Role of Nanotechnology in Treating of Toxoplasma Gondii

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ABSTRACT

Toxoplasma gondii, an intracellular protozoan parasite, poses significant health risks globally, affecting humans and animals alike. Conventional therapies for toxoplasmosis often encounter limitations such as poor bioavailability, drug resistance, and systemic toxicity. Nanotechnology has emerged as a promising avenue in the development of innovative therapeutic strategies, offering enhanced drug delivery, improved efficacy, and targeted action against Toxoplasma gondii. This abstract provides an overview of the role of nanotechnology in combating Toxoplasma gondii infection. Nanoparticle-based drug delivery systems have shown considerable potential in overcoming the drawbacks associated with traditional anti-toxoplasmosis medications. Various nanoformulations, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanomicelles, have been engineered to encapsulate and deliver anti-parasitic agents effectively. Nanocarriers offer several advantages, such as sustained release of drugs, protection of payloads from degradation, increased cellular uptake, and selective targeting of Toxoplasma gondii-infected cells. Additionally, surface modification of nanoparticles enables specific ligand-receptor interactions, facilitating targeted drug delivery to the parasite, thereby reducing off-target effects and enhancing therapeutic efficacy. Moreover, nanotechnology-based diagnostic tools employing nanoparticles have been developed for the sensitive and rapid detection of Toxoplasma gondii antigens or DNA, enabling early diagnosis and timely intervention. Challenges in the application of nanotechnology for toxoplasmosis treatment include scaling up production, ensuring biocompatibility, and addressing potential toxicity concerns associated with nanomaterials. Further research endeavors focusing on refining nanocarrier design, optimizing drug loading and release kinetics, and evaluating long-term safety profiles are crucial for clinical translation. In conclusion, nanotechnology holds immense promise in revolutionizing the management of toxoplasmosis by offering novel therapeutic and diagnostic approaches. The synergy between nanotechnology and anti-toxoplasmosis therapies presents an encouraging pathway towards more efficient, targeted, and safer treatments for combating Toxoplasma gondii infection.

Key words: Nanotechnology, Toxoplasma gondii, drug delivery, nanoparticles, nanoformulations, targeted therapy, diagnosis, anti-parasitic agents, nanocarriers, toxoplasmosis treatment.

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1. INTRODUCTION

Toxoplasma gondii (*T. gondii)* is a protozoan parasite and is widely distributed throughout the world (Dubey 2021; Ismael 2021). *T. gondii* is an obligatory intracellular parasite under the phylum Sporozoa that may cause serious clinical symptoms particularly, in pregnant women and immunocompromised people (Deng et al. 2018). It has three morphological forms includes: trophozoite (Tachyzoites), Tissue cyst (Bradyzoites), and sporozoites which are found within the oocysts. The life cycle of *T. gondii* is complex and has two parts, the first part, is the asexual reproduction which occurs in the intermediate host (such as man and cow), and the sexual reproduction which occurs in the final host (cats and other carnivorous) There are three infectious development stages: tachyzoites, bradyzoites (in tissue cysts), and sporozoites (within oocysts) (Delgado et al. 2022). Toxoplasmosis can be transmitted in many ways such as from mother to baby (Tachyzoites pass to the fetus), by ingestion of infective sporulated oocysts, drinking of undercooked milk, ingestion of undercooked meat, and also can be transmitted sexually (Milne et al. 2020). Congenital toxoplasmosis, which can result in abortion, ocular disease, hydrocephaly, microcephaly, and mental retardation for the fetus, can be brought on by the re-activation of parasites during pregnancy (Elsheikha 2008). Immunocompromised patients may also develop severe diseases, such as encephalitis and pneumonitis. Some psychiatric illnesses such as schizophrenia, depression, and bipolar disorder have been associated with toxoplasmosis (Wang et al. 2017; Liu et al. 2022).

The classical treatment of toxoplasmosis, as usual, is pyrimethamine and sulfadiazine and is usually given with folic acid (Katlama et al. 1996; Dard et al. 2018). The severity of the side effects and the fact that this drug combination is only effective against the tachyzoite form, failing to eradicate latent forms like slow-diverging bradyzoites within tissue cysts, contribute to the low therapeutic adherence of this drug combination (Silva et al. 2021). These drugs have various side effects and can lead to an increase in the level of liver enzymes, an increase of serum creatinine, a decrease in the number of platelets (thrombocytopenia), and suppression of bone marrow (Ben-Harari et al. 2017).

