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REVIEW

Unravelling *Toxoplasma* treatment: conventional drugs toward nanomedicine

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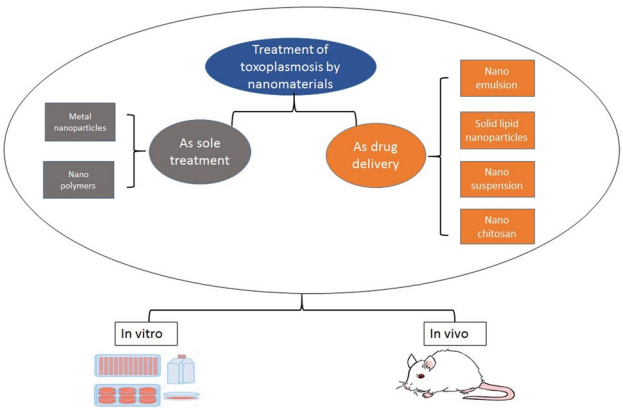
Abstract

Toxoplasma gondii is a worldwide protozoan parasite that infects almost all warm-blooded animals. Although human toxoplasmosis is mostly latent, pregnant women and immunocompromised patients need effective treatment. There are drugs of choice for treatment of toxoplasmosis; however, due to their side effects and/or their disease stage-specificity, prescription of them is limited. During recent years, nanomedicine has been employed to overcome limitations of conventional drugs. Here, we provided a state-of-the-art review of experimental toxoplasmosis treatment using nanotechnology.

Graphic abstract



Keywords *Toxoplasma gondii* · Acute toxoplasmosis · Chronic toxoplasmosis · Treatment · Conventional therapy · Nanomedicine

Introduction

Toxoplasmosis is a zoonotic disease caused by *Toxoplasma gondii.* This intracellular protozoan parasite infects humans and various animals. Seroepidemiological surveys show that near one third of the world's population probably are positive for toxoplasmosis (Jones et al. 2007; Mcauley et al. 2015; Torgerson and Mastroiacovo 2013). *T. gondii* has three infective forms including oocyst, tachyzoite, and tissue cyst. Cats are the definitive hosts of *T. gondii* which disperse immature oocysts via their feces. In environment, oocysts become mature and upon ingestion

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by mammals (including man), they convert to tachyzoites. Tachyzoites are rapidly dividing stage which can enter inside all the nucleated cells. After proliferation and cells rupture, released tachyzoites infect various tissues such as the central nervous system (CNS), the eye, skeletal and cardiac muscles, and the placenta. Under the pressure of the immune system, tachyzoites are transformed into bradyzoites to form cysts. However, in immunocompromised patients, bradyzoites may be released from cysts, transform back into tachyzoites, and cause recrudescence of infection (Montoya and Liesenfeld 2004). *T. gondii* has three clonal lineages consist of type I, II, and III, which are categorized based on their virulence in mice (type I being lethal, while type II and III are less virulent in mice). *T. gondii* type II is isolated from AIDS patients, while type I and II are recorded from congenital toxoplasmosis. In addition, *T. gondii* genotype III is mostly isolated from animals (Dardé et al. 1992; Mcauley et al. 2015).

Humans are commonly infected by consumption of either raw/undercooked meat containing tissue cysts or ingestion of oocysts via contaminated vegetable and water (Hill and Dubey 2016; Montoya and Liesenfeld 2004). In addition, tachyzoites may be transmitted during organ transplantation or transfusion from a *Toxoplasma* – infected patient. Mothers who are infected by *Toxoplasma* for the first time during the pregnancy can transmit active tachyzoites to developing fetus (Aliberti 2005; Hill and Dubey 2002).

