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REVIEW ARTICLE

Targeted Drug Delivery with Green Nanoparticles: A New Frontier in *Toxoplasma gondii* Infection Treatment

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ABSTRACT

Toxoplasmosis caused by the obligate intracellular parasite *Toxoplasma gondii* remains a notable health burden on animals and humans worldwide. Various chemical drugs have been utilized to treat *T. gondii* infections but are noted by low efficacy, high side effects, and high drug resistance. Such limitations necessitate the development of new therapeutic approaches to combat parasitic infections. Targeted drug delivery by nanoparticles (NPs), specifically by green synthesized NPs has been shown to be an effective technique for overcoming these limitations. Various NPs synthesized from different parts of plants, fungi, and bacteria offer better biodegradable, biocompatible, and environmentally friendly alternatives compared to traditional drug carriers. Such bioengineered NPs improve drug solubility, extended circulation time, and improve controlled release of drugs at the site of interest. In addition, they have a potential therapeutic effect because of their inherent physiochemical character with less toxicity. Their drug action can also be augmented through surface modification and functionalization, size and shape engineering, nano-carrier hybridization, gene silencing, and combination therapy. Targeted drug delivery using green synthesized NPs opens up a new avenue in *T. gondii* treatment towards the development of safer and more environmentally friendly therapeutic approaches.

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INTRODUCTION

Toxoplasma (T) gondii is an obligate intracellular protozoan parasite and have significant global importance (Adem and Ame, 2023). The life cycle of *T. gondii* is very complex and have both sexual and asexual reproduction (Tong *et al.*, 2021; Chen *et al.*, 2022). Felids including domestic and wild cats are served as definitive host where sexual reproduction occurs while it completes its asexual stages (tachyzoites and bradyzoites) in intermediate host that include humans, and a wide range of warm-blooded animals (Gubbels *et al.*, 2020; Gissot, 2022). This infectious parasite is infecting one third of the human population, but clinical toxoplasmosis happens relatively occasional, presenting a limited incidence despite its widespread nature (Dubey, 2021; Delgado *et al.*, 2022). The disease can occur in humans through the consumption of unprocessed or undercooked meat containing tissue cysts from intermediate hosts (Al-Biatee, 2024). Additionally, it can spread by ingesting food or water contaminated with oocysts shed by definitive hosts (Negesa and Kebede, 2024).

The control of *T. gondii* infections in the host body is mediated by the combination of innate and adaptive immune responses (Rovira-Diaz *et al.*, 2022; Sana *et al.*, 2022). The innate immune responses start when parasite recognition receptors i.e., toll-like receptors (TLRs) and NOD-like receptors (NLRs) present on macrophages and dendritic cells recognizes the pathogen-associated molecular patterns (PRRs) (Sasai and Yamamoto, 2022). These cells in return produce interleukin-12 (IL-12) and tumor necrosis factor-alpha (TNF-α) collectively known as pro-inflammatory cytokines. IL-12 and TNF-α both increase the production of interferon-gamma (IFN-γ) and nitric oxide (Mahmoudzadeh *et al.*, 2021). Nitric oxide and interferon are very essential to inhibit the replication and reproduction of parasites (Damasceno-Sá *et al.*, 2021; Ihara and Yamamoto, 2024). T cells (CD4+ and CD8+) are also stimulated by *T. gondii* infections which leads to the activation of adaptive immune response (Gao *et al.*, 2021). IFN-γ is produced by CD4+, and it activates macrophages which then generates more nitric oxide and TNF-α (Ferreira *et al.*, 2023). CD8+ T lymphocytes recognize antigenic peptides and cause direct elimination

of infected cells presented by major histocompatibility complex class-1 (MCH-1) molecules present on the surface of the target cells, and this subsequently initiates apoptosis (García-López *et al.*, 2024). B cells that are also involved in the production of antibodies also aid in the neutralization of rapidly dividing tachyzoites because the control of tachyzoites and bradyzoites relies heavily on the production of IFN-γ (Sasai and Yamamoto, 2019). Despite the natural defense mechanisms such as cytokine modulation and inhibition of apoptosis, the effective control of *T. gondii* infections often necessitates external therapeutic interventions to mitigate the severity of the disease.

Various chemical drugs, including pyrimethamine, sulfadiazine, clindamycin, spiramycin, and azithromycin, have been used to control toxoplasmosis (Rodriguez and Szajnman, 2023). The combination of these drugs has also been tried, but they are not used fearlessly due to the development of resistance and other eco-toxic threats (Shammaa *et al.*, 2021; Sharma *et al.*, 2021; Mohsin *et al.*, 2024; Yang *et al.*, 2024). Furthermore, these drugs are effective against tachyzoites but fail to show promising results against the latent form, i.e., bradyzoites within tissue cysts (Smith *et al.*, 2022). Similarly, vaccines were helpful in reducing congenital transmission of the parasite and severe *Toxoplasma* infections in livestock by inducing long-lasting immunity (Yu *et al.*, 2021). Vaccines also minimize oocyst shedding, therefore decreasing environmental contamination and zoonotic transmission (Yu *et al.*, 2022). However, due to variations in the life stages of *T. gondii*, improper handling, and limited shelf life, it has not been used as a potential drug to control infections (Chu and Quan, 2021; Yu *et al.*, 2021; Zhang *et al.*, 2023b). So, scientists have diverted their attention towards innovative and targeted alternatives that are safe and more precise for effective control of toxoplasmosis. Nanotechnology has brought new ways to treat infections by utilizing nanoparticles to deliver drugs to specific targets (Ambrose *et al.*, 2025). Various studies have confirmed their effective potential against bacterial, viral, and parasitic diseases (Asghar *et al.*, 2024; Hamidzade *et al.*, 2024; Mustafa *et al.*, 2024; Imdad *et al.*, 2025).