Like other parasites, drug resistance has been observed in this parasite as well (Antczak et al. 2016). Additionally, attempts to develop a new toxoplasmosis vaccine have failed (Foroutan et al. 2019). Nevertheless, we require drugs that are more lethal for all stages of the *Toxoplasma* life cycle, including bradyzoites in tissues and less toxic for the host (Antczak et al. 2016). Now-a-days, there is a rapid development of nanoparticles (NP), and is used throughout the world for the diagnosis, prevention, and treatment of specific types of cells and tissues (Bala et al. 2004). Nanoparticles, serve as a tool for improving pharmacological information like drug release, tissue specificity, and even cell specificity because it can pass blood-brain barriers (Akerman et al. 2002). Nanoparticles are a strong option now for the prevention of most infections including toxoplasmosis, COVID-19, and Hepatitis B virus (Peplow 2021).

Drug crystals have been successfully utilized as nanocarriers in several cases (Sordet et al. 1998; Schöler et al. 2001). Polymer-based NP can be coated with molecules that give them specific surface properties to bind to and be taken up by specific cells, or they can be loaded with drugs that release in a controlled manner. Despite these attractive objectives and 40 years of research, polymeric nanoparticles are not currently being used in pharmaceutical applications (Lherm et al. 1992; Alyautdin et al. 1997; Kreuter 2001). Nanoparticles may be used to deliver medications across the blood–brain barrier (Kayser et al. 2003)

2. NANOTECHNOLOGY AND NANOMATERIALS

Nanotechnology is an advanced technology, which depends on the nanometer scale, usually ranged between 0.1- 100 nm. As a branch of nanotechnology, nanomedicine describes highly specific therapeutic impacts at the nanoscale (Saha 2009). Nanoscale devices are used for the management and treatment of infectious diseases (Freitas 2002). Numerous ingredients, each having a measurement of less than 100 nm, are combined to form nanoparticles (Laurent et al. 2008). The general form indicates

that those substances might have 0, 1, 2, or 3 dimensions (Tiwari et al. 2011). When scientists learned that dimension might influence the material's physiochemical properties, they realized the importance of these substances (Dreaden et al. 2012).

Due to their useful surface reactivity and nanoscale sizes, nanoparticles are used in a wide range of biomedical applications today. Additionally, due to their small size and ability to cross membrane barriers, NPs can produce free radicals that can kill infectious agents (Alajmi et al. 2019). Metal nanoparticles, such as silver and gold, are of particular interest for this purpose because they have bioactivities such as selective inhibition of some enzyme (Venkataraju et al. 2014), antimicrobial (El-Khadragy et al. 2018) and antiparasitic activity (Khan et al. 2013).

2.1 NANOPARTICLES CLASSIFICATION:

Nanoparticles are generally classified into different types depending on their dimension, origin, and materials (Pokropivny and Skorokhod 2007). The first classification depends on the dimension and is classified into four groups including Zero-dimension nanomaterials (0D), One-dimension nanomaterials (1D), Two-dimension nanomaterials (2D), and Three-dimensional nanomaterials (3D) (Zaheer et al. 2022). The second classification depends on their source and is classified into two groups natural and artificial (Kumar and Kumbhat 2016). The last classification is depended on the type of material used to prepare and is classified into four groups: organic, inorganic, Carbon-based, and composite-based (Verma et al. 2003; Jeevanandam et al. 2018).

2.2. ROLE OF NANOMEDICINE IN THE TREATMENT

Nanotechnology is the most effective way to deliver drugs. Because of increasing the solubility area, stability, dissolution rate, and surface of a drug, and by modulating therapy and the permeability of the drug action through absorption into membranes, a drug's bioavailability is increased, which lowers the dosages of the drug that are needed (Wan et al. 2014). Different techniques for creating nanomaterials have been developed, but decrease of chemical has emerged as the most practical technique for creating these kinds of materials (Assolini et al. 2017).