The clinical symptoms of toxoplasmosis depend on the immune system. Toxoplasmosis is asymptomatic in immunocompetent subjects, but it could be even lethal in immunocompromised individuals (Esch 2010). Moreover, an association between toxoplasmosis and mental disorders like autism, schizophrenia, anxiety, and Alzheimer's has been reported in immunocompetent individuals (Flegr and Horáček 2019; Spann et al. 2017). Treatment of toxoplasmosis is necessary in pregnant women and patients with immunodeficiency. Moreover, immunocompetent subjects who suffer from psychiatric disorders are recommended to be considered for treatment of toxoplasmosis (Flegr et al. 2014).

Standard drugs for acute toxoplasmosis are sulfadiazine and pyrimethamine, which may have severe side effects such as hematologic toxicity, allergy, folic acid deficiency, and bone marrow suppression (Değerli et al. 2003; McLeod et al. 2006; Montoya and Liesenfeld 2004). Atovaquone is the only effective drug in the chronic stage of disease, but its limitation is inadequate oral bioavailability (Baggish and Hill 2002). In order to overcome these challenges, novel approaches are being designed and experienced. Today, the use of nanotechnology in the treatment of many diseases is becoming a common practice (Azami et al. 2018a). Therefore, we provided a state-of-the-art review about treatment of experimental toxoplasmosis using nanotechnology.

Clinical presentations

The primary infection of *T. gondii* is asymptomatic and may occasionally causes lymphadenopathy or a flu-like illness. The ocular form is either congenital or postnatal which both cause chorioretinitis (Montoya and Remington 1996). Toxoplasmosis in immunocompromised patients could be life-threatening and occurs after the reactivation of the chronic forms of *T. gondii* (Melchor and Ewald 2019). In these patients, the CNS is the most affected organ that may lead to encephalitis. Chorioretinitis, pneumonitis, multi-organ involvement, acute respiratory failure, and hemodynamic abnormalities similar to septic shock are the other reported manifestations.

The congenital toxoplasmosis has a wide spectrum of clinical manifestations from abortion to hydrocephalus, microcephaly, intracranial calcifications, chorioretinitis, strabismus, blindness, epilepsy, psychomotor, and mental retardation, depending on the trimester of pregnancy at the time of primary maternal infection (Mcauley et al. 2015; Montoya and Remington 2008).

Conventional treatment

Anti-*T. gondii* drugs are not usually recommended for immunocompetent subjects; however, treatment of ocular toxoplasmosis, *Toxoplasma*-positive immunocompromised patients, and pregnant women are recommended. *T. gondii* may affects the rate of several common mental health disorders in healthy subjects (Flegr and Horáček 2019; Flegr et al. 2014); therefore, treatment of toxoplasmosis in these cases may also be considered. The standard therapy for toxoplasmosis is the combination of sulfadiazine and pyrimethamine that due to the folate inhibitory mechanism of these two antibiotic, folic acid should be added as supplement (Kur et al. 2009; Montoya and Liesenfeld 2004). In addition to folic acid deficiency, bone marrow suppression, haematological toxicity, and hypersensitivity are the other reported side effects.

Apart from spiramycin, which is the only approved drug for infected pregnant women, routine drugs have teratogenic effects on fetus (Alday and Doggett 2017). In immunocompromised patients such as AIDS patients, clarithromycin, azithromycin, and atovaquone are also prescribed besides sulfadiazine and pyrimethamine (Montoya and Liesenfeld 2004). In addition, atovaquone is an anti-*Toxoplasma* drug that successful affects tissue cysts in murine models (Azami et al. 2018a).

Besides their side effects, anti-parasitic drugs have a couple of limitations including poorly absorption due

to their insolubility, low penetration across the biological membrane barriers of tissues and cells, which cause inadequate bioavailability, and lower therapeutic effects. Another frequently reported limitation is drug resistance (Sun et al. 2019).

