

Silver and Silver Chloride Nanoparticles and their Anti-Tick Activity: a Mini Review

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This overview highlights the importance of characterization of biogenic nanoparticles of silver and silver chloride in order to understand the action on ticks or pathogens transmitted by them. These nanoparticles appear as important active principles in this area. They can act against ticks or against major pathogens transmitted by the bite of ticks such as bacteria, viruses or protozoa with equal or better efficacy of antibiotics, antiviral or antiparasitic agents. Anti-tick activities on *Rhipicephalus* (*Boophilus*) *microplus*, *Hyalomma anatolicum*, *Hyalomma isaaci* and *Haemaphysalis bispinosa* are discussed. Perspectives of these nanoparticles acting on bacteria, viruses and protozoa infections are also discussed.

Keywords: ticks, silver nanoparticles, silver chloride nanoparticles, anti-tick agents

1. Introduction

Ticks are vectors of many infections as they are able to carry bacteria, virus and also protozoan agents.¹ Related to the bacterial diseases transmitted by ticks are Lyme disease, rickettsioses, and tularemia.²⁻⁷

Tiboviruses (tick-borne viruses) cause many symptoms with severe effects that affect the central nervous system, such as meningitis, meningoencephalitis with high sequelae, and hemorrhagic diseases.⁸⁻¹⁰

Protozoan infections, for example, the babesiosis (*Babesia bigemina*), may also be transmitted by ticks.¹¹⁻¹³ Toxin production can cause paralysis, from *Dermacentor andersoni* (Rocky Mountain wood tick), *Dermacentor variabilis* (dog ticks), and *Ixodes holocyclus* (marsupial ticks).¹⁴⁻¹⁶ In this last and rare case, the mainstay of treatment for tick's paralysis, tick removal, and the time to full neurological recovery after tick removal are generally estimated to be around 1.5 days with initial improvement within hours.^{17,18}

In Brazil, the main disease transmitted by ticks to humans is spotted fever (BSF) whose etiologic agent is *Rickettsia rickettsii*, which is an intracellular gram-negative bacterium. The main vector is *Amblyomma sculptum* and the disease is considered a major public health problem.^{19,20}

The rise in the number of notified cases and the expansion of transmission area and elevated lethality rate have been observed in the country since 80's. Lethality rate in the southeast region of Brazil ranges between 30 to 50%, and in São Paulo and Minas Gerais states one can find the most notifications of this disease.^{19,21}

An excellent alternative for treatment of these diseases is the use of nanobiotechnology as a novel strategy in this area. One important nanostructure is the silver nanoparticles (Ag^0) or also nanoparticles of the silver chloride (AgCl).

The silver nanoparticles biogenically synthesized are widely studied by many research groups in the world²²⁻³⁹ and Ag^0 nanoparticles were quite efficient against *Aedes aegypti*.⁴⁰

The biogenic silver nanoparticles effects on ticks were studied against ticks' larvae and adult ticks.^{41,42}

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It is important to be aware that the characterizations of these silver nanostructures are of paramount importance, since there are many reports in the literature in which erroneous characterization of silver structures were published. The X-ray diffraction (XRD) pattern for Ag⁰ as well as for AgCl nanoparticles, which are the most common silver nanostructures that are biogenically synthesized, were discussed recently by Seabra *et al.*⁴³ Based on aforementioned discussion on XRD characterization of biogenic silver nanostructures, herein the anti-tick activities are to be discussed.

The XRD patterns for Ag⁰ nanoparticles (JCPDS file No. 04-0783 or ICSD Code 64994) and for AgCl nanoparticles (JCPDS file No. 85-1355 or ICSD Code 64734) were used to construct Table 1.