Nanoparticles (NPs) have very small sizes and vary between the ranges of 1-100nm (Prakash *et al.*, 2020). They are in the two or three-dimensional aspects and due to their tiny sizes, they may or may not have unique size and shape-related properties (Ulusoy, 2023; Rukh *et al.*, 2024). NPs have the potential to revolutionize a great series of medical and biotechnological tools and procedures for new techniques so that they are portable, safer, cheaper, and easier to administer (Joseph *et al.*, 2023). NPs vary from their bulk counterparts in size, chemical reactivity, mobility, and energy absorption (Joudeh and Linke, 2022). Their size, shape, and surface area are dependent on the synthesis approach, parent material employed, and experimental conditions (Kumar *et al.*, 2022). Types of NPs include metallic NPs (Shah *et al.*, 2024), polymeric NPs (Jeong *et al.*, 2024), carbon quantum dots (Karimi *et al.*, 2024), liposomes (Jaikishan *et al.*, 2024), and magnetic NPs (Zeleňáková *et al.*, 2024) have been employed over the years. They can also be classified on the basis of their synthesis method. For example, various metallic NPs are synthesized from plants and microbes and are hence known as green-synthesized NPs (Pechyen *et al.*, 2024). This review article elaborated on the synthesis of plant-derived NPs, their properties, and their specific mode of action as drug delivery agents against *T. gondii*. Moreover, it describes the specific mode of action against *T. gondii* function at different cellular levels to inhibit its growth and cause mortality.

Synthesis of green NPs: Particles in dimensions of nanometers from 1-100 are engineered NPs that can be green synthesized (Rasool *et al.*, 2024). The particles thus formed are highly environmentally friendly because they entail biological systems or processes like that of biosynthesis (El-Sayyad *et al.*, 2024). During chemical synthesis, most of the time toxic reagents are used and introduced into environmental hazards accompanied by them (Banjara *et al.*, 2024). Green synthesis capitalizes on plant extracts and microbial systems through the employment of the natural reducing and stabilizing agents of such biological systems to synthesize NPs. Leaves, roots, and seeds of different plants are employed to synthesize green NP (Sheta *et al.*, 2024). Phytochemicals in these plant extracts, such as flavonoids, phenolic, alkaloids, and terpenes, serve as effective reducing agents that reduce metal ions into NPs (Kaur *et al.*, 2024). In one of the studies, it was confirmed that silver NPs (AgNPs) can be synthesized by reducing silver ions in a solution using extracts from plants such as Aloe vera or green tea (Sudhimon *et al.*, 2024). Similarly, the extracts from *Aloe vera* and *Moringa oleifera* can be utilized to synthesize silver NPs (Abdellatif *et al.*, 2024). Pomegranate fruit extract or banana peels are employed to synthesize Gold NPs (Serdar, 2024, whereas root extracts of *Cassia auriculata* are employed to synthesize zinc oxide NPs (Almuhayawi *et al.*, 2024). These processes not only yield biocompatible NPs but also yield control over size and morphology of the NPs, which become relevant in medical and agricultural applications (Abdel-Wahab *et al.*, 2024).

Aside from plants, many other microbes have also recently been found to have potential in nanoparticle synthesis (Alsaiari *et al.*, 2023). Some of the microorganisms utilized in NPs synthesizing include: bacteria and fungi (Tijani *et al.*, 2024). These fungi and bacteria could potentially have the deposition of metal ions in their structures (Verma *et al.*, 2024a). For instance, *Escherichia coli* or *Bacillus subtilis* cultures can be used to synthesize silver and gold NPs through intracellular and extracellular reduction of metal ions (Khan *et al.*, 2024). *Aspergillus niger* proves to be efficient for titanium oxide NPs preparation owing to secretion of enzymes (Abd El Hamid *et al.*, 2024). Moreover, secondary metabolites existing in the alga serve as reducing agents during the synthesis of various NPs. For instance, the production of copper NPs has been achieved with the assistance of green algae like *Chlorella vulgaris* (Mukherjee *et al.*, 2021). Microbial approach is advantageous with the ease of scalability along with the possibility of fabricating any NPs with specified properties (Behera *et al.*, 2024). Biogenic NPs prepared in these research works have enormous applications in industries and have been found widely in nanomedicine to serve as delivery drugs for the treatment of tumors