Treatment of toxoplasmosis by nanoparticles

There are two common therapeutic approaches during hiring nanoparticles: (1) employing as a drug and (2) employing as a carrier for conventional drugs. Antibacterial, anti-parasitic, and antifungal properties of many nanoparticles have been recorded, so far (Cern et al. 2018; Dar et al. 2020; Randhawa et al. 2015). Drug delivery can be an effective way to enhance the oral bioavailability and efficiency of anti-parasitic drugs (Ge et al. 2014). In addition, reduced effective dose and toxic side effects, increased sustained release and intracellular absorption, and tissue uptake are the other strengthens of nanocarriers that overcome the limitations of conventional drugs (Ge et al. 2014; Jaiswal et al. 2015). Nanoparticles including metal nanoparticles, polymer nanoparticles, solid lipid nanoparticles (SLNs), nanoemulsions, and nanosuspensions have been reported for anti-*Toxoplasma* treatment.

Several techniques have been developed to prepare nanoparticles. Nanoemulsions are a colloidal particulate system with submicron sizes from 10 nm to 1000 nm. The main components of nanoemulsions are oil, emulsifying agents, and water. There are two broad categories of techniques for the preparation of nanoemulsion: (1) high energy method, and (2) low energy method. The high energy method includes high-energy stirring, ultrasonic emulsification, high-pressure homogenization, microfluidizaiton, and membrane emulsification, while the low energy emulsification method includes phase inversion temperature, emulsion inversion point, and spontaneous emulsification (Jaiswal et al. 2015).

SLPs are nanosize particles immersed in water or aqueous surfactant solution with several applications. Different methods including high pressure homogenization, ultrasonication/high speed homogenization, solvent evaporation method, and spray drying method are used to prepare SLPs (Surender and Deepika 2016). High pressure homogenization is a common employed method to produce nanosuspensions from poorly soluble drugs, which is mostly classified into two groups: (1) dissoCubes (homogenization in aqueous media), and (2) nanopures (homogenization in water-free media or water mixtures) (Yadollahi et al. 2015) (Fig. 1).

Nanoparticles as a sole treatment

The use of metal nanoparticles such as silver, gold, platinum, and selenium for the treatment of *T. gondii* were studied in vivo and in vitro. Chemical, physical, and biotechnological methods have been employed to synthesize nanoparticles. Today, green synthesis of nanoparticles by plant extract has been considered due to its safety and availability (Nafari et al. 2020).

In biological synthesis of nanoparticles, bacteria, yeast, and fungi, which have reductase enzymes, are usually used (Rahman et al. 2019). Treatment of experimentally infected