Nanomedicine is the term for the application of nanomaterials in healthcare, and more nanoparticles are being evaluated for use in a variety of diagnostic, therapeutic, and preventive applications. Nanomaterials are defined as organic or inorganic, amorphous or crystalline particles that range in size from tens to hundreds of nanometers (Assolini et al. 2017; Soares et al. 2018). Nanomaterials be arranged as single particles, powders, aggregates, or dispersed in a matrix to create emulsions, suspensions, or nanolayer films. They are much more reactive than larger particles due to their size, which also results in a surface area-to-volume ratio (Gaafar et al. 2014). Due to their propensity to adsorb biomolecules upon coming into contact with biological fluids, colloidal nanoparticles develop a layer on their surface known as the corona. Additionally, due to their size, they can enter cells and react with intracellular molecules. Because of their diversity, nanoparticles are very adaptable (Gaafar et al. 2014).

2.3. NANOMEDICINE FOR TREATMENT OF TOXOPLASMOSIS

Sulfadiazine and pyrimethamine are the two most frequently prescribed medications for treating human toxoplasmosis, and both of them have serious adverse effects that include allergy, and complications with the kidneys and liver (Abou-El-Naga et al. 2017). Several antibiotics and anti-malarial medications have also been used, but they can also have harmful impact (Anand et al. 2015). By changing their pharmacokinetics, the distinct physicochemical properties of nanoparticles can be used to enhance drug delivery. According to Anand et al. (2015), this may lead to slow delivery of drugs, improved target

specificity, increased efficacy, and a decrease in side effects. Using nanotechnology-based methods, drugs that are toxic, poorly soluble, or easily degraded in the gastrointestinal tract can be administered to the body for more effective treatment at lower doses. Both the efficacy of using nanoparticles to deliver current anti-toxoplasmosis treatments and their potential as standalone anti-microbial agents have been studied (Pissuwan et al. 2009; Teimouri et al. 2018).

Chitosan is a natural polysaccharide that has been demonstrated to have antibacterial, antimalarial, and anti-Toxoplasma properties. All sizes of nanoparticles were used to demonstrate anti-*T. gondii* activity in vitro, but low molecular weight nanoparticles killed the exposed tachyzoites faster. In an in vivo model, smaller nanoparticles also worked best. They significantly reduced the load of parasites compared to infected untreated mice, but they were not as effective as sulfadiazine treatment (Etewa et al. 2018).

Spiramycin is a safe drug and is used for toxoplasmosis during pregnancy, but due to its poor bioavailability and unable to cross the blood-brain barrier, it is not very effective. In comparison to spiramycin or chitosan nanoparticles alone, loading spiramycin into chitosan nanoparticles increased its absorption and permeation, extending mice's survival time and lowering parasite burden. The spiramycin-chitosan nanoparticles had a direct impact on the parasites themselves, as evidenced by the reduced inflammatory response to infection in the treated animals and morphological deformities in the parasites that were isolated (Khalil et al. 2013; Hagras et al. 2019). In 2017, a study was done by Abou-El-Naga et al. (2017), who discovered that by giving PLGA nanoparticles in combination with anti-retroviral lopinavi/ritonavir to infected mice can reduce parasitic burden.

Investigations have been done on nanoparticles. The key attributes of NPs are reduced toxicity, alteration of pharmacokinetics, enhanced bioavailability, and the capacity to transport pharmacological components (Khalil et al. 2013; Torres-Sangiao et al. 2016). Because of this capacity, the medicine can be administered directly to the intended target. Till now, the range of available treatments for toxoplasmosis is limited (El-Ashram et al. 2015). These include using antibiotics and anti-malarial medications, both of which frequently have disadvantages like allergies (rashes on the skin) and suppression of bone marrow (Wigginton et al. 2010; Adeyemi and Sulaiman 2015). Therefore, toxoplasmosis is characterized by a significant global burden that is made worse by the limitations of the available therapeutic options (Kamau et al. 2012). These components emphasize the need for improved anti-Toxoplasma medications and/or novel toxoplasmosis treatment methods.