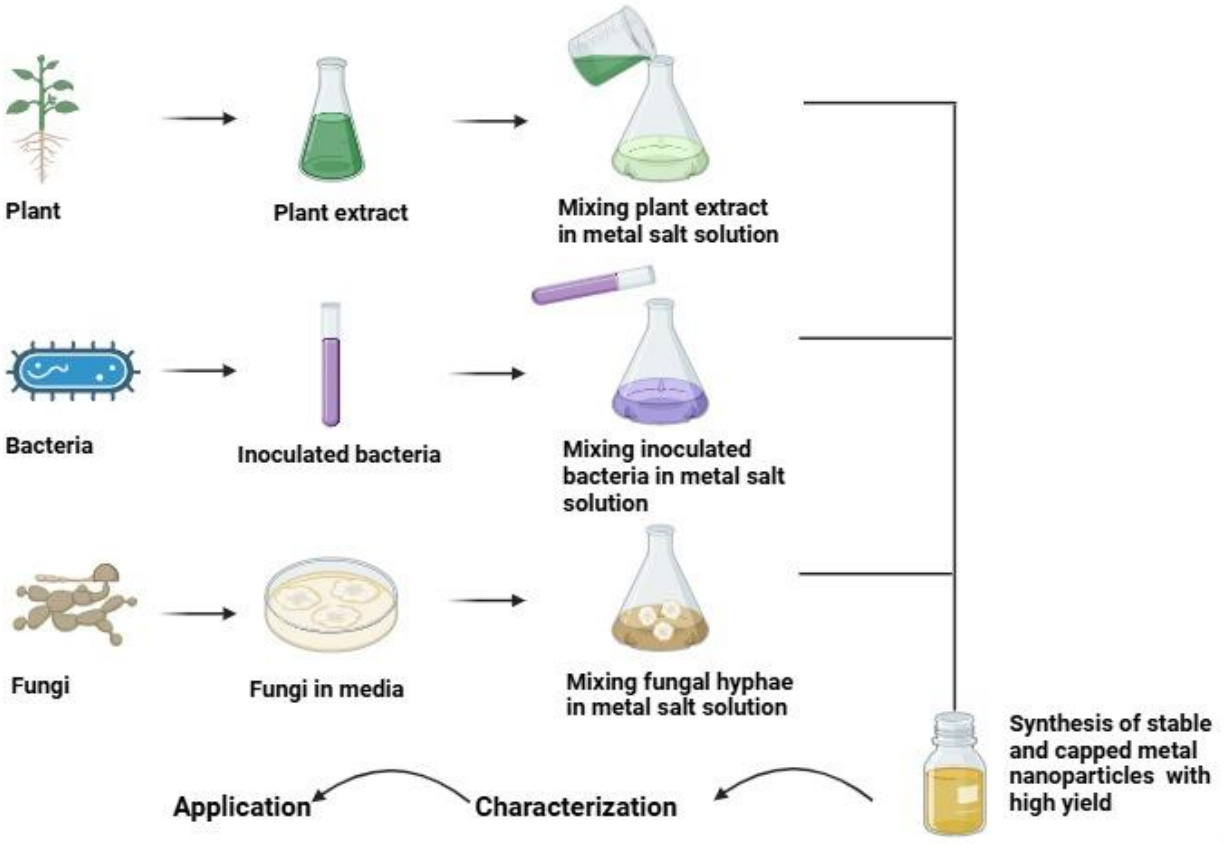

Fig.1: Synthesis of green NPs from plants, bacteria, and fungi as natural reducing and stabilizing agents for eco-friendly and biomedical application (www.Biorender.com).

(Ambrose *et al.*, 2025) and other antiviral, antibacterial, and anti-parasitic infections (Murugappan *et al.*, 2024; Zakir *et al.*, 2024; Abbas *et al.*, 2025). Fig. 1 shows the synthesis of green NPs from plants, microbes, and fungi.

Factors influencing the synthesis of green NPs: The synthesis of NPs is controlled by different factors that endow them with their physiochemical properties, such as size, shape, charge, surface area, and stability (Joudeh and Linke, 2022). For green NPs, the principal sources are plant extract, microbes, and biological molecules like polysaccharides and proteins (Jeevanandam *et al.*, 2022). Phytochemicals present in plant extracts, like flavonoids, alkaloids, polyphenols, and terpenes, function as reducing and stabilizing agents (Singh, 2022). The plant extract composition differs among plant species, which influences the quality of synthesized NPs. Additionally, the biological source plays a crucial role in such a way that increased concentrations may lead to a faster reduction of metal ions but can result in aggregation and irregular NP formation (Rana *et al.*, 2020).

Other parameters, including pH, temperature, reaction time, and the concentration of metal ions, have significant importance in green NP synthesis (Vijayaraghavan and Ashokkumar, 2017; Manosalva *et al.*, 2019). The pH results in the ionization of functional groups of biomolecules, changing their ability to stabilize NPs (Chatterjee *et al.*, 2022). Similarly, a rise in temperature can increase the kinetic energy of the molecules, leading to the production of more uniform particles (Arya *et al.*, 2021). Further, the reaction time determines the completion of the synthesis process. Inadequate timing may result in incomplete reduction while over time might result in NP aggregation (Shaba *et al.*, 2021). The concentration and type of metal salt or precursor also control the stability and yield of NPs (Gupta and Mao, 2021). The fine-tuning of these parameters is necessary for developing green synthesized NPs with responsible properties for anti-parasitic activities and drug delivery. Several other factors influencing morphological and physiochemical characteristics are elaborated in Fig. 2.

Role and mechanism of green synthesized NPs in drug delivery: Green synthesized NPs obtained from plants and microbes hold a significant role in drug delivery applications especially in the field like infectious disease control and parasitic infection (Noah and Ndangili, 2022). Their small dimensions allow the crossing of biological barriers and the delivery of drugs directly to target cells (Liu *et al.*, 2024). The surface of green synthesized NPs can also be modified for the attachment of specific biomolecules that can target these NPs to diseased cells (Georgeous *et al.*, 2024). For example, silver NPs obtained from plants are particularly intriguing due to their unique characteristics. One of the most captivating properties of AgNPs is their potential for antimicrobial activity. Their large surface area-to-volume ratio allows them to interact with a greater number of bacterial cells (Aliero *et al.*, 2025). Perhaps AgNPs have been suggested to directly act by interacting with the parasitic and bacterial cell walls and disrupting the integrity of these cells, which would cause leakage of their internal contents