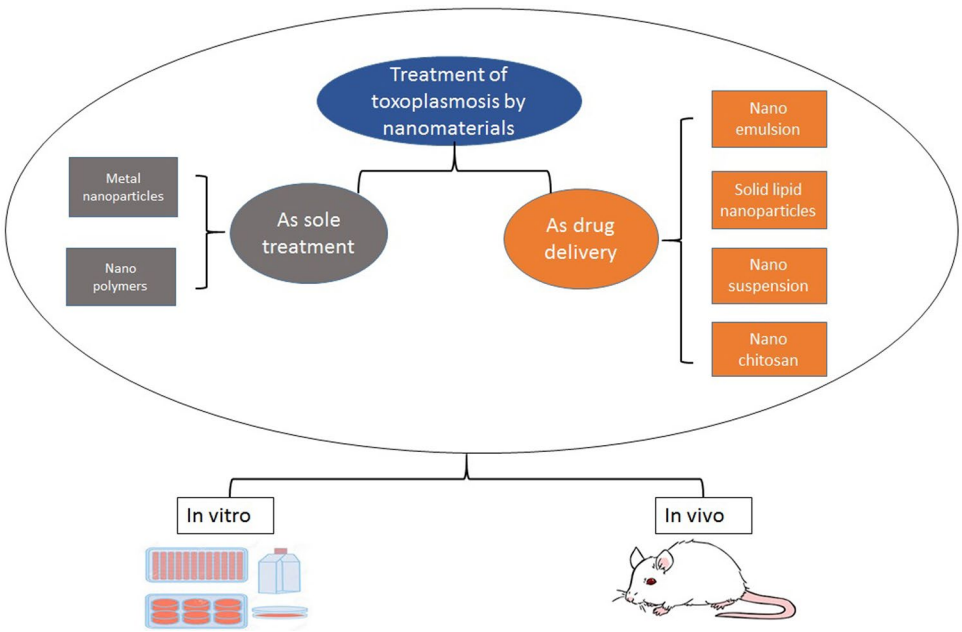

Fig. 1 The schematic overview of the applications of nanomedicine in treatment of experimental toxoplasmosis. Nanomedicine is employed in two main approaches against toxoplasmosis: (1) as sole treatment, (2) as drug carrier

mice with *T. gondii* Tehran strain by biogenic selenium nanoparticles reduced the mean number of brain-tissue cysts and increased the inflammatory cytokines compared to control group (Keyhani et al. 2020). Anti-*Toxoplasma* activity of biogenically synthetized nanosilver by *Fusarium oxysporum* with the size of 69 nm was reported on HeLa cells infected by *T. gondii* RH strain. Silver nanoparticles also did not significantly affect the inflammatory cytokines, while decreased interleukin (IL) 8 (Machado et al. 2020). Ultrastructural changes of *T. gondii* oocysts exposed to silver nanoparticles with the size of 10 nm were evaluated that the results showed rupture in the wall of the oocyst, which was directly related to viability of oocyst (Vergara-Duque et al. 2020). The morphological effects of silver nanoparticles on tachyzoites and tissue cysts of *T. gondii* were examined by light and electron microscopy, and both tachyzoites and tissue cysts showed structural changes (Shojaee et al. 2019). Biogenic nanosilver together with *Phoenix dactylifera* and *Ziziphus spina-christi* extracts with the size of 200 nm decreased histopathological changes and enzyme activity in the liver of mice infected with *T. gondii* RH strain (Alajmi et al. 2019). Metal nanoparticles including gold, silver, and platinum with the size of 5, 10, and 3 nm, respectively, were evaluated on ME49 strain of *T. gondii* in human foreskin fibroblast (HFF) cells that the findings indicated the capacity of nanoparticles to decrease bradyzoite burden and change the parasite cyst wall formation (Adeyemi et al. 2019). Metal nanoparticles including silver, gold, and platinum with diameter size range of 5–50 nm were reported to moderately suppress the in vitro growth of *T. gondii*. Furthermore, the anti-parasitic effect of nanoparticles on *Trypanosoma* spp., was also performed that the results were promising (Adeyemi et al. 2018). The anti-*Toxoplasma* activities of commercial inorganic nanoparticles including gold (5 nm), silver (10 nm), and platinum (3 nm) were evaluated that their anti-parasitic mechanisms were linked to redox signaling (Adeyemi et al. 2017). In addition, it was mentioned that the nanoparticles affected the mitochondrial membrane potential, parasite invasion, replication, and infectivity potential of *Toxoplasma* (Adeyemi et al. 2017). Gold nanorods conjugated with anti-*T. gondii* antibodies together with laser thermal therapy was the another way which was employed to kill parasite as well as tumor cells (Pissuwan et al. 2007).

Chitosan is a natural and nontoxic polysaccharide resulting from deacetylation of chitin in alkaline conditions which is composed of N-acetyl-d-glucosamine and d-glucosamine units (Goy et al. 2009). Studies on antimicrobial activity of chitosan nanoparticles have been carried out against various microorganisms including parasites. However, besides antibacterial, antitumor, and antifungal properties, chitosan nanoparticles are reported as promising system for drug deliveries (De Marchi et al. 2017; Wang et al. 2011). Evaluation of various molecular weights and concentrations of chitosan nanoparticles on tachyzoites of *T. gondii* RH strain was conducted which resulted convincing anti-*Toxoplasma* efficiency, particularly in low molecular weights (Teimouri et al. 2018). Silver and chitosan nanoparticles were synthesized to treat toxoplasmosis in mice, as well. Gaafar et al. (2014), showed that silver nanoparticles alone or in combination with chitosan led to a significant reduction of the parasite count in the liver and spleen of laboratory mice compared to the control group. In this study, tachyzoites aspirated from peritoneum of mice were deformed and immobilized, and the levels of IFNγ in the serum of animals receiving nanoparticles increased (Gaafar et al. 2014) (Table 1).

