Chapter 3
Silver Nanoparticles for Treatment of Neglected Diseases

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Abstract The study of neglected diseases is an important topic and deeply discussed in the newspapers, publications, and research foundations in the world. However, unfortunately no public or private attention has been paid on this issue. Still old drugs are being used, and very few are new for these diseases. Nanobiotechnology has appeared as a new strategy for the treatment of neglected diseases. The new developments in nanostructured carrier systems appear as promising in the treatment of many diseases with low toxicity, better efficacy and bioavailability, prolonged release of drugs, and reduction in the dosage of administration. This chapter is related to the use of nanobiotechnology in the treatment of neglected diseases by application of metallic nanoparticles on dengue virus, leishmaniosis, malaria, schistosomiasis, and trypanosomiasis.

Keywords Neglected diseases • Silver • Dengue virus • Leishmaniosis • Malaria • Schistosomiasis • Trypanosomiasis

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M. Rai, R. Shegokar (eds.), *Metal Nanoparticles in Pharma*,
DOI 10.1007/978-3-319-63790-7_3

3.1 Introduction

In general, the neglected diseases are getting slow but constant attention, than few years ago. Several reviews on this subject were published recently showing the importance of nanobiotechnology as a new approach to solve old problems in developing countries (Durán et.al. 2009, 2016a, b; Rai et al. 2014b; Rai and Kon 2015).

Metal nanoparticles play a pivotal role since they exhibit unique optoelectronic and physicochemical properties (Rai et al. 2014b). These properties depend on morphological aspects (e.g., shape, size, structure, crystallinity) (Duran et al. 2016b) and thus have led to a large range of applications in various areas such as electronics, molecular diagnostics, drug release, catalysis, and nanosensing (Rai et al. 2014a). Preparation methods for metal nanoparticles are diverse (e.g., physical and chemical methods). The use of biogenic synthesis of nanoparticles has drawn much attention, since they are green, efficient synthetic processes, and cost-effective procedure. There are many organisms able to synthesize nanoparticles, such as yeasts, bacteria, actinomycetes, fungi, and plants. In biomedicine, most importantly, it will play a crucial role in diagnostics, drug delivery, bandages, related cosmetics, etc. Although they are important in remediation through the absorption of pollutants, filtration, sterilization, etc., the most relevant example is the use of these nanoparticles as antimicrobial (Rai and Durán 2011). Silver nanoparticles are used as new generation of antimicrobials, with significant activity against many types of pathogens including multidrug-resistant organisms. Although there is interest in extensive applications, their possible toxicities must be studied (El-Nour et al. 2010; Durán et al. 2010, 2011a, b; Rai and Durán 2011; Rai et al. 2014a, b; Castro et al. 2014).

Nanobiotechnology is an important tool in order to develop new strategies for neglected diseases, which are of great importance in many countries in the world. This chapter will deal with role of silver nanoparticles in treatment of neglected diseases.

3.2 Neglected Diseases

3.2.1 Dengue

Dengue virus infection (DVI) exhibits a spectrum of illnesses from asymptomatic although in apparent infection, or a flu-like mild fever, to classic dengue fever (DF) or worst to DF with hemorrhagic consequences. Many other diseases or nonspecific viral syndrome can mimic DVI (Mungrue 2014). DVI is the wildest mosquito-borne infection which appeared on 2.5 billion people in many regions, including tropical and subtropical areas in the world. It is transmitted by female *Aedes aegypti* or *Aedes albopictus* to humans (Beatty et al. 2010) (Fig. 3.1). Unfortunately, the only treatment against dengue is the prevention and a supportive care; although some attempts were made, still now they are not proved to be efficient (Idrees and Ashfag 2013; Durán et al. 2016a).

