**REVIEW ARTICLE**

# The Possible Mechanisms of Silver Nanoparticles against Sars-Cov 2

**Samir Derouiche [1,2*], Sara Chetehouna [1], Anfal Djouadi [1,2], Islam Boulaares [1], Iman-Yosra Guemari [1]**

[1] *Department of Cellular and Molecular Biology, Faculty of Natural and Life Sciences, El-Oued University, El Oued 39000, El Oued, Algeria*

[2] *Laboratory of Biodiversity and Application of Biotechnology in the Agricultural Field, Faculty of Natural Sciences and Life, University of El Oued, El-Oued 39000, Algeria*

*Corresponding Author: Samir Derouiche
Email: dersamebio@gmail.com

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## Abstract

**Purpose:** Coronavirus disease (COVID-19) has killed a large number of people, threatening public health around the world. Many drugs and materials that have an antiviral therapeutic effect are still being tested, including silver nanoparticles.

**Materials and Methods:** It has been proven that Synthesis of silver Nanoparticles (Ag NPs) (Ag NPs) possess strong antifungal, antibacterial, anti-angiogenesis, and anti-inflammatory potential. Green synthesized of Ag NPs are a promising source of new antiviral agents considering the multiplicity of its mechanism and the multiple target areas in the virus. The Ag NPs or Ag+ ions, which are released from the Ag NPs, interact directly with some biological molecules of the viruses that contain phosphorous or sulfur, such as some proteins, Deoxyribonucleic Acid (DNA), and Ribonucleic Acid (RNA).

**Results:** This reaction generates Reactive Oxygen Species (ROS), causing damage to the membranes in the virus. Metal nano-therapies such as Ag NPs are granted research consideration for COVID-19 treatment.

**Conclusion:** The biocompatibility achieved through green synthesis suggests its possible use not only in these specific coronavirus conditions but also in other types of virus infections without any risk of toxicity of these molecules.

**Keywords:** Nano-Therapy; Ag Nano Particles; Green Synthesis; Antiviral; Sars-Cov 2.


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## 1. Introduction

The sudden outbreak of the 2019 coronavirus in China occurred due to the Severe acute respiratory syndrome Coronavirus 2 (Sars-Cov 2) virus, in just two months, after which the epidemic spread rapidly in the whole world [1]. Currently, many drugs and materials that have an antiviral therapeutic effect are still being tested to determine the rates of their effectiveness against the new coronavirus, however, research is still underway for an effective treatment against Coronavirus disease (COVID-19) [2]. There are many different strategies for treating coronavirus viruses associated with infection with Coronavirus and SARS, including the use of viral and retroviral protease inhibitors [3]. Recently, viral-mediated diseases have become more prominent and deadly worldwide; therefore, it highlights the necessity of developing antiviral agents and drugs. Among the new methods for the Synthesis of silver Nanoparticles (Ag NPs), there is a biosynthesis by natural materials of plant, animal, or microbiological origin [4,5]. Among the nanoparticles that know antiviral activity is Ag NPs. Several studies confirm that Silver salts such as silver sulfadiazine have several therapeutic properties, as it has been proven that they are used as anti-infectives for some infectious diseases and some microbes, which encouraged giving anti-bacterial and anti-viral properties of silver nanoparticles (Ag NPs) [6]. The current review focuses on highlighting the importance of Ag NPs, as a treatment against several diseases, including corona virus, and this in the absence of any clear and specific treatment course.