The ideal anti-Toxoplasma medication should be safe, effective, and capable of curing latent infection (Das et al. 2013). According to research, nanoparticles could make up the majority of future biomedical treatment strategies for a variety of diseases as interest in using nanotechnology increases (El-Khadragy et al. 2018). Nanoparticles are currently employed in a wide range of biomedical applications due to their nanoscale dimensions and other advantageous surface reactivity. Additionally, because of their small size and ability to cross membrane barriers, NPs can produce free radicals that can kill infectious agents (Adeyemi et al. 2017). Nanoparticles may also accumulate in tissues, providing cysts in host tissues with a strong foundation (Adeyemi and Sulaiman 2015).

Liposomal carriers played a crucial role in the development of a new strategy for battling protozoans in the 1990s. Stearylamine-bearing liposomes were used for the treatment of RH strain of toxoplasma by Tachibana et al. (1990) both in the laboratory and in live animals during the tachyzoite phase. They discovered that as liposome concentration is decreased, the in vitro viable activity of SA/PC liposomes gradually decreased and had both therapeutic and preventive benefits, according to in vivo results. Elsaid et al. (1999; 2001) investigated the impact of liposomes on toxoplasmosis. They investigated mouse-specific liposomal antigens against *T. gondii*. All mice that were given the *T. gondii* antigen had higher ELISA antibody levels after vaccination, but there was no statistically significant difference between the groups. However, immunization with liposomal-encapsulated total trophozoites and/or tissue cysts antigen and pure tachyzoite antigen (L/pTAg) increased the protective immunity (both

cellular and humoral immune response), likely helping to reduce the transmission of toxoplasmosis and mainly decreased congenital transmission.

A study by Pissuwan et al. (2009) reported gold nanoparticles coated with anti-*T. gondii* antibodies were successful at treating the acute strain of *T. gondii* antigen by using the light of the laser. They came to the conclusion that while a specific laser dose boosted the mortality rate of tachyzoites in the laboratory (in vitro), the mortality rate changed remarkably when the light of laser was utilized as one of the primary methods of production for these materials. In a different study, Kunjachan et al. (2011) compared using Chitosan and silver nanomaterials separately or together to treat toxoplasmosis in experimental animals. Combining them demonstrated a notable decrease in the number of parasites in both the liver and spleen.

Azami et al. (2018) assessed the therapeutic benefits of curcumin nano-emulsion in infected mice with acute and chronic toxoplasmosis. They found that the survival period of mice treated with the emulsion was considerably longer than that of the control group during the acute phase of infection. The emulsion also markedly reduced the mean counts of tachyzoites in the peritoneum of acutely infected mice as compared to control untreated mice. In a separate work, Alajmi et al. (2019) found that the treatment of toxoplasmosis by using silver nanoparticles was more effective than traditional treatments in reducing liver toxicity. According to another study by El-Shafey et al. (2020), by using Curcumin as a treatment for chronic toxoplasmosis in infected rats significantly decreased the mean number of parasite cysts in rats' brains.

A further investigation by El-Shafey et al. (2020) revealed that the use of curcumin for the treatment of chronically infected rats (strain ME49) resulted in a considerable decrease in the mean number of parasite cysts in these rats' brains. Triclosan (TS) and liposomes loaded with triclosan (liposomal-TS) were tested by El-Zawawy et al. (2015) in Swiss albino mice against a potent strain of *T. gondii*. Oral medication was used to treat the intraperitoneal infection. After treatment, tachyzoites load was significantly reduced by both TS and liposomes-TS, but the latter was more efficient. Additional measures like mouse mortality and survivability, morphological modification, and infectivity of tachyzoites from infected mice revealed a similar profile when compared to non-infected mouse controls. The authors concluded that TS's activity in peritoneal fluid and living organisms was prolonged by its longer release phase when it was loaded in liposomal structures.

As previously mentioned, other researchers suggested testing a common medication, like pyrimethamine, after it has been modified by nanotechnology for the therapeutic use of toxoplasmosis. In 2014 a study was done by Pissinate et al. (2014) who compared the effectiveness of PYR-loaded lipid-core nanocapsules and SU-PYR (surfactant prepared) against *T. gondii*. In an in vitro experiment, they used the LLC-MK2 (kidney, Rhesus monkey, Macacamulata) strain. Mice were used in in-vivo experiments by utilizing intraperitoneal injections. Comparative formulations using only LNC (lipid-core nanocapsules) were created.