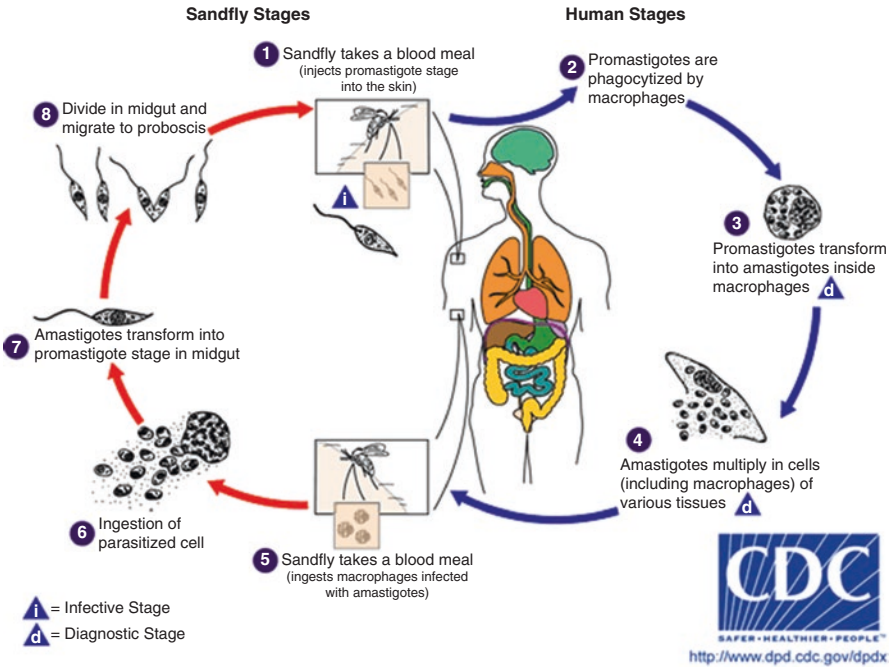

Fig. 3.1 Graphic panel of dengue virus infection (From http://factsanddetails.com/world/cat52/sub334/item1195.html)

Metallic nanoparticles have demonstrated efficacy against mosquito larvae (Salukhe et al. 2011; Soni and Prakash 2012a, b, c, d, 2013, 2014a). The leaf extracts from plants were used for silver nanoparticle (AgNP) production as an eco-friendly alternative for adulticidal activity against filarial, dengue, and malaria vector mosquitoes (Suganya et al. 2013; Veerakumar et al. 2014a, b).

Reviews on biogenic AgNPs against mosquitoes were recently published (Hajra and Mondal 2015; Rai and Kon 2015; Durán et al. 2016a, b), together with important results on biogenic AgNPs on biological systems (Durán et al. 2010; Gaikwad et al. 2013; Mashwani et al. 2015).

The efficacy of biogenic silver nanoparticles on *Aedes aegypti* and *Culex quinquefasciatus* demonstrated that the median lethal concentrations (LC_{50}) of AgNPs that killed fourth instars of *Aedes aegypti* and *Culex quinquefasciatus* were 0.30 and 0.41 μg mL^{-1}, respectively. Adult longevity (days) was reduced by 30% in male and female mosquitoes exposed as larvae to 0.1 μg mL^{-1}AgNPs, whereas the number of eggs laid by female larvae decreased in 36% when exposed to this concentration (Arjunan et al. 2012).

Related to mosquito larvae mortality with metallic nanoparticles, it has been found LC_{50} at the range of 0.56–606.5 μg mL^{-1} and also lower than those values cited on Table 3.1 (Hajra and Mondal 2015; Durán et al. 2016a). These large differences are probably due to synthesis of AgNPs with different kinds of capped pro-

Table 3.1 Lethal dose (LD_{50}) (μgmL^{-1}) of silver nanoparticles effective on mosquito