### 1.1. Green Synthesis of Silver Nanoparticles

The green synthesis of Ag NPs by biological methods is due to the presence of bio compounds (including alkaloids, phenolic compounds, terpenoids, enzymes, co-enzymes, proteins, and sugars, etc.) which reduce metal salts from a positive oxidation state ($Ag^+$ ions) to zero oxidation state [7]. Various parameters such as concentration of metal ions, the composition of biomaterials, potential of Hydrogen (pH) of the reaction mixture, and reaction period basically affect the size and shape of the silver nanoparticles [8]. Biomolecules serve as a secondary option to form a monolayer on the surface of nanoparticles to prevent agglomeration. Thus, the enhanced biological activities of extract-mediated nanoparticles are due to the biomolecules attached to the surface of nanoparticles [9]. Most of the researches reveal that a basic medium is more suitable for the synthesis of Ag NPs due to monodispersity, better stability, good yield, and more reduction of silver ions compared to acidic and neutral medium [10]. However, the drawback was also associated with the formation of Ag NPs in very high pH (>11) due to agglomeration and unstable nanoparticles. Thus the use of green materials like plant, microbial, fungi, and algal extracts (Figure 1) as reducing agents possesses great advantages which can play an essential factor in the targeted therapeutic effect of Ag NPs [11].

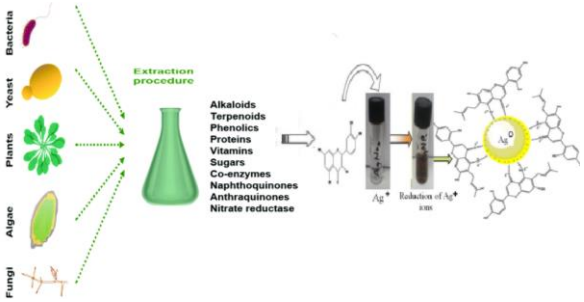


**Figure 1.** Mechanism of green synthesis of Ag NPs

### 1.2. Antioxidant Activity of Ag-NPs

There are many studies published recently that have proven the antioxidant effect of nano-silver particles, which necessitated their use on a larger scale [12]. The determination of in vitro antioxidant power of Ag-NPs prepared either by biological or chemical methods is by different protocols of DPPH (2,2-Diphenyl-1-picrylhydrazyl), ABTS (2,2'- azinobis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt radical cation), superoxide anion, nitric oxide, and hydroxyl radical scavenging assays, also FRAP assay (ferric reducing antioxidant power) [13,14]. Studies of Yugal K. Mohanta *et al.* and NV Reddy *et al.* revealed that Ag NPs biosynthesized by Erythrina suberosa and Perilla frutescens leaves extracts respectively possess a significant radical scavenging potential compared to standards. They proposed that the green synthesized nanoparticles can be used as a potential free radical scavenger and this evaluation is required before the use of Ag NPs in vivo model [15,16]. In many papers, the authors compared the inhibitor activity against the free radical of the plant extract and the Ag NPs green synthesized by them, as Esma Nur Gecer, who revealed that Ag NPs phytosythesized by Salvia aethiopis L. had more activity than the extract of S.aethiopis L. [17]. Also, Achyuta Kumar Biswal and Pramila Kumari Misra confirmed that biosynthesized Ag NPs by using the oil cake of Madhuca latifolia L. have higher antioxidant

activity compared to the aqueous extract alone, while the free electrons donated by Ag NPs react with the free radicals for their stabilization [18]. Another study demonstrated that the green synthesized of Ag NPs provide a high antioxidant activity which may be due to bioactive molecules attached with nanoparticles [19]. According to Mina *et al.*, oxygen and nitrogen reactive species generated in mitochondria in response to successive inflammatory stimulation induced by cutaneous leishmaniasis in mice neutralized by Ag NPs biosynthesized using fig and olive and improve anti-apoptotic signaling [20].

### 1.3. Anti-Inflammatory Activity of Ag NPs

Inflammation is a major health problem worldwide and is stimulated by irritants and pathogens [21]. Some pro- and anti-inflammatory mediators are also commonly produced during inflammation, including cytokines, chemokines, tumor necrosis factor-α (TNF-α), and some enzymes, including NO synthase and Cyclooxygenase-2 (COX-2,) which play some key regulatory roles [22]. To defeat inflammatory action, we should find efficient anti-inflammatory agents [23]. Therefore, silver nanoparticles were selected to be the appropriate materials with anti-inflammatory properties through inhibiting COX-2 and 5-Lipoxygenase (5-LOX) enzymes, which could be the active ingredient for several anti-inflammatory drugs [24, 25]. Silver nanoparticles protect against inflammation after Hypoxia-Inducible Factor 1-alpha (HIF-1α) binds to Deoxyribonucleic Acid (DNA) at the Hormone Response Element (HRE) level, activating inflammatory genes, where the expression of hypoxia-inducible factor is decreased, or some inflammatory factors can inhibit TNF-α and Vascular Endothelial Growth Factor (VEGF) (Figure 2) [26, 27]. In addition, epithelial cells produce an important factor that increases antigen sensitivity, as it increases the extracellular leakage of plasma proteins, these proteins have a role in physiological abnormalities, as thickening appears in the airway wall and increases immune cells, especially T helper type-2, which stimulates some factors inflammation (IL-9, IL-4, IL-5, and IL-13) [28]. However, there are some studies that enhance the anti-inflammatory role of silver nanoparticles such as the study of Abdellatif *et al.* and the study of Tyavambiza *et al.* [29, 30].