Nano based drug delivery systems

A couple of studies have evaluated the potential of nanoparticles as drug carriers. Khosravi et al. (2020) evaluated mannosylated paromomycin-loaded SLNs on *T. gondii* tachyzoites in an in vitro system and showed significant anti-parasitic activity without considerable host cell toxicity. Atovaquone is a powerful inhibitor of protozoan parasites with a broad-spectrum activity, but with extremely low water solubility (Darade et al. 2018). Therefore, many studies were performed to improve its bioavailability. Nanoemulsion of atovaquone was prepared to enhance bioavailability and efficacy of this drug for treatment of toxoplasmosis, which showed in vitro anti-*Toxoplasma* effects. Azami et al. (2018a) tested the oral administration of atovaquone nanoemulsion in mice infected by both Tehran and RH strains of *T. gondii*, and reported increased oral bioavailability, tissue distribution, and survival time besides reduction in the number and size of the brain cysts. Effective therapeutic activity of atovaquone at a reduced dose was the major achievement of the study. Schöler et al. (2001) synthesized atovaquone nanosuspensions (ANS) using by high-pressure homogenization and assessed its anti-parasite activity on *T. gondii* BK strain in vitro that the results showed excellent efficacy besides low cytotoxicity. Moreover, intravenous administration of 10.0 mg/kg of ANS in mice suffered from toxoplasmic encephalitis (TE) increased tissue uptake of atovaquone and protected the animals against development of TE and death (Schöler et al. 2001). In another study performed on mice with acute and reactivated toxoplasmosis, sodium dodecyl sulfate (SDS)-coated atovaquone nanosuspensions were synthesized to improve penetration through the blood-brain barrier and oral bioavailability of the drug. In this study, SDS enhanced the transport of molecules across epithelial barriers, stabilized nanoparticles loaded with drugs, and improved tissue uptake of atovaquone compared to commercial form of atovaquone. Furthermore, parasitemia, DNA

Table 1 Selected studies, nanoparticles and loaded drugs against *Toxoplasma*

Author	Purpose	Nanoparticle	Loaded drugs	Size	Zeta potential	*Toxoplasma* strain	Laboratory animals
Keyhani et al. (2020)	Evaluation the therapeutic effects of selenium nanoparticles against chronic toxoplasmosis	Selenium	–	≤ 200 nm	–	Tehran strain	Male BALB/c mice
Machado et al. (2020)	Anti-proliferative and immunological actions of biogenic silver nanoparticle in HeLa cells	Silver	–	69 nm	–	RH strain	HeLa cells
Vergara-Duque et al. (2020)	Effects on the morphology of *T. gondii* and *Salmonella braenderup*	Silver	–	10 nm	–	Oocysts of *T. gondii*	–
Shojaee et al. (2019)	Evaluation the effects of nanosilver colloid on tachyzoites and bradyzoites of *T. gondii*, RH and Tehran strains	Silver	–	70 nm	–	RH strain, Tehran strain	–
Alajmi et al. (2019)	Evaluation the effects of silver nanoparticles on anti-*T. gondii*	Silver	–	200 nm	–	RH strain	Female BALB/c mice,
Adeyemi et al. (2019)	Prevention and/or elimination of the cystic forms of *T. gondii* in vitro.	Silver, gold, and platinum	–	3–10 nm	–	ME49 strain	HFF cells
Adeyemi et al. (2018)	Anti-tachyzoite activity of metal nanoparticles	Silver, gold, and platinum	–	5–50 nm	–	RH strain	HFF cells
Adeyemi et al. (2017)	Anti-*T. gondii* via changes in redox status and mitochondrial membrane potential	Silver, gold and platinum	–	5–50 nm	–	RH strain	HFF cells
Pissuwan et al. (2007)	Anti-*T. gondii* tachyzoites using nanorad photothermal therapy	Gold nanorod	–	39.5 ± 0.5 nm (length), 20.0 ± 0.1 nm (width)	–	RH strain	Vero cells and U937 line
Teimouri et al. (2018)	Anti-*Toxoplasma* activity of various molecular weights and concentrations of chitosan	Chitosan	–	200–400 nm	–	RH strain	Female BALB/c mice
Gaafar et al. (2014)	Prophylaxis and treatment	Chitosan and silver	–	Chitosan nanoparticles: 93.65 nm. Silver nanoparticles: 6.43 nm	–	RH stain	Male Swiss albino mice