LD_{50} (μgmL^{-1})	Reference
0.05 (from *A. indica*) (pupae *C. quinquefasciatus*) (41–60 nm)	Poopathi et al. (2015)
34.5 (from *Euphorbia hirta*) (pupae *A. stephensi*) (30–60 nm)	Priyadarshini et al. (2012)
25.3 (from *C. indica*) (pupae of *A. stephensi*) (30–60 nm)	Kalimuthu et al. (2013)
23.8 (from *C. indica*) (pupae of *C. quinquefasciatus*) (30–60 nm)	
0.59 (from *Rhizophora mucronata*) (fourth-instar larvae of *C. quinquefasciatus*) (60–95 nm)	Gnanadesigan et al. (2011)
1.10 (from *Plumeria rubra*) (third-instar larvae of *A. stephensi*) (32–200 nm)	Patil et al. (2012)
1.74 (from *Plumeria rubra*) (fourth-instar larvae of *A. stephensi*) (32–200 nm)	
10.0 (from *Cinnamomum zeylanicum*) (fourth-instar larvae of *A. stephensi*) (12 nm)	Soni and Prakash (2014b)
4.90 (from *Jatropha gossypifolia*) (fourth-instar larvae of *A. stephensi*) (163 nm)	Borase et al. (2013)
54.9 (from *Feronia elephantum*) (third-instar larvae of *A. stephensi*) (20–60 nm)	Veerakumar et al. (2014b, c)
67.1 (from *Feronia elephantum*) (third-instar larvae of *C. quinquefasciatus*) (20–60 nm)	
26.7 (from *Heliotropium indicum*)(adult mosquitoes of *A. stephensi*) (18–45 nm)	Veerakumar et al. (2014a)
32.1 (from *Heliotropium indicum*) (adult mosquitoes of *C. quinquefasciatus*) (18–45 nm)	
21.9 (from *Sida acuta*) (late third-instar larvae of *A. stephensi*) (18–35 nm)	Veerakumar et al. (2013)
26.1 (from *Sida acuta*) (late third-instar larvae of *C. quinquefasciatus*) (18–45 nm)	
32.1 (from *Murraya koenigii*) (pupae of *A. stephensi*) (20–35 nm)	Suganya et al. (2013)
1.0 (from *Hibiscus rosasinensis*) (fourth-instar larvae of *Aedes albopictus*) (35 nm)	Sareen et al. (2012)

teins on them or due to the presence of different silver nanostructures (e.g., silver chloride or/and silver oxides nanoparticles) (Durán et al. 2016b).

Silver nanoparticles (AgNPs) were prepared from the latex of the plant *Euphorbia milii.* Latex-synthesized AgNPs were evaluated against the second- and fourth-instar larvae of *Aedes aegypti* and *Anopheles stephensi*. *E. milii* AgNPs showed a LC_{50} of 8.76 ± 0.46 and 8.67 ± 0.47 μgmL^{-1}, for second instars of *Ae. aegypti* and *An. stephensi*, respectively, showing similar activities to different mosquitoes (Borase et al. 2014) (Table 3.2).

3.2.2 Leishmaniasis

Leishmaniases are vector-borne zoonotic diseases caused by various species of the genus *Leishmania* (protozoa). These pathogens are transmitted by sandflies (e.g., phlebotomine) and infect humans where the vectors and reservoirs coexist (Fig. 3.2).

Table 3.2 Mortality of *Aedes aegypti* with biogenic silver nanoparticles

Plants used for synthesis	Life stages	Size (nm)	LD_{50} (μg mL^{-1})	Ref.
Murraya koenigii	Instar I	20–35	10.8	Suganyaet al. (2013)
	Instar II		14,7	
	Instar III		53.7	
	Instar IV		63.6	
	Pupa		75.3	
Feronia elephantum	Adult (3–4 days)	18–45	20.4	Veerakumaret al. (2014a, b, c)
				Veerakumar and Govindarajan (2014)
Azadirachta indica	Instar III	41–60	0.006	Poopathi et al. (2015)
Bacillus thuringiensis (*Bacteria*)	Instar III	44–143	0.14	Banu et al. (2014)
Rhizophora mucronata	Instar IV	60–95	0.89	Gnanadesigan et al. (2011)
Plumeria rubra	Instar II	32–220	181,7	Patil et al. (2012)
	Instar IV		287.5	
Pedilanthus tithymaloides	Instar I	15–30	0.029	Sundaravadivelan et al. (2013)
	Instar II		0.027	
	Instar III		0.047	
	Instar IV		0.086	
	Pupa		0.018	
Jatropha gossypifolia	Instar II	30–60	5.9	Borase et al. (2013)
	Instar IV		4.44	
Euphorbia milii (*Latex*)	Instar II	208	8.76	Borase et al. (2014)
Sida acuta	Instar IV	18–35	23.9	Veerakumar et al. (2013)

Modified from Durán et al. (2016a)