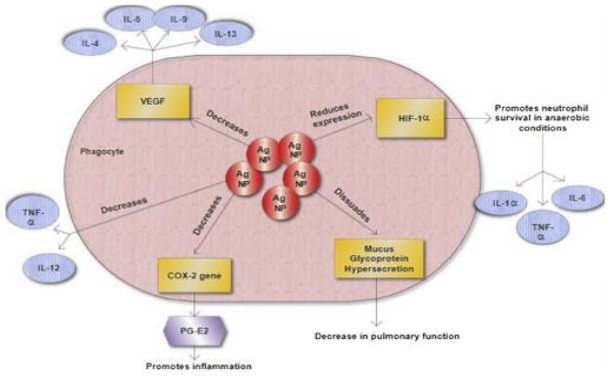


**Figure 2.** Anti-inflammatory mechanism of Ag NP

### 1.4. Anti-Bacterial Activity of Ag NPs

Silver nanoparticles can have anti-microbial properties such as bacteria, either by inhibiting the growth of biofilms or by directly interacting with the bacterial or viral genome (DNA or RNA) [31,32]. According to Pal *et al.*, the anti-bacterial activity of Ag NPs is by inhibiting the proteins of these cells, which causes skeletal changes and thus cell death, or also by inhibiting some internal enzymes of bacterial cells, which leads to the generation of oxidative stress that causes the death of these cells [33, 34]. Also, it has been explained that Ag NPs have a wide surface area to interact with bacteria. This makes the nanoparticles easily reach the bacteria by sticking to their outer membranes [35]. Silver nanoparticles act as antibacterial agents with different mechanisms. The silver ions emitted by nanoparticles penetrate the bacterial cell wall and reach the ribosomes that destroy them and thus prevent the synthesis of proteins. Interruption of adenosine triphosphate (ATP) production: ATP production is terminated because silver ions deactivate respiratory enzymes on the cytoplasmic membrane. Membrane disruption by reactive oxygen species: free radical release by the broken respiratory chain and it causes membrane disruption (Figure 3). Interference of DNA replication: Silver particles can inhibit bacterial reproduction by binding to and destroying DNA or by destroying the cell membrane to which it sticks and perforates, and the organelles are released from it [36].