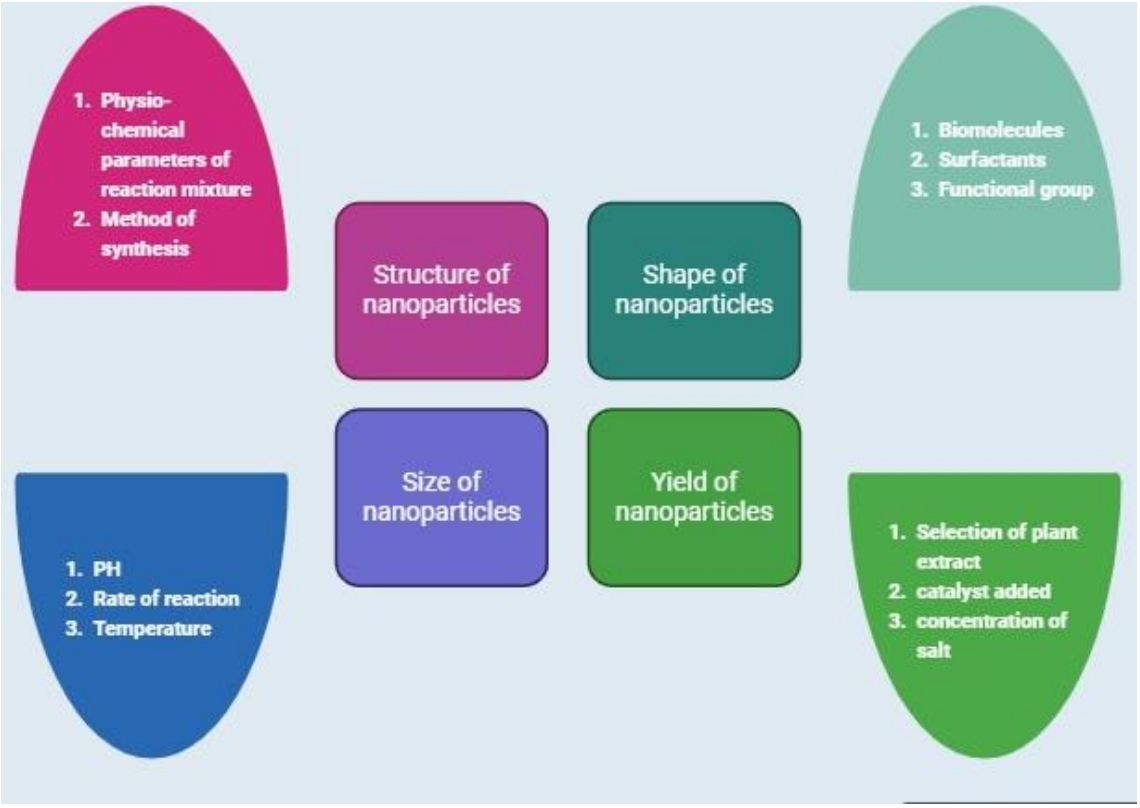

Fig. 2: Various factors affecting the size, structure, shape, and yield of green NPs (www.canva.com).

(Barua and Buragohain, 2024). Whether or not AgNPs generate reactive oxygen species (ROS) inside these cells, oxidative stress and final cell death can occur. Such prominent anti-parasitic and antibacterial activity makes NPs revolutionary for new or more efficient drug development and drug delivery systems in the field of medicine (Murugappan *et al.*, 2024). This way of delivering drugs has the potential to increase the effectiveness of the drug while minimizing side effects for healthy tissues.

The unique optical properties of various metallic NPs that are synthesized from plants can also be utilized for drug delivery (Shiraz *et al.*, 2024). Light-responsive green NPs can be planned so that they will release their drug bound to them upon exposure to specific wavelengths of light, providing a very high degree of control over drug release ability (Pare *et al.*, 2024). They are very effective as drug delivery vehicles owing to their unique physicochemical properties. The tiny size of NPs enables them to penetrate tissues and be internalized by cells very readily and their huge surface area to volume ratio increases drug loading compared to other systems (Sahin *et al.*, 2024). Surface modifications like conjugation with targeting ligands or immobilizing them on polymers such as polyethylene glycol (PEG) render them biocompatible while extending circulation time and enabling the application of targeted drug delivery (Verma *et al.*, 2024b). Green synthesized NPs possess great benefits over traditionally synthesized NPs due to their eco-friendly, cost-effective, improved stability, extended circulation time, and biocompatible nature (Banjara *et al.*, 2024; İpek *et al.*, 2024). Fig. 3 highlights several key mechanisms, which are explored in detail in the following section.

Enhanced cellular internalization: Green NPs, because of their small size, high surface area, and favorable charge, can penetrate the host cell through a process known as endocytosis (Peng *et al.*, 2024). These properties allow the NPs to cross the cellular membranes and target the organelles where the *T. gondii* parasite resides (Alsharedeh *et al.*, 2024). Once NPs reach the target site, they release their drug payloads in a precise manner. Many green synthesized NPs are positively charged because of their natural polymers, like chitosan that enable them to bind strongly with the negatively charged membrane, which results in adhesion and internalization (Hanafy, 2025). Similarly, chemical components of plant extracts present on the surface of NPs enhance the compatibility and receptor targeting in parasitic-infected host cells (Mahmoud *et al.*, 2025). Binding NPs with ligands or antibodies can give targeted drug delivery at *T. gondii* infected cells, helping to recognize specific markers present in the infected cells. Drugs or therapeutic agents are released directly into the cytoplasm or Parasitophorous vacuole of the infected host cell once they enter it as they can escape endosomes (Brito *et al.*, 2023). They provide better drug delivery concentration at a specific site with no harm and toxicity to surrounding cells. Zinc and silver NPs obtained from plant extracts or polymeric NPs, for instance, provided enhanced biocompatibility and target drug delivery within the cell that was infected by *T. gondii* (Cheraghipour *et al.*, 2023). Green synthesized NPs are not only renowned for their therapeutic effects but they also can reduce drug resistance and off-target effects. CuNPs obtained from the green synthesis are not only used as targeted drug delivery but are used to treat resistant parasitic infections and tumor cells (Krishna *et al.*, 2024).

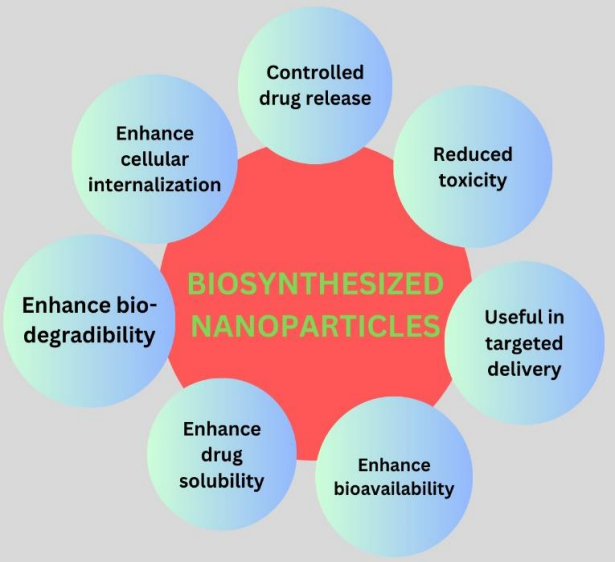

Fig. 3: Potentials of green synthesized NPs as drug delivery agents.

Controlled drug release: Synthesis of green NPs imparts unique properties to NPs, and they act as nanocarriers for controlled drug release. These NPs are designed and prepared with particular mechanisms (stimuli-responsive) that allow drugs to be released under specific conditions (Herdiana *et al.*, 2022; Naghib *et al*., 2024). For example, NPs prepared by stimuli-responsive mechanisms remain stable at the physiological pH of the healthy tissue, but in an acidic environment, they degrade themselves (İlgar *et al.*, 2022). This controlled degradation is very effective in releasing encapsulated or surface-bound drugs into the infected cells, hence increasing the therapeutic potential and reducing collateral damage to healthy tissues (Zeb *et al.*, 2022). Chitosan and plant-based materials facilitate pH-sensitive behavior and biocompatibility (Iqbal *et al.*, 2023; Felicia *et al.*, 2024). In addition to this green NPs also facilitate sustained drug delivery which ensures a prolonged therapeutic effect. The encapsulation of the biodegradable matrix of the plants makes NPs release the drug through matrix diffusion and degrade slowly with time (Mondéjar-López *et al.*, 2024). This sustained release benefits in two ways. Firstly, it maintains the effective drug concentration at the target site and secondly, it avoids multiple dosing hence improving patient compliance. Plant-synthesized polymeric NPs can carry clindamycin or pyrimethamine, ensuring their constant release within the parasitic infected tissues (Wani *et al.*, 2021).