Table 1 (continued)

Author	Purpose	Nanoparticle	Loaded drugs	Size	Zeta potential	*Toxoplasma* strain	Laboratory animals
Khosravi et al. (2020)	Evaluation of mannosylated paromomycin on acute toxoplasmosis	Solid lipid nanoparticles	Parmomycin	246 ± 32 nm	–	RH strain	Vero cells
Azami et al. (2018a)	Nanoemulsion of atovaquone against acute and chronic toxoplasmosis.	Nano emulsion	Atovaquone	20 ± 3 nm	0.074 mV	RH strain, Tehran strain	Female BALB/c mice HeLa cells
Schöler et al. (2001)	Testing the therapeutic efficacy of atovaquone nanosuspensions via intravenous injection.	Nano suspension	Atovaquone	279 ± 7 nm,	–	BK strain, ME49 strain	Mcrophages. Inbred male ICSBP mice
Shubar et al. (2011)	Evaluation the effects of SDS and P188 in the oral bioavailability and uptake of atovaquone nanosuspension	Nano suspension	Atovaquone	440 nm; 469 nm	–	ME49	C57BL/6 mice
Azami et al. (2018b)	Synthesizing curcumin nanoemulsion and test its efficiency on acute and chronic toxoplasmosis	Nano emulsion	Curcumin	215.66 ± 16.8 nm	−29.46 ± 2.65 mV	RH strain, Tehran strain	Female BALB/c mice
Etewa et al. (2018)	Evaluation the effects of spiramycin loaded chitosan nanoparticles in treatment of acute and chronic toxoplasmosis	Chitosan	Spiromycin	60.08 ± 2.009 nm	–	RH strain, ME49 strain	Male Swiss albino mice,
Hagras et al. (2019)	Evaluation the effects of spiramycin loaded chitosan nanoparticles	Chitosan	Spiromycin	385.16 nm	43.8 mV	RH strain	Male Swiss albino mice

concentration of *T. gondii*, and inflammation in the brains of treated mice reduced. (Shubar et al. 2011).