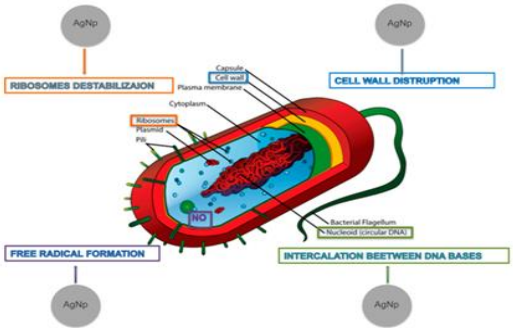


**Figure 3.** Antibacterial activities of silver nanoparticles

### 1.5. Antiviral Activity of Ag NPs

Determining the structure of viruses, especially the proteins through which they interact with the target cells, helps in the development of nanomaterial against these viruses in a way that prevents their access to the cells and thus neutralizes them [37]. There are several mechanisms through which nanoparticles act as antivirals, either by generating an oxidative stress state, direct physical interaction with the cell membrane, or by releasing ions and electrolytes from the nanoparticles themselves, all of which gives the antiviral property of Ag NPs on a large scale (Figure 4) [38,39]. The increasing interest in silver nanoparticles through their antiviral role has given them respectable medical and biological importance [40]. Among the antiviral mechanisms of Ag NPs is by releasing monovalent silver ions from nanoparticles, which leads to interaction with and inhibition of microbes [41]. Also, some silver ions interact positively and have a greedy attitude towards proteins or molecules carrying amine or thiol functions, known as a low dynamic effect, which leads to a change in the structure of these biomolecules and the loss of their functions, thus destroying microbes [42]. In addition to the mechanism of oxidative stress generated by silver nanoparticles against microbes, the silver ion has an antiviral effect, which is purified from the nanoparticles themselves, which leads in both cases to inhibition and stoppage of DNA activity [43].

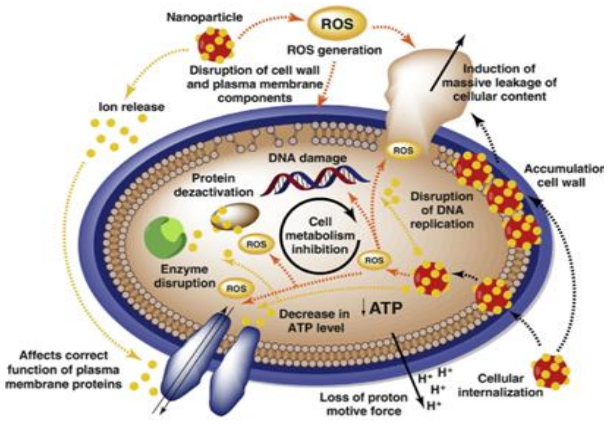


**Figure 4.** Different ways of metal nanoparticle-based antiviral strategies

## 2. Discussion

Depending on the structure, size and shape of silver nanoparticles, which are surrounded by a layer of active molecules of the biological compound, as well as on the biological activities that we mentioned earlier, there are many proposals for therapeutical strategies of silver nanoparticles against the COVID-19 virus, as these strategies can be based on treating complications of this virus or eliminating the virus itself. As for the theory of the effectiveness of silver nanoparticles against complications of the COVID-19 virus-induced inflammation and oxidative stress which are the mechanisms by which the virus affects the body of the infected person. COVID-19 infection causes excessive activation of monocytes and macrophages, resulting in a cytokine storm and, as a result, the emergence of acute respiratory distress syndrome [44]. COVID-19 symptoms include pulmonary inflammation, and fibrosis, which are caused by the generation of active Interleukin-1 (IL1) via toll-like receptors when it interacts with cytokine pro-inflammatory. An increase in pro-inflammatory cytokines is connected to inflammatory reactions and acute lung damage generated by Sars-Cov-2 Protein N, demonstrating that pulmonary inflammation is induced during COVID-19 infection [45]. Extracellular cyclophilins, which are one of SARS-interaction Cov's targets in lung cells, are pro-inflammatory proteins that play a role in the development of a variety of inflammatory disorders. One of the key events of the inflammatory response is oxidative stress, which impacts repair mechanisms and the immunological control system [46]. These inflammatory reactions and oxidative stress caused by the COVID-19 virus can be effective against them by silver nanoparticles, as the green synthesis of these molecules ensures anti-inflammatory and anti-oxidant activities, and therefore the complications of the Covid virus can stop, which contributes to the possibility of controlling the virus and neutralizing its danger to patients, especially those with chronic diseases.

On the other hand, as another therapeutic strategy of green synthesis of Ag NPs silver against the Sars- Cov 2, these nanoparticles can benefit from their biological antiviral ability to eliminate and destroy the coronavirus by several mechanisms. An antiviral mechanism of nanoparticles is based on the interaction of these particles with the virus core, just like the way Ag NPs work in protecting Vero cells from the attacks of the Peste des Petits Ruminants Virus (PPRV) [47]. Also from the anti-virus mechanisms, the Ag NPs or Ag+ ions, which are released from the Ag NPs, interact directly with some biological molecules of the viruses that contain phosphorous or sulfur, such as some proteins, DNA, and RNA, this reaction generates reactive oxygen types

