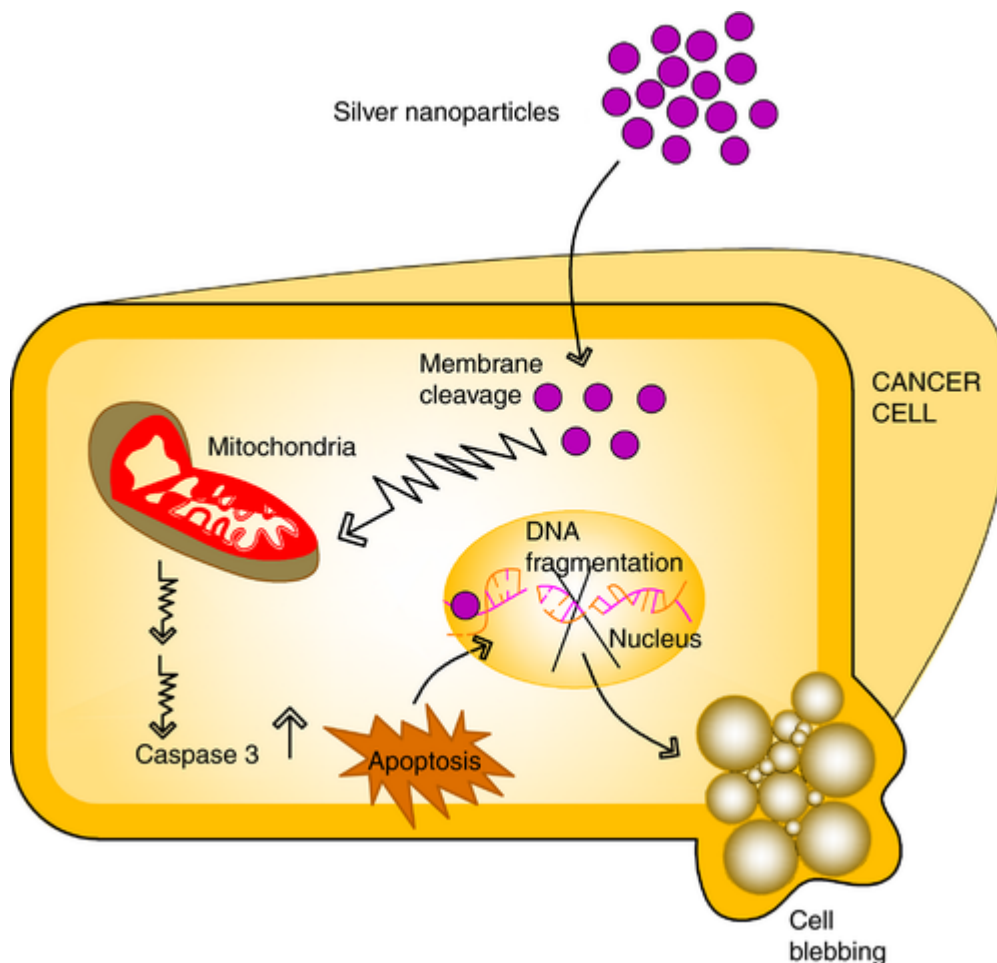


Figure 5

Caspase-mediated cancer cell apoptosis by silver nanoparticles. [Colour figure can be viewed at wileyonlinelibrary.com]

- It has long been suspected that **infectious agents** are **associated with solid tumour cancers** like Kaposi 's sarcoma as well as nontumour-based cancers such as leukaemia and many other types of cancers like adenocarcinoma, lymphoma and breast cancer.
- Many **mechanisms of carcinogenesis by infectious micro-organisms** have been **proposed** such as induction of **chronic inflammation, production of mutagenic compounds by bacterial metabolism, transformation of cells by inserting active oncogenes** into the **host genome, inhibiting tumour suppressors** or **stimulating mitosis** and infectious agents like human immunodeficiency virus leading to induction of **immunosuppression** with consequently **reduced immunosurveillance** (Parsonnet 1995; Kuper *et al.* 2000).
- Hence, **nanosilver** may have the potential to play a **dual role by either destroying the infectious aetiological agent of the cancer and/or the cancer cells.**' ⁽¹⁾

6) It may offer protection against alcohol toxicity:

- Although the exact mechanism of action isn't discussed in the Silver Lining paper, this could possibly be because **silver may abrogate the hepatotoxic effect of alcohol.**
- The authors state that 'CC1(4) solvent, a **kidney and liver toxin** was used to damage the livers of mice after which the mice were treated with AgNPs.
- It was observed that the silver **cured** the mice of **majority of the liver damage caused by the toxin.**
- **Silver was effective in revival of all biological parameters to near normal in all intoxicated groups** indicating the curing effects of **AgNPs at low dosages** on CC1(4)-induced liver injury.
- This **hepatocurative** effect of damaged mice livers was attributed to the **strong antioxidant effect** of silver (Suriyakalaa *et al.* 2013).'⁽¹⁾

Silver's toxicology profile:

There has been **much controversy** about the potential toxicity of silver and silver-based products, especially **silver nanoparticles** and, as a result, this important topic is discussed at length in the Silver Lining paper:

- **'High degree of commercialization** of nanosilver-related applications has led to a **rapid increase in widespread use of numerous consumer products containing nanosilver**.
- Hence, **thorough investigations on safe design**, use and disposal without creating new risk to humans or the environment is warranted (Tran *et al.* **2013**).
- The **toxic effects of nanosilver** are dependent on the **size, concentration, and time of exposure**.
- A comprehensive review of the possible risks of nanosilver to mammalian cells *in vitro* has been discussed in detail by Tran *et al.*
- In the present review, the authors have **summarized** the impact of nanosilver on human health and animals based on several ***in vivo* toxicity** studies.
- Silver is reported to exhibit **low toxicity in the human body**, and **minimal risk is expected** due to clinical exposure by **inhalation, ingestion, dermal application or through the urological or haematogenous route**.
- However, **long-term occupational exposure of silver or chronic ingestion or inhalation of silver preparations can lead to deposition of silver particles in the skin and eyes** termed as **Argyraemia**.
- These conditions are **not life-threatening** but **cosmetically undesirable**.
- When silver is **absorbed into the human body**, it enters the **systemic circulation as a protein complex** which is then **eliminated by the liver and kidneys**.
- Silver metabolism is **modulated by induction and binding to metallothioneins**. This complex **mitigates the cellular toxicity of silver** and **contributes to tissue repair** (Lansdown **2006**).

- ***In vivo* porcine skin exposure** studies conducted to assess the inflammatory and penetrating potential of AgNPs into porcine skin have shown that the **toxicity is influenced by the residual contaminants in the AgNPs solution**, and that the **AgNPs themselves might not be responsible for an increase in cell mortality**.
- Hence, **complete characterization** of not only the nanoparticles but also the vehicle is **suggested in order to distinguish between AgNPs and contaminant toxicity** (Samberg *et al.* **2010**).
- Studies on the effects of AgNPs on gene expression in mouse brain suggest **that AgNPs may produce neurotoxicity** by generating **free radical-induced oxidative stress** and by altering gene expression, producing apoptosis and neurotoxicity at **high concentrations; 100–1000 mg kg⁻¹ body weight** (Rahman *et al.* **2009**).
- In another study, mice exposed to 1.91×10^7 particles per cm³ for 6 h d⁻¹, 5 d week⁻¹ using the nose-only exposure system for 2 weeks exhibited modulation in the expression of several genes associated with motor neuron disorders, neurodegenerative disease and immune cell function, indicating potential neurotoxicity and immunotoxicity (Lee *et al.* **2010a**).
- Oral toxicity of AgNPs assessed over a period of 28 days in Sprague–Dawley rats has shown that doses above 300 mg resulted in slight liver damage as indicated by dose-dependent changes in the alkaline phosphatase and cholesterol levels.
- A dose-dependent accumulation of silver in all the tissues examined (bone marrow, kidneys, etc.) was also noted, however, there was no indication of genetic toxicity in male and female rat bone marrow (Kim *et al.* **2008b**).
- ***In vivo* studies on lung toxicity** as a result of **inhalation** of subacute doses of AgNPs (3.3 mg m⁻³, 4 h d⁻¹ for 10 days) in mice showed **minimal pulmonary inflammation or cytotoxicity** which was in contrast to published *in vitro* studies (Stebounova *et al.* **2011'**.⁽¹⁾

Silver's **toxicology** is also addressed specifically in the '**Safer Products and Practices for Disinfecting and Sanitizing Surfaces**' study (Alicia Culver, 2014) by the **San Francisco Department of the Environment** staff and their consultants.