Selenium is required for good human health. When the body lacks this component, serious symptoms like deficiencies and immune system cognitive deficits may manifest (Shakibaie et al. 2011). Nanostructured materials have a variety of bioactive benefits because of their high surface-to-volume ratios. The fact that they can enter cells more easily than other particles is one of their biomedical benefits (Whanger 2004). Recent studies have demonstrated that SeNPs can stop the growth of several bacterial pathogens, such as *Leishmania* species and *Escherichia coli* (Yang et al. 2009; Kojouri et al. 2012). According to recent studies, these inorganic forms can cause membrane peroxidases to produce oxygen-free radicals like superoxide radicals (Shubar et al. 2011; Mohammadinejad et al. 2019).

Toxoplasmic encephalitis is one of the clinical signs of toxoplasmosis. If the patient doesn't get treatment, it could be fatal. The classical treatments have side effects that can results in allergy and

change in the hematological parameters. To reduce these disadvantages, Shubar et al. (2011) used nanoscale suspensions formed by atovaquone and coated with sodium dodecyl sulfate (SDS) and poloxamer 188 (P188).

A new approach for the treatment of toxoplasmosis had been discovered by Costa et al. (2021) to decrease the disadvantages of the classical treatment and enhance infection control. They discovered that AgNp-Bio, independent of mediators in the chorionic villus, can reduce infection in trophoblast cells and villous explants by inducing inflammatory mediators in the cells. These findings led them to conclude that AgNP-Bio-based treatment is an effective way to treat toxoplasmosis

2.3. TOXICITY AND SAFETY OF NANOMATERIALS

As they can lead to a chronic type of sickness, parasites are thought to be more dangerous to both animals and humans than bacteria (Gupta and Xie 2018). Each stage of development causes a distinct sensitivity to the same medicine, which allows them to survive for years in their environment and with their hosts due to their complicated life cycle stages (Sarangi et al. 2018). Due to their insolubility and short half-life, antiparasitic drugs have an extremely low bioavailability. Important antiparasitic medications like ivermectin and praziquantel, for instance, are more susceptible to enzymatic degradation and have poor cell membrane penetration. As a result, the drug's expected therapeutic effect is not realized and its bioavailability is decreased (Parish 2019). When treating these parasitic infections, doctors and other medical professionals face a significant challenge (Yang et al. 2018). Blind use of antibiotics, which may lead to a big issue is resistance to many antibiotics (Li et al. 2018). According to several researches, chemotherapeutic medicines are often used, which causes bacteria to change and become resistant to conventional medication. Therefore, effective antiparasitic therapy has been made possible by nanomedicine (Kashyap et al. 2018; Sun et al. 2019). There are currently a variety of nanocarriers that can be administered orally, intravenously, or through pulmonary route. Solid lipid nanoparticles, liposomes, and nanocrystals are some examples of these nanocarriers. They offer physical stability as well as targeted and controlled drug release (Adeyemi et al. 2018; Aziz et al. 2021; Jalil et al. 2021).

Because they aren't biodegradable as other substances, such as liposomes or chitosan, and they can accumulate in organs, metal nanoparticles can be harmful. However, according to research done so far, the nanoparticles studied are hazardous to the parasite but not to the host cells both in vitro or in vivo (Park et al. 2013). Due to the pharmacokinetic alterations brought about by packaging these drugs in nanoparticles, lower doses of drugs may still be efficacious. This raises the possibility that this strategy will result in more patient-friendly and side effects-free treatments. However, it is important to recognize that nanoparticles can interfere with pregnancy, which may limit their usefulness (Elsharawy et al. 2020).

3. CONCLUSION

T. gondii is an obligatory opportunistic parasite that affect humans and animals, mainly the immune-compromised patients. More research is needed to develop safe and efficient therapeutic agents due to more adverse effects of the old medication and medication deficiencies. Technological developments on a nanometer scale are referred as nanotechnology. The only physicochemical properties of nanomaterials are their extraordinarily small size, high surface area to mass ratio, and unusual activity. They have enhanced bioavailability and medication delivery.

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