(ROS), causing oxidative stress and damage to the membranes in virus [48,49]. With these mechanisms by which Ag NPs can affect the activity of viruses, these particles gain anti-virus characteristics and properties that can be widely used, especially for nanoparticles biologically synthesized [50]. As another mechanism of action, Ag NPs may bind to the Envelope Glycoprotein (GP120) on the outer surface of the virus, thus preventing the virus from binding to target cells in vivo [51]. Also, He *et al*. suggested in a recent study that Ag NPs may be bound to virus glycoproteins and this, in turn, represses the virus and loses its ability to adhere or interact with target cells [52]. Whereas, nano-silver has been successfully applied against hepatitis, influenza, and human immunodeficiency virus [53]. Recently, it has been reported that a number of Ag NPs have antiviral activities by producing free radicals, which encouraged its use to treat COVID-19 in patients [54]. In addition, silver nanoparticles bind to viral DNA or RNA, preventing viral reproduction and proliferation within the living cell [55]. Ag NPs' potent antiviral properties could reduce the risk of infection or potentially prevent a pandemic viral epidemic like Sars-Cov-2 [56]. Sarkar *et al.* have earlier proposed the use of Ag NPS as a therapeutic agent for Sars-Cov-2 infection [57]. Ag NPs bind to the viral spike glycoprotein, preventing the virus from binding to living cells. As a result, the release of silver ions causes the pH of the respiratory epithelium, where the COVID-19 virus usually lives, to become more acidic, making it antagonistic to the virus [58].

Given the theoretical effectiveness of nano-silver particles against the COVID-19 virus or its complications in the body, an important issue may arise, which is the toxicity of these particles, as they can cause damage to the recipient's body. Toxicity is a concern when metal is converted to its nanoform. This is also true in the case of silver, and it is dependent on the Ag NPs' sizes, shapes, and densities. Some studies found no harmful effects, while others found a range of negative consequences, from a minor inflammatory response to the existence of inflammatory lesions [59]. However, there is a need to investigate the consequences of increased exposure of animals, humans, and normal cell lines to nanoparticles; particularly Ag NPs in terms of acute and chronic toxicity. Several factors such as dose, exposure time, size, shape, and cell types play important roles in mediating cellular responses [60]. Furthermore, the latest studies demonstrated neurotoxicity, hepatotoxicity, cytotoxicity, pulmonary inflammation, and genotoxicity which are the outcome of overdosage of Ag NPs of different shapes and sizes [61]. This was confirmed by Petrarca *et al.*'s (2015) study that Ag NP size is one of an important factor for evoking an immunological state in monocytes [62]. Among the toxic manifestations of nano-Metals, some studies have shown that the application of Ag NPs resulted in impaired mitochondria function and leakage via cell membrane in vitro, which induces toxicity in mouse germline stem cells. It was also demonstrated that Ag NPs resulted in a toxic response on the expression of cytokines and proliferation through peripheral blood mononuclear cells (PBMC) production [63]. It was found that coating Ag NPs reduced their toxicity and increased their stability, especially when it comes to the green production approach in their synthesis [64]. The coating, which is generally biocompatible in nature, is the primary cause of the nominal toxicity. Although the coating's major function is to stabilize the nanoparticle and prevent agglomeration, its biocompatibility makes green-produced Ag NPs appropriate for a variety of biomedical applications [65]. It was affirmed also that the cytotoxicity of uncoated Ag NPs is higher than that of coated Ag NPs. The surface coating with different substances usually prevents the release of the ionic form of silver and changes in the shape and size of Ag NPs [66]. However, more in vivo cytotoxicity and genotoxicity of chemically produced Ag NPs were found than green synthesized Ag NPs which suggests green synthesized Ag NPs are less toxic and biologically compatible than chemically synthesized ones [67]. The study of Mukherjee *et al.* (2014) has observed the biocompatible nature of bio-Ag NPs (Olax scandens) towards rat cardiomyoblast normal cell line ($H_9C_2$), Human Umbilical Vein Endothelial Cells (HUVEC), and Chinese Hamster Ovary cells (CHO) [68].