2. Anti-Tick Activity

Marimuthu *et al.*⁴² biosynthesized silver nanoparticles from leaf extract of *Mimosa pudica* Gaertn. (Mimosaceae) and tested those nanoparticles against the larvae of *Rhipicephalus* (Boophilus) *microplus* Canestrini, 1887 (Acari: Ixodidae) (*R. (B.) microplus*). In this case the silver nanostructure was classified as Ag⁰ nanoparticles. Analyzing the XRD pattern data the nanostructure studied also exhibited values that correspond to AgCl nanoparticles (low presence) Ag⁰ and/or silver oxides as

spherical morphology. Reported nanoparticles exhibited an efficacy of LC₅₀ of 8.98 µg mL⁻¹ against the larvae of *R. (B.) microplus*. At the concentration of 15 and 20 µg mL⁻¹, a 51 and 89% of mortality was found, respectively. The size of the nanoparticles by transmission electron microscopy (TEM) was around 25-60 nm and by scanning electron microscopy (SEM) were 25-50 nm.

The synthesis of mainly AgCl nanoparticles and with presence of low Ag⁰ nanoparticles silver nanoparticles from leaf extract of *Ocimum canum* Sims (Labiatae) against the larvae of *Hyalomma anatolicum* (*a.*) *anatolicum* Koch, 1844 (actual name *H. anatolicum*) and *Hyalomma marginatum* (*m.*) *isaaci* Sharif, 1928 (Acari: Ixodidae) (actual name *H. isaaci*) was achieved.⁴¹ SEM analyses were crucial to determine the size of the synthesized AgCl nanoparticles that was estimated to be 25-110 nm. The particles exhibited spherical and after drying formed rod and cubic morphology. These nanoparticles exhibited effect against *H. anatolicum* and *H. isaaci* with the LC₅₀ values of 0.78 and 1.00 µg mL⁻¹, respectively, and caused 100% mortality at 2.5 µg mL⁻¹. Probably, in this case the cubic form of AgCl exerted a better activity than AgCl in its spherical morphology.⁴⁷ It is known that spherical and cubes as in the case of AgCl in this case, exhibits similar biological activities.

Stem aqueous extract of *Cissus quadrangularis* biosynthesis of AgCl nanoparticles and their effects

Table 1. Anti-tick activities of silver and silver chloride nanoparticles

Biomaterial	XRD pattern designation	Size / nm Structure	Ticks	LD ₅₀ / (µg mL ⁻¹)	Concentration (mortality) / (µg mL ⁻¹) (%)	Reference
<i>Musa paradisiaca</i> (L.) (Musaceae) (plant)	Ag (low AgCl presence)	50-150 (SEM) spherical	larvae of <i>Haemaphysalis bispinosa</i> Neumann (Acarina: Ixodidae)	1.87	5.0 (100)	44
<i>Euphorbia prostrata</i> Ait (plant)	Ag	25-80 (SEM) spherical	adult cattle tick <i>Haemaphysalis bispinosa</i> Neumann (Acarina: Ixodidae)	2.30	10.0 (100)	45
<i>Manilkara zapota</i> (L.) (plant)	Ag	70-140 (SEM) spherical	larvae <i>Rhipicephalus</i> (Boophilus) <i>microplus</i>	3.44	10.0 (100)	46
<i>Streptomyces</i> sp. LK3 (bacteria)	AgCl	5-20 (TEM) spherical	larvae <i>Rhipicephalus microplus</i> and <i>Haemaphysalis bispinosa</i>	16.10 16.45	–	47
<i>Ocimum canum</i> Sims (Labiatae) (plant)	AgCl (low Ag presence)	25-100 (SEM) spherical and after drying formed rod and cubic structures	larvae of <i>Hyalomma anatolicum</i> Koch, 1844	0.78	2.5 (100)	41
			<i>Hyalomma isaaci</i> (Acari: Ixodidae)	1.00	2.5 (100)	
<i>Cissus quadrangularis</i> (plant)	AgCl (low Ag presence)	43 (SEM) spherical	larvae of <i>Rhipicephalus</i> (Boophilus) <i>microplus</i>	7.61	25.0 (100)	48
<i>Mimosa pudica</i> Gaertn (plant)	AgCl and Ag presence	25-50 (SEM) spherical	larvae <i>Rhipicephalus</i> (Boophilus) <i>microplus</i> Canestrini (Acari: Ixodidae)	8.98	15 (51) 20 (89)	42
<i>Carissa carandas</i> (plant)	silver non characterized	40-50 (TEM) spherical	adult cattle ticks <i>Rhipicephalus</i> (Boophilus) <i>microplus</i>	–	5.0 mg mL ⁻¹ (40) low reproductive index	49