Enhanced drug solubility and bioavailability: Green synthesizes NPs have to potential for solubility and bioavailability of the drugs for poorly soluble and hydrophobic therapeutic agents (Bhalani *et al.*, 2022). Various chemical drugs used to treat toxoplasmosis in humans and other animals are not soluble in water (Hajj *et al.*, 2021). To get better results and to make them more soluble for effective treatment, NPs are coated with some plant materials that enhance the solubility of the drugs at the tissue level because every tissue has water in its compartments (Xu *et al.*, 2021). This is useful in oral administration and systemic treatment where drug bioavailability is a key challenge. For example, selenium and AgNPs, when blended with the plant extract of *Punica granatum*, enhanced their solubility and bioavailability against *Hemonchus contortus* infections (Kaiaty *et al.*, 2023).

Enhanced biodegradability and reduced toxicity: Chemically and physically synthesized NPs, when used for drug delivery, may accumulate inside the cells after delivering drugs and can cause long-term toxicity (Anwar *et al.*, 2021). On the other hand, green synthesized NPs are synthesized in such a way that after delivering drugs, they degrade easily and are converted into non-toxic byproducts (Soni *et al.*, 2021)**.** It reduces the risk of NP accumulation in the body, which is important for long-term or repeated drug treatments. Furthermore, the natural synthesis of these NPs ensures their biocompatibility, reducing the risk of immune reactions and toxicity (Mehnath *et al.*, 2021). In one of the research studies, it was confirmed that silver NPs obtained from *Azadirachta indica* leaves, when targeted at specific sites, degrade easily without being toxic to healthy tissues. These make green synthesized NPs a safer alternative in the drug delivery system for immunocompromised patients who are at high risk of toxoplasmosis (Nemati *et al.*, 2022).

Mechanism of action of green synthesized NPs against *T. gondii:* Green synthesized NPs provide an innovative and sustainable approach to controlling the *T. gondii* parasite, the major cause of toxoplasmosis (Cheraghipour *et al.*, 2023). Their mechanism of action against *T. gondii* relies on plant extracts and their bioactive molecules that enhance their antiparasitic potential (Arrighi *et al.*, 2023). They control the *T. gondii* by producing ROS inside the cytoplasm of the infected host cell, damaging to parasitophorous vacuole, inhibiting cell signaling and metabolic pathways, enhancing host immune response, disrupting biofilms, and preventing of adhesion of parasite to host membrane (Arrighi *et al.*, 2023; Majeed *et al.*, 2024; Shim and Youn, 2024). Fig. 4 highlights the main strategies for controlling *T. gondii* with some important points explained and described below.

Production of ROS and inhibition of parasitic adhesion: Green-synthesized NPs are very important for their biological and therapeutic actions. The bioactive compounds or substances present on the surface of green NPs can interact with oxygen and produce superoxide ions (O^{-1}), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^{-1}) (da Silva Sanfelice *et al.*, 2022). These substances or radicals are collectively known as ROS and interact with the lipid present in the cellular membrane of *T. gondii* and cause lipid peroxidation (Green-Ross, 2023). The peroxidation process destabilizes the cellular membrane, creates pores inside it, and results in the leakage of essential intracellular components and ions. This in return disturbs the homeostasis mechanism of the parasite (Zheng *et al.*, 2024). Furthermore, these ROS have the potential to oxidize proteins of the *T. gondii* and impair enzymes to take part in metabolic pathways including cellular respiration, hence denaturing structural proteins which are very important for the cytoskeleton formation and its associated structures (Li *et al.*, 2023). The production of ROS and impaired metabolic pathways

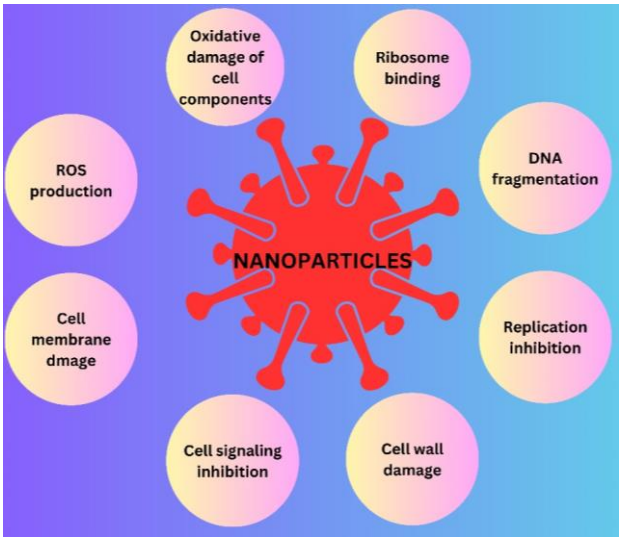

Fig. 4: Various processes carried by green synthesized NPs against *T. gondii*

change the shape of the parasite and block its invasion into the host cell (Zhang *et al.*, 2023a). Sometimes, when *T. gondii* is invaded due to the changed structure, it does not proliferate inside the host cell, hence reproduction blocks. Additionally, the ROS penetrates the nucleus of the parasites and causes DNA denaturation by breaking DNA strands, base modifications, and replication errors, which trigger apoptosis and cause hindrance in the reproduction of the parasite (Haldar *et al.*, 2024). The bioactive molecules that are present in green synthesized NPs, such as flavonoids and polyphenols, further enhance the production of ROS and increase oxidative stress (Balkrishna *et al.*, 2021). All these mechanisms, when combined, create a conducive environment for the *T. gondii* and eliminate the infection. The outer membrane of tachyzoites contains surface proteins that facilitate the attachment with the host cell membrane. NPs also interact with the protein membranes of tachyzoites by creating electrostatic forces and altering their anatomy and physiology. These will bring about the attenuation of the parasites' affinity to bind with the host's membrane (Thomas and Latha, 2023). Production of ROS and suppression of adhesion allow the green NPs to be effective tools for modulating toxoplasmosis as shown in Fig. 5.