Anthroponotic cycles have been documented for some species of *Leishmania* (e.g., *Leishmania donovani* in India, *Leishmania major* in Afghanistan). Visceral leishmaniasis (VL) is caused by *L. donovani* (Indian and East Africa) and by *L. infantum* or *L. chagasi* (e.g., Asia, Europe, Africa, and the New World). Tegumentary leishmaniasis (TL) is caused by many species of parasites in Europe (e.g., *L. major*, *L. tropica*, *L. aethiopica*, and sometimes *L. infantum*), in America (e.g., *L. (Viannia) braziliensis*, *L. amazonensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, *L. mexicana*, *L. pifanoi*, *L. venezuelensis*, *L. (V.) peruviana*, *L. (V.) shawi*, and *L. (V.) lainsoni*), in Mexico, Argentina, and Brazil (e.g., subgenus *Viannia* and *L. amazonensis*), and in Mexico and Central American countries (e.g., *L. mexicana*) (Lindoso et al. 2012). The recent treatment for VL involved miltefosine and paromomycin. These compounds were evaluated only few times and should be evaluated in different epidemiological scenarios (Marinho et al. 2015).

AgNPs as an alternative therapy for leishmaniasis are effective, specifically by subcutaneous intralesional administration for cutaneous leishmaniasis (CL). AgNPs, as discussed in many publications, can be prepared by chemical, physical, or

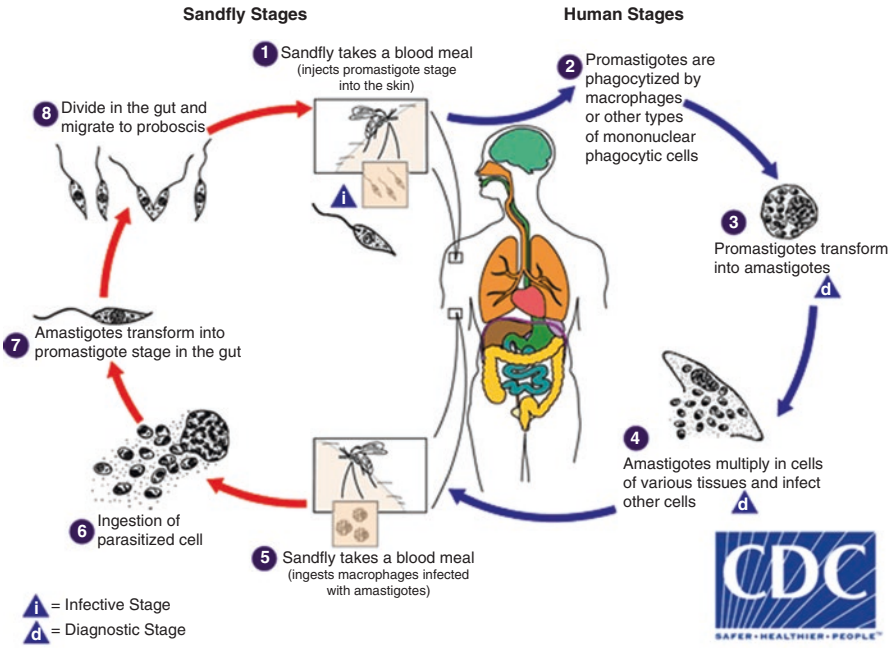

Fig. 3.2 Graphic panel of leishmaniasis (From https://www.cdc.gov/dpdx/leishmaniasis/)

biological procedures (Durán et al. 2011a, b). Besides these, biosynthetic methods generate more effective NPs in medical applications because of their protein-coated surface (Prasad et al. 2011). In addition, both chemically and biologically synthesized NPs were studied first by in vitro experiments against *Leishmania amazonensis* promastigotes. Biologically generated AgNPs (Bio-AgNPs) were shown to be threefold more effective than chemically generated ones (Chem-AgNPs). Later, in vivo studies in infected mice demonstrated that Bio-AgNPs dose showed the same effectiveness than 300-fold higher doses of amphotericin B and also threefold higher doses of Chem-AgNP. Important results such as no hepato- and nephrotoxicity were found in comparison with amphotericin B and Chem-AgNPs (Rossi-Bergmann et al. 2012).

The viability of *L. tropica* promastigotes after 72 h recorded maximum cytotoxic effect of AgNPs (no size was described) at a concentration of 2.1 μg/mL with an IC50 of 1.749 μg/mL, and from *L. tropica* amastigote phase the IC50 was 1.148 μg/mL (Gharby et al. 2017).