- They maintain that '**Silver has low toxicity to humans, and most silver that is ingested is rapidly excreted.**' ⁽⁷⁾
- Furthermore, '**Silver ions and citric acid are not classified as respiratory sensitizers or other types of asthmagens** by the AOEC or other sources.
- **Silver is not known to have human carcinogenic potential and does not appear to be a mutagen**, according to the **U.S. EPA RED** for this AI.
- **Silver is not listed by the State of California as a developmental or reproductive toxicant**, and **no other sources reviewed indicated that silver causes reproductive or developmental toxicity.**' ⁽⁷⁾
- Additionally, '**The toxicity and bioaccumulation potential of silver are very low, with biomagnification very low in herbivores and with no evidence of biomagnification in carnivores.**
- Silver is **considered persistent but not bioaccumulative** by **Environment Canada** based on the ***Canada Domestic Substances List***.
- Silver does **biomagnify somewhat**, however, in **plants and bivalves** (such as clams, to which it is toxic and inhibits reproduction).
- While these products are **not likely to contribute significantly to the silver load** in wastewater or sewage sludge at **current use levels**, the **increasing use of silver** as a biocide overall **warrant considering how this product may contribute** to the silver load in discharge waters. ⁽⁷⁾

The attached **2014 European Commission** report, titled '**Are silver nanoparticles safe?**' (European Commission, 2014) indicates that

- '**The toxicity of silver, including nanoparticles of silver, to humans is generally low.**

- **Skin-contact with textiles containing silver** is one of the main ways people are exposed to silver nanoparticles.
- In general, consumer products release **only small amounts of silver, not resulting in significant health effects.**' ⁽⁸⁾

The **Medical Uses of Silver: History, Myths and Scientific Evidence** paper (Serenella Medici, 2019) proposes the following:

- 'Furthermore, the **contrasting evidence** regarding silver (both **ionic and nanometallic**) toxicity should be **solved once and for all** with **studies involving more complex models** in order to guarantee a **safe use in therapeutic applications**.
- At the very least, **toxicity limits should be univocally assessed.**' ⁽⁹⁾
- In addition, '**Different strategies can also be sought in order to decrease AgNPs's toxicity**, for instance tuning the rate of silver ion release and using proper capping or coating on the nanoparticle surface.'
- Finally, **strict quality controls** and **safety protocols** should be established both in manufacturing silver compounds and nanoparticles and in their **potential therapeutic applications**, in order to **ensure safety and efficacy.**' ⁽⁹⁾
- The authors further note that 'A final remark concerns the practice of **homemade and uncontrolled self-administration of colloidal silver**, which can be **dangerous for human health**.
- **Silver nanoparticulate** suspensions can be **pure in theory**, but in practice they are **most likely to be mixtures consisting of silver ions, nanoparticles, subnanosized particles, and aggregated nanoparticles that are either nanosized or greater**.
- Moreover, the **sources of silver** in **do-it-yourself preparations** cannot always be **controlled** and **certified** so that they may also contain dangerous metals as **impurities** that could **pose serious health threats** from allergies to poisoning.' ⁽⁹⁾

Various studies indicate that the nanoparticle size, amongst others, plays an important role in determining potential cytotoxicity.

Conclusion:

'The Silver Lining' paper (K.Naik, 2017) summarizes the use of silver as follows:

- **'Historically silver has been used as a major therapeutic agent in medicine especially in infectious diseases** including surgical infections (Alexander **2009**).
- However, there have been apprehensions associated with the usage of **nanosilver** through this long and diverse history of its applications.
- **A continuous debate on the benefits and drawbacks of the use of silver-incorporated products in healthcare and medicine has prevailed ever since.'** ⁽¹⁾
- Importantly, they also conclude that, when used sensibly, the **risk: benefit ratio** is very **favourable**.

Silverlab Healthcare remains **committed** to conducting all necessary research, as **safety and quality** are **paramount** to the **integrity** of the company and the brand, as is **staying abreast** of the latest trends and developments.

Of particular concern to Silverlab Healthcare are the various concerns being raised in literature regarding the **potential dangers of nanoparticles**.