Damage to Parasitophorous vacuole: The vacuolar membrane is disrupted by creating invaginations of green synthesized NPs into the Parasitophorous vacuole (PV) (Marques-Santos *et al.*, 2024). PV is a unique compartment constructed by the parasite in the infected host cell from the lysosomal enzymes and host immune response. It serves as a selective barrier for vital nutrients such as glucose, lipids, and amino acids essential for parasite survival in the host cell (De Santis *et al.*, 2015). The entry of cytotoxic substances into the vacuolar space is mediated through disruption of the PV membrane and causes the immobilization of the parasites. The bioactive phytoconstituents found in the green synthesized NPs, such as polyphenols and flavonoids, are responsible for interaction with the phospholipid-rich PV membrane of *T. gondii* (Olajide and Cai, 2020). Moreover, the presence of phospholipids makes the PV membrane slightly negative, and it increases its binding affinity for the positively charged NPs. Moreover, some parasitic-releasing proteins are also secreted by the PV membrane is which are referred to as dense granule proteins (GRAs). Pores are formed throughout the membrane, which destabilizes it due to the capacity of the NPs to interact with the phospholipids and GRAs of the PV membrane (Olajide and Cai, 2020). *T. gondii* is therefore destroyed by the exposure of the protective environment to lysozymes, which are critical for the breakdown of cellular debris and pathogens that then target *T. gondii*, resulting in its death. Some parasitic enzymes and proteins are also leaked due to the disruption of the PV membrane, which leads to self-digestion of the *T. gondii* (Olajide and Cai, 2020). After disruption, the antigens of *T. gondii* are exposed, and they interact with the immune system of the host, triggering the production of macrophages and cytotoxic T cells and leading to the elimination of the parasite. During all these processes, the overall internal integrity of the parasite is also compromised, impairing its growth and reproduction. The exact mechanism is described in Fig. 6.

Modulation of host immune response: Green synthesized NPs modulation of host immune response is a crucial role in the elimination of the *T. gondii* parasite (Cheraghipour *et al.*, 2023). These green NPs, owing to their bioactive molecules such as polyphenols, alkaloids, terpenes, and flavonoids, can get attached to the negatively charged membranes of macrophages and dendritic cells and initiate innate and adaptive immune responses (Ahamad *et al.*, 2021). They can also interact with immune cells because of their functional groups like hydroxyl (OH^-) and carboxyl ($COOH^-$) on their surface. Some rod and star-shaped green NPs can have immunostimulatory molecules like proteins, polysaccharides, and secondary metabolites that directly stimulate the macrophages and dendritic cells (Hu *et al.*, 2023). When NPs are engulfed by the immune cells, they engage with the endosomal TLRs and trigger an immune response (Zhi *et al.*, 2023). The phagocytic function of activated macrophages increases against *T. gondii*. Activated dendritic cells activate *T. gondii* antigens and trigger the adaptive immune response. Cytokine production such while IL-12 and IFN-γ has also been initiated which in turn activates the natural killer (NK) cells and IFN-γ against *T. gondii* (Sana *et al.*, 2022). Furthermore, NPs also cause the immune cells to produce ROS and nitric oxide that is highly toxic to the cellular compartments and promotes parasitic elimination (Palomino-Cano *et al.*, 2024). Green NPs also activate the nuclear factor-kappa B (NF-kB) of immune cells that are involved in the transcription of genes involved in the immune responses (Liu *et al.*, 2021). Mitogen-activated protein kinase (MAPK) involved in cell signaling is also activated by green NPs that lead to the production of inflammatory mediators. In addition, these NPs can also cause M1 polarization of macrophages that leads to parasitic killing, inflammation, and recruitment of the immune cells (Zhao *et al.*, 2023). Some NPs due to their composition promote M2 polarization that increases tissue repair and resolute inflammation (Azadpour *et al.*, 2021). Modulation of host immune response is shown in Fig. 7 and various plant derived NPs that are used against *T. gondii* are mentioned in Table 1.

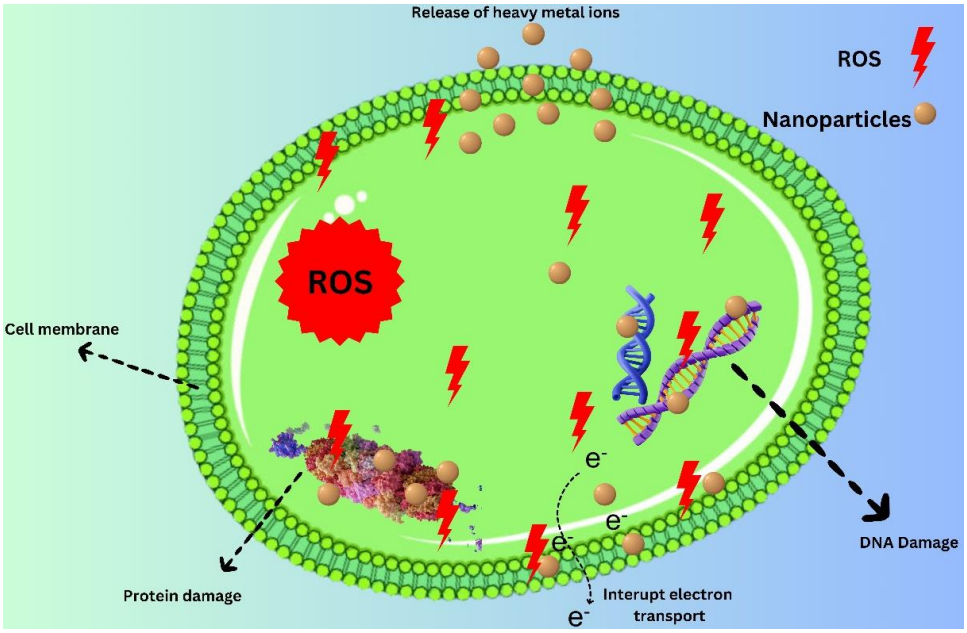

Fig. 5: Production of ROS and damage of cell by green synthesized NPs against *T. gondii* infected cell.