3.2.3 Malaria

Plasmodium species *P. malariae*, *P. knowlesi*, *P. ovale*, *P. falciparum*, and *P. vivax* infect human with malaria (Fig. 3.3). A decrease of 42% in malaria death was achieved due to many efforts to control and eradicate malaria through insecticides

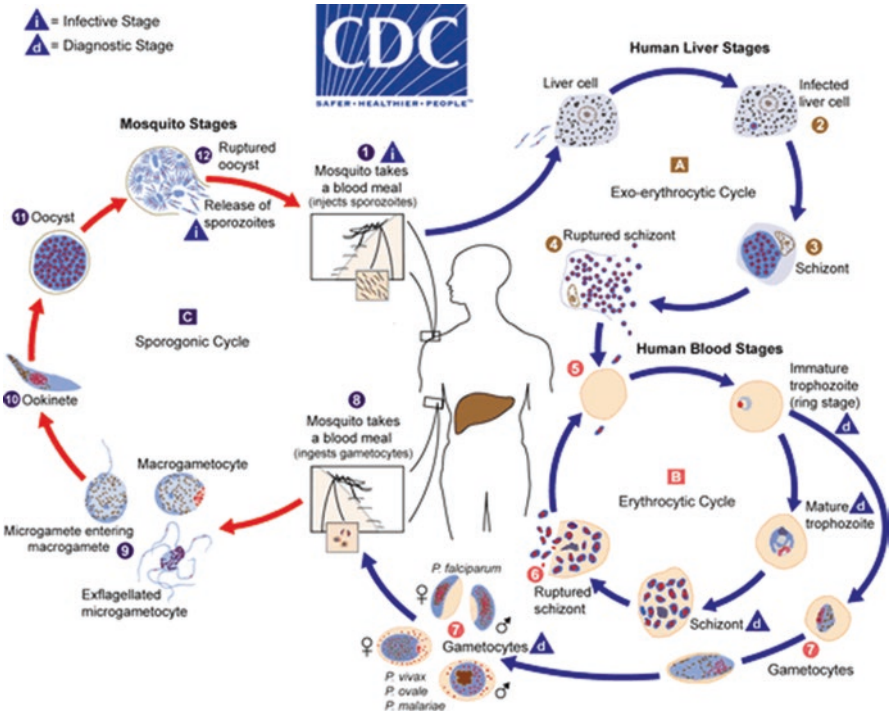

Fig. 3.3 Graphic panel for malaria (From https://www.cdc.gov/malaria/about/biology)

and antimalarial treatments (e.g., artemisinin-combined therapies). However, one of the challenges is the increasing drug resistance, and no effective malaria vaccine exists today. One malaria vaccine in phase III is under testing by GSK (Glaxo Smith KlineRTS,S/AS01 vaccine), but its vaccine efficacy is around 30% (Siu and Ploss 2015).

AgNPs produced from aqueous extracts of leaves and bark of *Azadirachta indica* (neem) (10.5 nm in leaf and 19.2 nm in bark) showed activities against mosquito (e.g., larvicides, pupicides, and adulticides) and against the malaria vector *Anopheles stephensi* (*An. stephensi*) and filariasis vector *Culex quinquefasciatus* at different doses. The larvae, pupae, and adults of *C. quinquefasciatus* were found to be more susceptible to AgNPs than *An. stephensi*. The I and the II instar larvae of *C. quinquefasciatus* show a mortality rate of 100% after 30 min of exposure. The results against the pupa of *C. quinquefasciatus* were recorded as LC_{50} 4 μg mL^{-1} (3 h exposure). In the case of adult mosquitoes, LC_{50} 1.06 μL/cm^2 was obtained (4 h exposure). The authors suggested that biogenic AgNPs were environment friendly for controlling malarial and filarial vectors (Soni and Prakash 2014a).

AgNP synthesis using plant extract of *Pteridium aquilinum*, acting as a reducing and capping agent, showed that AgNP ($10 \times LC_{50}$) led to 100% larval reduction after 72 h and reduced longevity and fecundity of *An. stephensi* adults. Furthermore, the

antiplasmodial activity of AgNPs was evaluated against CQ-resistant (CQ-r) and CQ-sensitive (CQ-s) strains of *P. falciparum*. *P. aquilinum*-synthesized AgNPs achieved IC_{50} of 78.12 μgmL^{-1} (CQ-s) and 88.34 μgmL^{-1} (CQ-r). Overall, their results highlighted that *P. aquilinum*-synthesized AgNPs could be candidate as a new tool against chloroquine-resistant *P. falciparum* and also on *An. stephensi* (Panneerselvam et al. 2016).