SEM: Scanning electron microscopy; TEM: transmission electron microscopy.

against the larvae of *R. (B.) microplus* were studied.⁴⁸ The size of the nanoparticles as determined by FESEM was 43 nm. The activity against the larvae of *R. (B.) microplus* exhibited LC₅₀ values of 7.61 and at 25 µg mL⁻¹ and 100% of mortality for adult *R. (B.) microplus* was also observed. This nanostructure exhibited lower activity than any Ag⁰, since this nanoparticle is spherical as in Marimuthu *et al.*⁴²

Aqueous leaf extract from *Musa paradisiaca* (L.) (Musaceae) led to the synthesis of silver nanoparticles (mainly) and some AgCl nanoparticles were also present and their application against the larvae of *Haemaphysalis bispinosa* Neumann (Acarina: Ixodidae) (*H. bispinosa*) was reported.⁴⁴ By SEM the size was 20-30 nm and exhibiting the LC₅₀ of 1.87 µg mL⁻¹ and at concentration of 5 µg mL⁻¹, those nanoparticles provoked 100% of mortality. The spherical morphology in Ag⁰ exerted an important biological activity.

Aqueous leaf extract from *Euphorbia prostrata* Ait. was used for the synthesis Ag⁰ nanoparticles (mainly with traces of AgCl nanoparticles) and studied against the adult cattle tick *H. bispinosa*.⁴⁵ SEM analysis showed a size of 25-80 nm. The LC₅₀ value observed was 2.3 µg mL⁻¹ and 100% of mortality at 10 µg mL⁻¹ nanoparticles. In this preparation the Ag⁰ presented a spherical morphology and similar activities than in the work of Marimuthu *et al.*⁴²

Rajakumar and Rahuman⁴⁶ synthesized from aqueous extract of *Manilkara zapota* (L.) mainly Ag⁰ nanoparticles (spherical morphology) and traces of AgCl nanoparticles as seen by XRD pattern. A size of 70-140 nm by SEM was determined. LC₅₀ values against *R. (B.) microplus* was 3.44 µg mL⁻¹ and at a concentration of 10 µg mL⁻¹ exhibited a 100% mortality.

The synthesis of AgCl nanoparticles from *Streptomyces* sp. LK3 showed acaricidal activity against *R. (B.) microplus* and *H. bispinosa* with LC₅₀ values of 16.10 and 16.45 µg mL⁻¹, respectively.⁴⁷ In this case, the exhibited plasmon absorption can be associated to a very low Ag⁰ nanoparticles concentration present. The presence of AgCl in its spherical form exerts a low activity as compared with Ag⁰.

Evaluation of acaricidal efficacy (against *R. (B.) microplus*) of plant mediated synthesis of silver nanoparticles using *Carissa carandas* leaf extract (40-50 nm by TEM) was reported. Adult immersion test was used to evaluate the efficacy of silver nanoparticles against cattle ticks. Results showed 40% mortality with silver nanoparticles (non characterized by XRD diffractions pattern and probably AgCl) using a high concentration (5 mg mL⁻¹, 72 h). The effect was further observed on the reproductive indices of ticks which exhibited significant decrease in this index with increasing concentrations of silver nanoparticles.⁴⁹

Larvae and adult *H. bispinosa* were affected in the same extension (LD₅₀ ca. 2 µg mL⁻¹) and similar mortality percentage from Ag⁰ nanoparticles from different sources (*Musa paeadisiaca*)⁴⁴ and *Euphorbia prostate*.⁴⁵ However, AgCl nanoparticles from *Streptomyces*⁴⁷ showed to be 8-fold less effective than ones obtained from the plant sources.