- A 2022 nanoparticle study, which appeared in the Journal of Hazardous Materials Advances, indicates that 'It was reported that **materials of 300 nm or less in diameter can be taken up by individual human cells** ([Garnett and Kallinteri, 2006](#)), and **nanomaterials less than 70 nm** can even be taken up by a **cell's nuclei**, where they can cause **major damage** ([Chen and von Mikecz, 2005](#); [Geiser et al., 2005](#)).'⁽¹⁰⁾
- The 2018 study, 'Nanoparticle crossing of blood-brain barrier: a road to new therapeutic approaches to central system diseases', states that 'As indicated above, the final pathway of nanoparticle entry into the endothelial cells by transcytosis is determined by the initial step of endocytosis. **Nanoparticles with a size smaller than 200 nm** (the **estimated limiting size for a nanoparticle** to undergo **endocytosis**

through a clathrin-mediated mechanism) have more chances to efficiently cross the BBB [12].’⁽¹¹⁾

- The study ‘Silver Nanoparticle Induced Blood-Brain Barrier Inflammation and Increased Permeability in Primary Rat Brain Microvessel Endothelial Cells’, which was published in the Toxicological Sciences Journal in 2010, states that ‘Silver nanoparticles (Ag-NPs) are **small (1–100 nm in size) metallic colloidal particles** widely used in the engineering, manufacturing, and biomedicine.’⁽¹²⁾ Furthermore, ‘Together, **the data** in the current report provide **compelling evidence** that systemic exposure of Ag-NPs can result in cerebral microvascular damage and dysfunction **dependent on Ag-NPs size**, with **smaller Ag-NPs producing stronger inflammatory responses** correlated with **increased cerebral microvascular permeability**, whereas the **effects produced by the larger Ag-NPs were much less profound.**’⁽¹²⁾

Recent studies conducted by Silverlab Healthcare at an E.U. accredited laboratory indicate that the **average nanoparticle size of its 18 ppm ionic flagship product is 473 nm.**⁽¹³⁾ This **comparatively high nanoparticle size** results in an **exceptionally favorable safety profile, without compromising on its efficacy.** Despite the fact that most studies propose the very **small nanoparticles for use as antivirals, Silverlab’s ionic⁽⁺⁾ Colloidal Silver’s** efficacy in this regard can perhaps be explained by the fact that **silver is well known to be biologically active** when it is **dispersed into its monoatomic ionic state (Ag⁺).** Silverlab’s ionic⁺ Colloidal Silver contains **97,4 % ionic silver**, thereby **ensuring optimal bioactivity.**⁽¹⁴⁾