Synthesis of AgNPs using β-caryophyllene isolated from the leaf extract of *Murraya koenigii*, as reducing and stabilizing agent (5–100 nm), exhibited promising activity on chloroquine-sensitive *Plasmodium falciparum* (3D7) with an IC50 of 2.34 ± 0.07 μg/mL) was reported (Kamaraj et al. 2017).

3.2.4 Schistosomiasis

Three species of parasitic flatworms of the genus *Schistosoma* (*S. mansoni*, *S. haematobium*, and *S. japonicum*) caused schistosomiasis that is also considered a neglected tropical disease (Fig. 3.4). These parasites cause a chronic infection and often debilitating the infected individual that impairs development and productivity. In an estimate, the World Health Organization (WHO) indicated that over 250 million people have been infected in around 80 endemic countries (e.g., sub-Saharan Africa, the Middle East, the Caribbean, and South America) resulting in approximately 200,000 deaths annually. Unfortunately, praziquantel (PZQ) is the actual product used due to the absence of an effective vaccine. PZQ offers oral administration, high efficacy, tolerability, low transient side effects, and a low cost. However, PZQ resistance is actually detected (Neves et al. 2015).

Another strategy for controlling schistosomiasis is combating the vector *Biomphalaria glabrata* (mollusk) through the use of AgNPs as a molluscicidal with low toxicity to other aquatic organisms (Yang et al. 2011; Guang et al. 2013).

3.2.5 Trypanosomiasis

Human African trypanosomiasis (HAT) caused by infection with the parasite *Trypanosoma brucei gambiense* or *T. b. rhodesiense* and its vector is tsetse fly (Fig. 3.5). Around 70 million people worldwide were at risk of infection, and probably over 20,000 people in Africa are infected with HAT (Nagle et al. 2014; Sutherland et al. 2015).

American trypanosomiasis or Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi*. This disease is endemic in 21 Latin American countries, with a strong economic impact because it affects economically active people. Over ten million people are infected, and over 25 million people are within the endemic countries. After many years of infection, 10–30% of infected people develop symptoms of chronic phase. In general, the effect on the heart is the most common organ

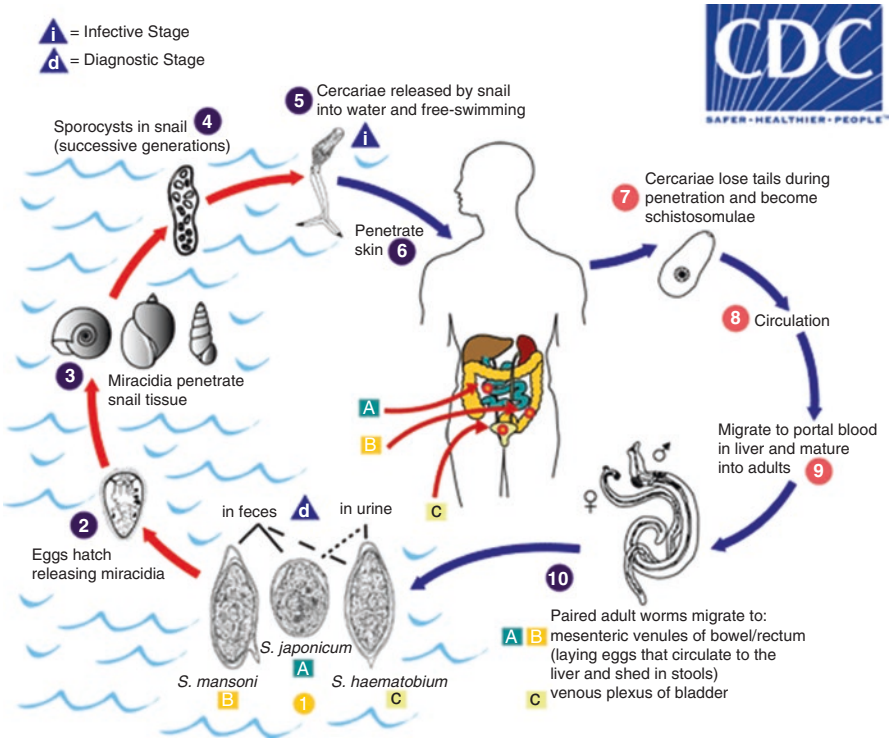

Fig. 3.4 Graphic panel of schistosomiasis (From https://www.cdc.gov/dpdx/schistosomiasis/)

problem; symptoms include cardiomyopathy and thromboembolism. The patient's death usually occurs from heart failure (Rodrigues-Morales et al. 2015).