Larvae *R. (B.) microplus* was affected by Ag⁰ nanoparticles differently when different sources of the Ag⁰ nanoparticles were used. The LD₅₀ from *Manilkara zapota* (3.44 µg mL⁻¹)⁴⁶ and from *Mimosa pudica* (8.98 µg mL⁻¹)⁴² were found. At the same extension mortality were 3-fold more efficient in *Manilkara* than in *Mimosa*. In the presence of AgCl nanoparticles, the same value of LD₅₀ (7.61 µg mL⁻¹) was obtained by the source of *Cissus quadrangularis* with a similar mortality⁴⁸ against the ticks. AgCl nanoparticles produced by *Streptomyces* exhibited a lower effect against the tested ticks (LD₅₀ ca. 16 µg mL⁻¹) (Table 1).

Larvae of *H. anaticum* and *H. marginatum* were affected significantly by AgCl nanoparticles synthesized by *Ocimum canum* Sims with LD₅₀ of 0.78 and 1.0 µg mL⁻¹, respectively.⁴¹ Probably, in this case the spherical form that after drying formed rod and cubic structures exerted a high biological activity in a similar or better profile than Ag⁰.

It is known that silver triangular nanoplates have basic {111} surface, nanospheres and nanocubes mainly have {100} planes, and nanorods have {100} side surfaces and {111} end facets. Then, the data said that {111} crystal plane of silver nanoparticles may play a prime role in antibacterial progress. Recently was reported that silver triangle nanoplates had the best antibacterial activity, while nanospheres, nanocubes and short nanorods showed similar efficacy.⁵⁰

This was reinforced with MIC values of Ag⁰ nanoparticles (60 nm) in which the cubic form and spherical one were 37.5 and 75 µg mL⁻¹, respectively.⁵¹ The fact is, the particles covered by {100} facets (cubic form) showed stronger antibacterial activity than those covered by {111} facets (spherical). This was demonstrated on Table 1.

The Table 1 shows a summary of all the anti-tick activities of biogenic silver nanoparticles. Fortunately, with the discrimination of the XRD pattern, it was possible to get some conclusions.

In conclusion, Ag⁰ and AgCl nanoparticles are efficient anti-tick agents, however, their activities depend on the source of production of nanoparticles and from their morphologies. Due to this factor, AgCl in its spherical morphology exhibited less activity than spherical Ag⁰.

Another factor that has to be considered when evaluating effects of the cited nanoparticles are the effects of the capped proteins from the biogenic nanoparticles,

which probably due to the specificity of the protein corona interaction may strongly affect nanoparticles' activities.²⁶

3. Tick-Borne Diseases

3.1. Bacteria

Bacteria genera most common in the ticks' infection are *Borrelia* (a genus of Gram-negative, aerobic, spirochete bacteria), *Francisella* (a genus Gram-negative, aerobic, coccobacillary or rod shaped, nonmotile bacteria), *Coxiella* (a genus of Gram-negative, aerobic, rod-shaped or spore-like particles, acidophilic bacteria), *Rickettsia* (a genus of non motile, Gram-negative, aerobic, obligate intracellular parasites, non spore-forming, highly pleomorphic bacteria that can present as cocci) and *Ehrlichia* (a genus of Gram-negative, aerobic, obligate intracellular parasites, rickettsia-shaped bacteria).