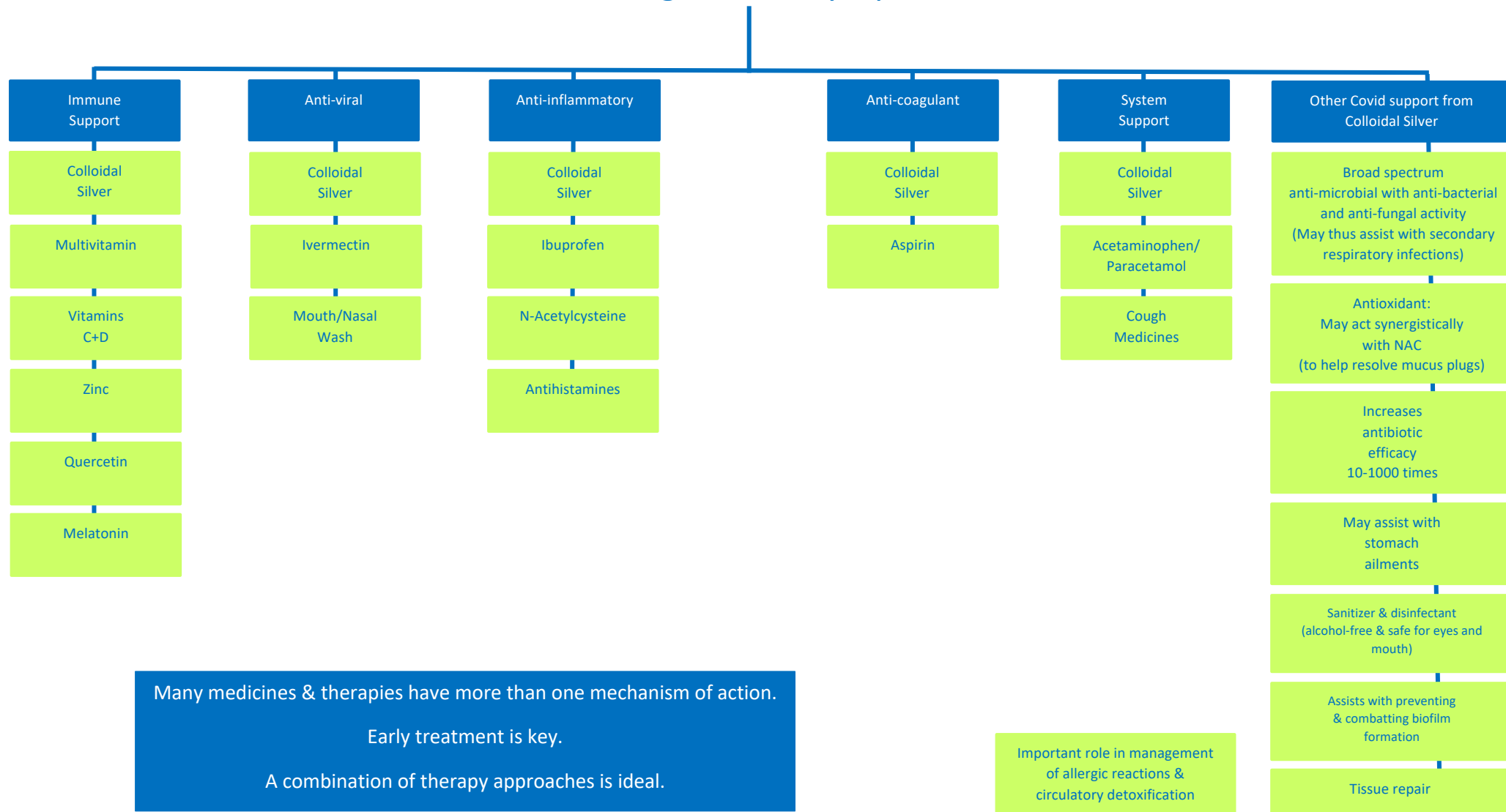
The product’s safety is further substantiated by our most recent in-vitro CSIR study, which was conducted to determine cytotoxicity of the **Silverlab ionic colloidal silver** on lung cells, and which indicates that ‘The IM/Q610/419-01A-18 **Silverlab Healthcare sample showed no toxicity to A549 lung cells *in vitro*** with the MTT assay conducted. Due to the lack of cytotoxicity, the **sample can be declared safe**, which is **desirable for drug candidates.**’⁽¹⁵⁾

As summarised in the tables below, it is evident that **silver has tremendous potential** to provide **many and diverse health solutions**. Considering the prolonged duration and the serious repercussions of the **COVID-19 pandemic**, it seems more **critical** than ever for **all colloidal silver manufacturers** to conduct their own **product-specific research** to ensure the **safety and quality of their products**. This would help allay the various concerns so that this **versatile, cost-effective, and efficacious product** can finally be utilised to its **full potential** to assist in the **global battle against COVID-19 and beyond**.