Unfortunately, very few compounds are in development, and drug discovery efforts are limited. Nifurtimox and SCYX-7158 are the only two compounds in clinical trials for HAT showing the need for novel chemical entities or new strategies (Nagle et al. 2014).

Against Chagas disease, in human trials, are nifurtimox and benznidazole. Benznidazole is still being used in Brazil (Pereira and Navarro 2013). Unfortunately, limited human data and better supported by the findings in animal models suggest that *T. cruzi* strains may vary in their drug susceptibility (Bern 2015).

The enzyme arginine kinase (AK) is absent in humans, and important for the Trypanosoma development, fact that makes it an attractive target choice for a trypanocide development. Adeyemi and Whiteley (2014) performed a thermodynamic and spectrofluorimetric study on the interaction of metal nanoparticles (i.e., AuNPs and AgNPs) with AK. AgNPs and AuNPs bound tightly to the arginine substrate through a sulfur atom of a cysteine residue (Cys^{271}). This interaction controls the electrophilic and nucleophilic profile of the substrate arginine-guanidinium group, absolutely important for enzyme phosphoryl transfer from ATP to *Trypanosoma*.

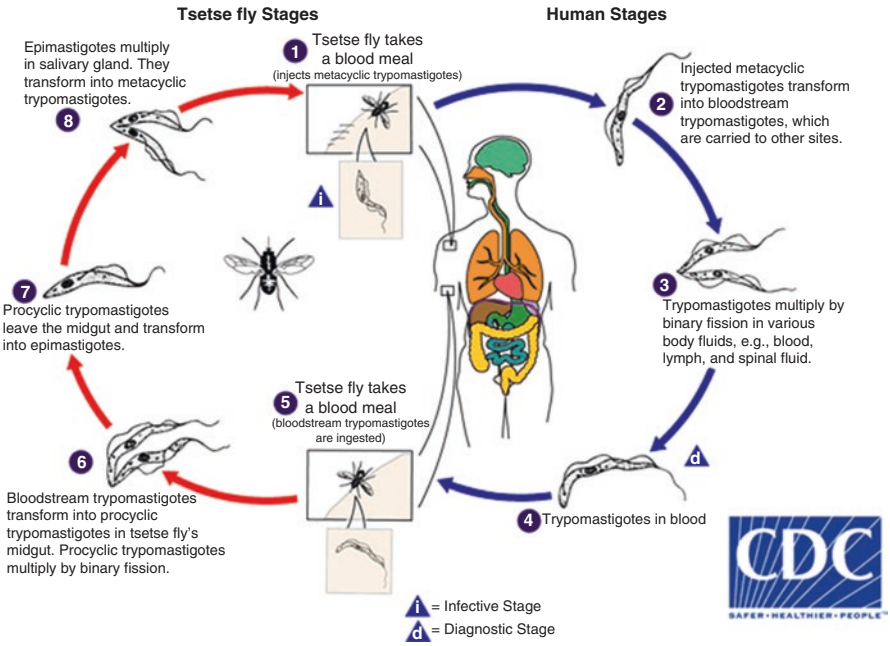

Fig. 3.5 Graphic panel of trypanosomiasis (From https://www.cdc.gov/dpdx/trypanosomiasisafrican/)

3.3 Conclusion

Actually, there are a few recently published reviews focusing on dengue virus, leishmaniasis, malaria, schistosomiasis, and trypanosomiasis with alternative strategies. The present review pointed out the most important advances in the metallic nanoparticles action on these diseases. Silver nanoparticles appeared as a possible alternative in the therapy of many of these diseases and also on vectors with low toxicity and with enhanced efficacy. This revision dealt with the current status of nanobiotechnology through silver nanoparticles acting on neglected diseases. Therefore, it is clear that it is possible to use nanotechnology to manage safety to these humans' diseases.

Acknowledgments Support by FAPESP, INOMAT (MCTI/CNPq), NanoBioss (MCTI), Brazilian Network on Nanotoxicology (MCTI/CNPq) is acknowledged.

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