Burgdorfer,⁵² who is well known researcher in Lyme diseases, tested *in vitro* proteinate silver (colloidal silver or Argyrol) up to 1500 ppm (1.5 mg mL⁻¹) on bacteria that cause Lyme disease (*Borrelia burgdorferi* spirochetes).^{53,54} These bacteria disappeared in less than five minutes and twenty-four hours later, none of the crops treated contained any living spirochetes. Similar results were observed with another bacterium, such as *Borrelia hermsii* (HS-1), the agent of relapsing fever.

As far as we know, no other bacteria in this area were studied under influence of silver nanoparticles. However, it is known from the literature,^{23,35-38,55} that Gram-negative bacteria are effectively eliminated by Ag⁰ nanoparticles. Then, the antibacterial studies regarding tick-borne infections are an open area for research.

3.2. Virus

The most known viruses from tick infections are the tick-borne viruses of the families Asfarviridae, Rhabdoviridae and Orthomyxoviridae, Reoviridae, Bunyaviridae and Flaviviridae, genus *Flavivirus* (around 200 viruses).⁸

Argovit (12 mg mL⁻¹) that is spherical silver nanoparticles of 35 ± 15 nm functionalized with poly(vinylpyrrolidone) (PVP, 10-30 kD) were tested on Rift Valley fever virus (RVFV) in a Vero cell cultures and on mice lacking the type I interferon receptor (IFNAR [-/-] mouse infection model). In cells infected with RVFV a viral reduction of 50% of the total virus was found. But, pre-incubation of RVFV with silver nanoparticles at concentrations of 0.2 mg mL⁻¹, abolished almost completely viral propagation, leading to 98% reduction of infectivity. Daily administration of silver nanoparticles by oral gavages

to lethally infected mice, previously incubated with 20 mg mL⁻¹ of silver nanoparticles showed a delayed-onset clinical disease and mortality, with a survival rate of 60%. The authors suggested that these results revealed the potential application of the microbicide properties of silver nanoparticles to control the infectivity of this important zoonotic pathogen.⁵⁶

In addition to the antimicrobial activity against bacteria of silver nanoparticles, there is strong evidence that they are also active against several viruses, including human immunodeficiency virus, hepatitis B virus, herpes simplex virus, respiratory syncytial virus and monkey pox virus. These metal nanostructures generate an important opportunity for the development of new antiviral therapies with a large number of targets, reducing viral resistance that can commonly happen with conventional antivirals.⁵⁷

3.3. Protozoan

Protozoan infection babesiosis (*Babesia bigemina*) is transmitted by ticks¹³ and, in a similar way, leptospirosis by *Ixodes ricinus*⁵⁸ and leishmaniasis by *Rhipicephalus sanguineus*.⁵⁹

The effectiveness of silver nanoparticles as an alternative therapy for leishmaniasis, specifically by subcutaneous intralesional administration for cutaneous leishmaniasis was demonstrated.⁶⁰ Biogenic silver nanoparticles (mainly Ag⁰ nanoparticles) against *Leishmania amazonensis* promastigotes showed to be 4-fold more effective than silver nanoparticles chemically synthesized. *In vivo* studies in infected mice demonstrated that the biogenic silver nanoparticles were equally effective as 300-fold higher doses of amphotericin B, and more effective than 4-fold higher doses of chemically synthesized one.⁶¹

The possibility of using silver nanoparticles on protozoan infections was summarized by Rai *et al.*⁶² These facts demonstrated that we need more research in order to eliminate these types of contamination provoked by ticks.

4. Perspectives and Final Remarks

It is important to mention that it was clear from these analyzed data that reliable nanoparticles characterization and morphology are important in the biological activities. Then, the data said that {111} crystal plane of silver nanoparticles may play a prime role in antibacterial progress.

Another important conclusion is also that either Ag⁰ or AgCl nanoparticles or both together were effective against ticks or the propagation of the tick-borne infections. All

data indicated that the antibacterial and antiviral studies regarding tick-borne infections are an open area for research.

Then, we hope that this overview might incentive the researchers to study ticks-producer diseases more thoroughly in order to eradicate this problem globally.

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