Studies on medicinal plants have been considered for many years (Cowan 1999; Sepulveda-Arias et al. 2014). In a most recent study by Mohammad Rahimi et al. (2020) although there were some cell toxicity effects, the anti-*Toxoplasma* activity of crude aquatic extracts of *M. pulegium* L. and *R. idaeus* L. in an in vitro system showed promising results. Therefore, nanomaterials can use to reduce the toxicity of herbal components. Curcumin is a natural phenolic compound extracted from ground rhizomes of the perennial herb, *Curcuma longa Linnaeus*. Curcumin has provided a broad spectrum of biological and pharmacological activities and its biosafety has been proved. It also possesses anti-oxidant, anti-inflammatory, anti-bacterial, and anti-carcinogenic properties (Yallapu et al. 2015). Despite such phenomenal advances of curcumin in medicinal applications, the efficacy of this potent agent is hindered due to its low bioavailability and absorption (Koide et al. 2002; Yallapu et al. 2015). Azami et al. (2018b) prepared nanoemulsion of curcumin as an herbal medicine for treatment of acute and chronic toxoplasmosis in mice. The authors mentioned that curcumin nanoemulsion showed better results compared to atovaquone-treated mice as positive control group. Treatment of the chronic stage of toxoplasmosis by reducing the number of cysts and their size was the most important finding of the study (Azami et al. 2018b). Besides antibacterial and natural properties, chitosan is widely used in nanotechnology as a drug delivery system. Evaluation of spiramycin-loaded chitosan nanoparticles was conducted in two separated in vivo studies. Efficacy of treatment was assessed using parasitology and histopathology techniques that the findings showed increased anti-parasitic effects of spiramycin on acute and chronic toxoplasmosis in mice (Etewa et al. 2018; Hagras et al. 2019) (Table 1).

Toxicity of nanoparticles

The focuses on nanoparticles have increased over years because of their anti-bacterial, antifungal, antiviral, and anti-parasite potentials. Besides the capacities of nanoparticles as novel delivery system, they may have toxicities and can cause various health problems (Korani et al. 2015). Therefore, evaluation of the biosafety of the studied nanoparticles is necessary.

The cell viability against nanoparticles have usually been studied by tetrazolium-based assays such as MTT, MTS, and WST-1. Different types of cell cultures, including cancer cell lines have been utilized as in vitro toxicity models (Bahadar et al. 2016). In addition, histopathological studies, evaluation the liver functions, and study the physical changes in experimental animal models are recommended to evaluate the toxicities of nanocomponents (Azami et al. 2018a).

Among the metal nanomaterials, anti-*Toxoplasma* activities of silver nanoparticles have been frequently studied. However, the antimicrobial features of silver nanoparticles are related to the release of silver cation, its ability to alter the cell permeability, and production of reactive oxygen species (ROS) (Jin et al. 2010). It is mentioned that silver nanoparticles are ionized in the cells which lead to activation of ion channels, changing the permeability of the cell membrane to both potassium and sodium, interaction with mitochondria, induction of the apoptosis pathways via the production of ROS, and finally cell death (Carlson et al. 2008; Hsin et al. 2008; Kone et al. 1988).

In vivo biosafety assay of silver nanoparticles indicates absorption of the silver components in blood and the brain, and the other organs such as heart and the kidney. Aggregation of smaller nanoparticles may also happen which leads to obstruction of the immune system. It is usually suggested that toxicity of nanoparticles is inversely related to the shape, size, and composition of nanoparticles. In fact, the most biosafety assays are based on the in vitro studies and relatively short-term animal experiments, and there are no many studies to evaluate the toxicity of nanoparticles in the human body. However, due to the importance of human health, more studies are needed in this field (Ge et al. 2014; Korani et al. 2015).

Conclusion

Currently, the most effective treatment for toxoplasmosis is a combination of pyrimethamine plus sulfadiazine, which cause bone marrow suppression, haematological toxicity, and life-threatening allergic reactions. These issues can be overcome by replacing an alternative drug with less side effects, including atovaquone, paromomycin, and spiramycin. It is worth noticing that the mentioned drugs have poor pharmacokinetics and bioavailability. Therefore, a new drug delivery system would be a reliable approach to enhance the therapeutic efficacy, minimize drug dosage, and reduce the side effects. Moreover, the synergistic effect of nanoparticles in combination with anti-parasitic drugs can also be a suitable option to improve the efficacy of conventional drugs. Therefore, more studies (in vitro and in vivo) are needed to approve and improve the applicability of nanoparticles in clinical practices.

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Data availability All generated data from the current study are included in the article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in this study were in accordance with the ethical standards (IR.SBMU.RIGLD.REC.1398.034) released by the Ethical Review Committee of the Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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