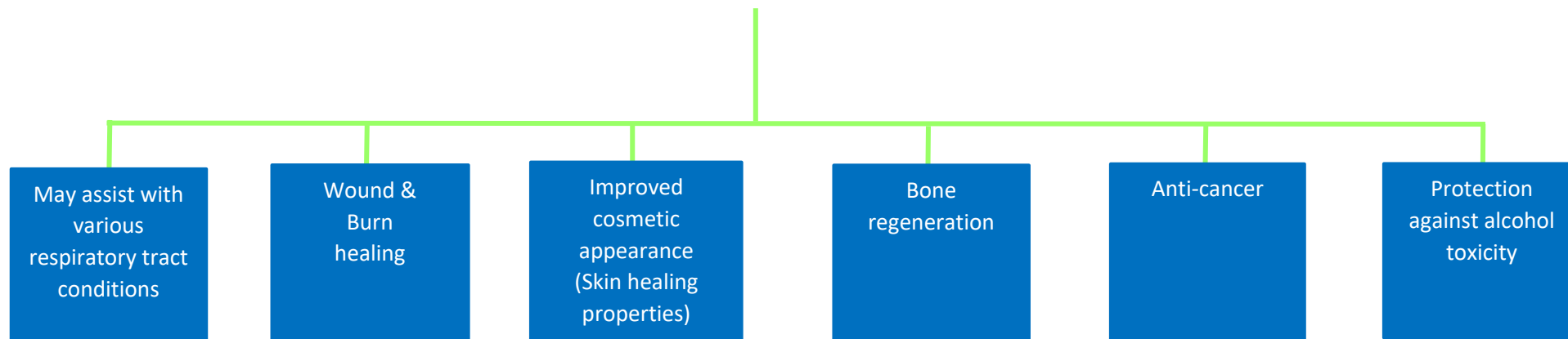
Summary Tables Below

Covid-19 at-home early treatment essentials

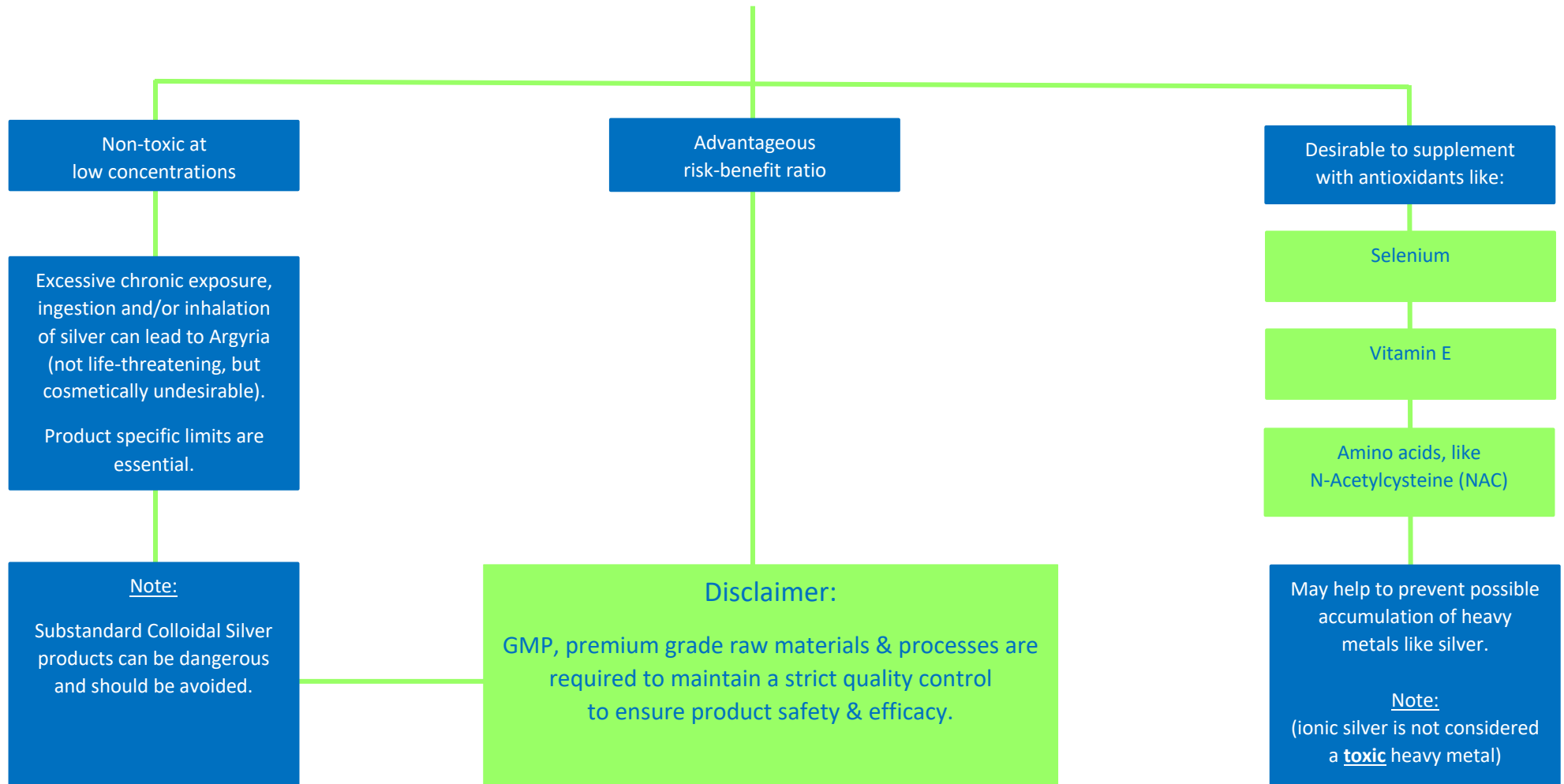
For diagnosis or symptoms



Other Colloidal Silver treatment benefits



Colloidal Silver safety studies



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