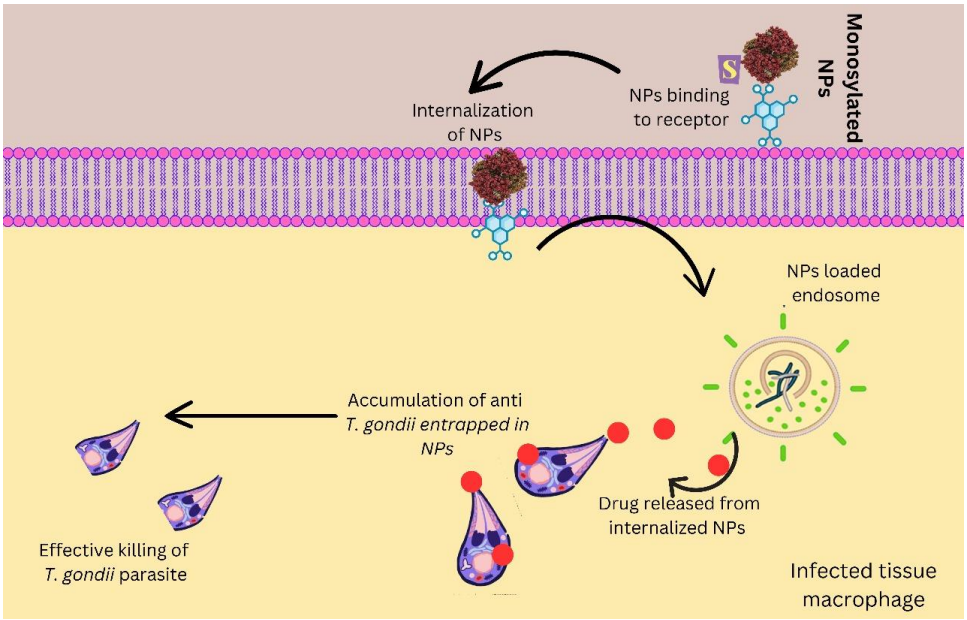

Fig. 6: Binding of green synthesized NPs to surface receptors, their internalization, and controlled release against *T. gondii.*

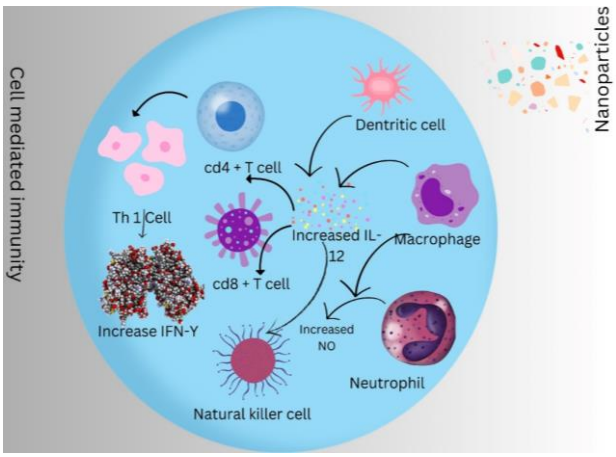

Fig. 7: Modulation of host immune response by green synthesized NPs.

Future directions: Green synthesized NPs offer a promising, non-toxic, and eco-friendly approach for drug delivery against *T. gondii* before addressing the drawbacks of conventional therapies. However, their efficiency can further be enhanced through the adoption of advanced methodologies and strategic combinations. Future research should focus on increasing cyst-specific targeting, optimizing biocompatibility, and exploring their potential in nano-vaccine development. The production of improved targeting mechanisms is a critical future direction for enhancing the efficiency of green synthesized NPs against *T. gondii*. NPs with appropriate surface ligands and specific antibodies for infected cells would provide targeted delivery of the therapeutic agent along with minimizing the side effects on healthy tissue. Scientists are developing stimuli-responsive NPs to deliver therapeutic drugs based on parasite intracellular response, including its pH, ion levels, and enzymatic activity. Nanotechnologists should focus and design new NPs that can penetrate the cyst wall and provide effective anti-*T. gondii* therapy. Similarly, combinations of advanced NPs with novel therapeutic agents could safely lyse tissue cysts, excluding the possibility of reactivation in immunocompromised individuals. Co-loading NPs with therapeutic molecules or immunostimulant molecules