The dose provided and the duration of exposure to nano-silver particles may be factors that contribute to reducing or increasing their toxicity and this is what is proven by the Zhang *et al.*'s (2016) study that the accumulation of Ag NPs in the cell causes cytotoxicity, changes in the morphology of endothelial cell monolayers, and promotes cytokine release [69]. Also, the study by Kittler *et al.* showed a significant increase in toxicity following the storage of Ag NPs (in water) up to 6 months and this was correlated with the release of Ag ions [70]. Overdose of Ag NPs reported also to induce toxic effects on the reproductive system in males. A research study reported the cytotoxicity of Ag NPs on rats in vivo.

Histopathological studies revealed the more frequent bile duct hyperplasia, pigmentation, and fibrosis associated with excessive use of Ag NPs [71]. However, green synthesized of Ag NPs and dose controlled can reduce the adverse effects induced by ROS generation. In the given context, a study reported that alkaloids, tannins, and polyphenols are potent ROS scavengers, thus nanoparticles with their coating can inhibit the ROS generation and avoid cellular damage [72]. For example, Samberg *et al.* showed no toxicity for progenitor human adipose-derived stem cells up to 100 µg/mL (10 and 20 nm (AgNPs for 24 h [73]. The study of Ferdous and Nemmar (2020) show that no significant changes in hematology or blood biochemistry were observed in male or female rats after exposure to 11–14 nm Ag NPs at doses of 1.73x104/$cm^3$, 1.27x105/$cm^3$, and 1.32x106 particles/$cm^3$ in a 28-day inhalation toxicity study [74]. Polymer-coated Ag NPs with a concentration of 1.5 ppm were shown to be hemocompatible. It is worth noting that materials with a hemolysis ratio of less than 5% were considered hemocompatible [75]. A hetero polymer derived from Lentinus squarrosulus was used to produce polysaccharide capped Ag NPs with a diameter of 2.78 1.47 nm in another investigation (Mont.). At the LD50 dosage, these nanoparticles were similarly compatible with human Red Blood Cells (RBCs). When tested against normal human fibroblasts and blood erythrocytes, phytosynthesized Ag NPs from aqueous extract of Salacia Chinensis (SC) bark exhibit perfect biocompatibility. 253 As a result, the biocompatibility obtained through green synthesis suggests that it could be used in a variety of biomedical applications [76]. In the study of Mohanta *et al.* (2017), Ag NPs have not been observed of inhibition against NCTC clone 929 [L cell, L-929, derivative of Strain L cell line at lower concentrations. The percentage of cell viability of normal fibroblast cells is declined with an increase in the concentration of Ag NPs. The IC50 value of Ag NPs against normal L-929 cell lines was calculated as 600.28 ± 0.75 µg/mL. The IC50 value indicates the high biological compatibility and safe use of Ag NPs in human body [77].

However, there is a need to explore toxicological attributes together with pharmacodynamics and pharmacokinetics of silver nanoparticles for the use as an anti-Sars-COv2 without toxicity or side effects.

## 3. Conclusion

Silver nanoparticles synthetized by green materials like plant, microbial, fungi, and algal extracts as reducing agents have different applications as an antioxidant, anti-inflammatory, and antimicrobial agents. Viruses can be inhibited by silver nanoparticles in a variety of ways, including losing their capacity to target cells, which prevents them from reproducing and spreading, and so limiting their ability to infect cells. Furthermore, this study brings new insights into the toxic actions of Ag NPs against viruses, including COVID-19. Metal nano-therapies such as Ag NPs are granted research consideration for many viruses, including COVID-19 treatment. Such therapeutic approaches may then be found useful not only in these specific coronavirus conditions, but also in other types of bacteria and virus infections. The biocompatibility achieved through green synthesis suggests its possible use in the varying field of biomedical application with a low risk of toxicity of these molecules. However, clinical trials of green synthesized Ag NPs based nanomedicines are needed to find the future direction of their application. Currently, biodegradability, dose, and Ag NPs route of administration involving studies are the most significant concerns to be tackled out in clinical trials.

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