Table 1: Various green synthesized NPs were used against *Toxoplasma gondii*

Plant name	Plant part	Extraction method	Nano-particles (NPs)	Synthesis method	Dose	Duration of the dose	Shape of NPs	Size of NPs	Form of the parasite	Animal model	Key finding	References
Lupines arcticus	Aerial parts	Percolation method	Copper NPs	Precipitation	5-10 mg/ Kg	Two weeks	Circular shape	10-85 nm	Tachyzoites	Mice	↓Number and size of oocyst, ↓Oxidative stress ↑Cytokines production ↓ Toxicity	(Alanazi and Alnomasy, 2023)
Phoenix dactylifer	Seeds	Aqueous extraction	Silver NPs	Reduction	100 mg/ kg	Two weeks	The majority are Irregular but some are spherical	13.2 - 22.8 nm	Adults and tachyzoites	Mice	↑Liver function enzymes (AST, ALT), ↑Nitric oxide (NO) level. ↓Superoxide dismutase (SOD) and catalase (CAT)	(Alajmi *et al.*, 2019)
Ziziphus spina-christi	Leaves	Methanolic extraction	Silver NPs	Reduction	100 mg/ kg	Two weeks	The majority are Irregular but some are spherical	13.2 - 22.8 nm	Adults and tachyzoites	Mice	↑Liver function enzymes (AST, ALT), ↑Nitric oxide (NO) level. ↓Superoxide dismutase (SOD) and catalase (CAT)	(Alajmi *et al.*, 2019)
Capparis spinosa	Dried fruits	Percolation method	Copper NPs	Biogenic	2-4 mg/ kg	14 days	Spherical	17-41 nm	Bradyzoites and tachyzoites	Mice	↓*T. gondii* tissue cysts, ↑level of interleukins-12(IL-12), interferons γ (IFN-γ), and NO levels	(Albalawi *et al.*, 2021)
Lupines arcticus	Arial parts	Percolation technique	Silver NPs	Biogenic	20 mg/ kg	14 days	Spherical	25-90 nm	Bradyzoites and tachyzoites	Mice	↓Size and number of tissue cysts, ↓Oxidative stress and oxidative factors	(Majeed *et al.*, 2024)
Lavandula angustifolia	Aerial parts	Percolation method	Zinc NPs	Microwave assisted	32.5, 75, and 150 mg/ kg	14 days	Spherical	30-80 nm	Brain tissue cysts of *T. gondii*	Mice	↓Brain tissue cysts, ↑IFN-γ), ↓ROS ↓ NO	(Saadatmand *et al.*, 2021)
Zingiber officinale	Stem	Ethanolic extraction	Zinc oxide	Biogenic	10 mg/ kg	14 days	Non-spherical	17.45 nm	Tachyzoites	Mice	Distortion of tachyzoites, ↓ALT and AST ↓NO, ↑ CAT	(El-Kady *et al.*, 2023)
Phoenix dactylifer	Fruits	Aqueous and Methanolic extraction	Selenium NPs	Biogenic	-	14 days	Spherical with no aggregation	40-42.5 nm	Tachyzoites and bradyzoites	Murine	↓ Tissue cysts, IL-4, IL-10, and IFN-γ	(Wakid *et al.*, 2023)
Eugenol	Liquid	-	Zinc oxide NPs	Chemical method	200 µg/mL	14 days	Spherical	96.5 nm	Spleen, liver, and peritoneal tissue Tachyzoites	Cells from infected tissue, mice	↓Tachyzoites up to 56.3%, less toxic	(Cheraghipour *et al.*, 2023)
Streptomyces fulvissimus	Bacterial culture	-	Selenium NPs	Microbial biosynthesis or reduction	-	15 days	Spherical	2-10 nm	Tachyzoites	Mice	Deterioration of tachyzoites, excessive vacuolization, and lysis of cytoplasm	(Arafa *et al.*, 2023)
Cinnamon zeylanicum	Essential oil	Hydrodistillation	Selenium NPs	Biogenic method	1-100 µg/ mL	-	Spherical	365 nm	Tachyzoites	Cultural cell lines	Killed tachyzoites up to 85% with low toxicity	(Mottaghi *et al.*, 2024)
Moringa oleifera	Essential oil	Hydrodistillation	Selenium NPs	Biogenic method	1-100 µg/ mL	-	Spherical with rounded edges	411 nm	Tachyzoites	Cultural cell line from infected tissues	Killed tachyzoites up to 90%	(Mottaghi *et al.*, 2024)
Sambucus ebulus	Fruits	Methanol based	Silver NPs	Biogenic	40 mg/	5 days (*In vitro*)	Spherical and oval	35-50	Vero cell lines,	Vero cell lines from	↓Cell viability, ↓Proliferation	(Hematizadeh *et al.*, 2023)

		maceration			kg	and 14 days *in vivo*		nm	tachyzoites	infected tissues (*In vitro*) and mice (*in vivo*)	index, ↓ *T. gondii* infection	
Feijoa sellowiana	Fruits	Methanol based maceration	Silver NPs	Biogenic	40 mg/ kg	5 days (*In vitro*) and 14 days *in vivo*	Spherical and oval	35-50 nm	Vero cell lines, tachyzoites	Vero cell lines from infected tissues (*In vitro*) and mice (*in vivo*)	↓Cell viability, ↓Proliferation index, ↓ *T. gondii* infection	(Hematizadeh *et al*., 2023)
Zingiber officinale	Stem	Aqueous extraction	Silver NPs	Biogenic	40 ppm	24 hours	-	-	Infected cells infected contain tachyzoites	Vero cell lines of infected tissues	Lethal effect on *T. gondii*	(KarimiPourSaryazdi *et al*., 2019)
Fusarium oxysporum	Fungal culture	-	Silver NPs	Biogenic	3-6 µM	24 hours	Spherical	69 nm	HeLa cells infected with *T. gondii*	Mice	↓Cell viability, ↓Proliferation index, ↓ *T. gondii* infection	(Machado *et al*., 2020)
Fusarium oxysporum	Fungal culture	-	Silver NPs	Biogenic	1.5-6 µM	24 hours	Spherical	420 nm	HeLa cell infected with *T. gondii*	Laboratory	↓Cell viability, ↓Proliferation index, depolarization of mitochondrial membrane increased ↑ROS,	(da Silva Sanfelice *et al*., 2021)
Azadirachta indica	Essential oil	Hydrodistillation	Neo loaded solid lipid NPs	Biogenic	100 µg/ mL	24 hours	Round	337.6 nm		Vero cell lines infected with tachyzoites	↓Cell viability, 70% tachyzoites killed,	(Nemati *et al*., 2022)

could provide synergistic effects, promoting more effective eradication of the parasite. Such treatments will also decrease the dosage of traditional drugs while decreasing possible side effects. To exploit NPs for therapeutic use, they must also be optimized for long-term safety with emphasis on the use of biodegradable and biocompatible material to reduce the side effects. Nanovaccine research where green synthesized NPs are used as carriers for *T. gondii* antigens, offers an exciting platform. Such vaccines may induce robust immunity, with DNA or RNA vaccines being very promising because they can induce humoral and cellular immune responses. In addition, researchers and scientists are collaborating with pharmaceutical industries to mass-produce them to verify their efficacy and safety in human application rather than their production in the laboratory.

Conclusions: The use of green NPs as drug delivery systems is a new approach in the treatment of *T. gondii* infection. The conventional method of treatment is replaced by green NPs due to their biocompatible, biodegradable, and less toxic nature. They are preferable due to their target-specific nature at the infection site without toxicity to the neighboring cells. Scientists and researchers are developing improved treatments against *T. gondii* infection using NPs obtained from plants, bacteria, and fungi. These plant-based, bacterial-based, and fungal-based natural NPs assist in targeting the parasite more exactly so making the treatment more efficient. Additionally, their environmentally friendly production is in line with the increasing need for natural and sustainable medical treatment. With the development of this field, green NPs will bring new innovations in biomedical science by offering more efficient, safer, and environmentally friendly therapies against *T. gondii* and more.

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