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REVIEW ARTICLE

Anti-parasitic Applications of Nanoparticles: A Review

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A B S T R A C T

Parasites are known to cause diseases of acute, chronic and debilitating nature. The control of parasites and their vectors is one of the most prioritized tasks in the rearing of animals. In the face of rising resistance and limited options of chemical control for parasites, the alternative ways to prevent them become pivotal. The use of nanoparticles for control of parasitic diseases has shown great promise at the laboratory scale. Research has been directed to come up with different nano-based preparations, having different structural and functional characteristics. Green nanomaterials have proved to be more eco-friendly, safer, less toxigenic and effective alternatives to routinely used anti-parasitic agents. This review provides a quick inventory regarding nanoparticle use against parasites. Moreover, the areas for future research and development have been highlighted to encourage the application of nanoparticles with known safety and efficacy at commercial scale.

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INTRODUCTION

Parasites can attack both humans and animals and they are life-threatening to both of them. Parasites are more dangerous than bacteria because bacterial diseases show clear-cut symptoms but on the other hand, parasitic infections may not show any obvious signs, therefore; they are difficult to diagnose and treat (Zaheer *et al*., 2022). Trypanosomiasis, malaria, and leishmaniasis are those parasitic infectious diseases that have high death rates in developing countries (Wang *et al*., 2017). Humans suffer from malaria by four species of plasmodium, especially from *Plasmodium falciparum* which causes a high death rate in the world (White, 2004). Twelve million people suffered from leishmaniasis including 1.5 to 2 million cutaneous and 0.5 million visceral leishmaniases and also 17 different species of parasite protozoan are responsible for this infection (Croft *et al*., 2006). *Trypanosoma brucei* causes sleeping sickness which is a neglected tropical disease Barrett *et al*., 2011). Due to resistant strains of parasites, their infections have become global health problems (McCoy *et al*., 2013). Antiparasitic drugs are important for the safety of animal health and animal husbandry development, but they require a persistent dosage of antiparasitic drugs due to their short life cycle and insolubility which decrease their bioavailability (Ceylan *et al*., 2021). The effects of antiparasitic drugs are enhanced by using nanomedicines that take away these restrictions (Wanger *et al*., 2006). Nanoparticles are used as nanomedicine to control, monitor, diagnose, prevent, and treat parasitic infectious diseases (Nafari *et al*., 2020). Physically and chemically nanoparticles are loaded with antiparasitic drugs through conjugation, absorption, and encapsulation. Through degradation, dissolution, and disruption, these drugs are released into the body. Concerning drug characteristics and disease conditions, they are applied through intravenous, skin, oral, intra-gastric, and other routes (Zhang *et al*., 2012). Parasites have been shown to respond well to nanomedicine (Schulz *et al*., 2010). Organic and inorganic and polymer-based nanoparticles have promising effects and applied *in vivo* and *in-vitro*

(Albalawi *et al*., 2020). A large number of nanoparticles are available for the treatment of parasitic infections (Banumathi *et al*., 2016). History of parasitic infections is given in Table 1.

Nanoparticles (NPs) are those substances that range in size from 10-100 nm in at least one or more dimensions. They are distinguished from other particles present in environment due to their size which provides them unique physiochemical characteristics (Chaudhry *et al*., 2017; Lan *et al*., 2021). Phosphate buffer saline (PBS) and other nanomaterials were used by Egyptians a long time ago (Walter *et al*., 2006). First synthetic nanomaterial (NM) prepared by Egyptians was "Egyptian Blue" by the mixture of glass and quartz (Johnson-McDaniel *et al*., 2013). The commencement of metallic nanoparticle era was from 13^{th}-14^{th} BC, when Mesopotamians and Egyptians began to prepare glass using metal (Schaming and Remita, 2015). The inauguration of scientific era was from 1857 when Michael Faraday prepared colloidal Solution of Gold (Nilechi *et al*., 2021). The SiO2 NPs were formulated and used instead of carbon black in rubber manufacturing in 1940s (Raji *et al*., 2020). About 20 countries had been using 1814 nanoparticle-based products by 2014 (Vance *et al*., 2015).

Classification: Nanoparticles are classified on the following basis into different categories. These categories are on the basis of material, dimension and origin. Then Nanoparticles were classified by Leiter *et al*. on the basis of crystalline forms and chemical composition (Leite, 2000) but that did not prove satisfactory (Hamidi *et al*., 2016). Later on, Pokropivny and Skorokhod (2007) added to that and also classify on basis of Dimensions like 0D, 1D, 2D and 3D. These dimensions are on the basis of either electrons are revolving without any fixed dimension or are moving in one, two or three dimensions respectively. Nanoparticles are also classified into four categories on the basis of material formulated: (i) Organic Based Nanoparticles, (ii) Inorganic Based Nanoparticles, (iii) Carbon-Based Nanoparticles, (iv) Composite Based Nanoparticle. These classifications are on the basis of what kind of material they are made from (Hochella *et al*., 2015). NPs are also classified as natural or artificial on the basis of origin. Natural ones are those originating from air, water, soil and organisms. Water includes seas, lakes, rivers, canals and other water bodies while soil may include rocks, deserts, agricultural land magma, lava etc. Organisms can be either microorganisms or large macro-organisms like humans (Sharma *et al*., 2015; Zaheer *et al*., 2020). Synthetically, they are produced from physical, biological, chemical methods and may be combo of any two or three methods. They may also originate from smoke, engine exhaust etc. Due to increasing demand and application of NPs nowadays different synthetic sources are being used for this purpose (Demirci *et al*., 2018). Classification has been described in a flow chart given below in Fig. 1.

Table 1: History of some important parasitic infections

Sr. No.	Name of parasite	Disease	Scientist	Date of discovery	Region	References
1	Giardia	Giardiasis	Van Leeuwenhoek	1682	United State	Chaudhry *et al*., 2017; Lan *et al*., 2021
2	Leishmania	Leishmaniasis	William Leishman	1901	India	Walter *et al*., 2006
3	Trypanosoma	African sleeping sickness	Robert Michael Forde	1901	Uganda & Congo	Johnson-McDaniel *et al*., 2013; Schaming and Remita, 2015
4	*Entamoeba histolytica*	Amoebiasis	Friedrich Losch	1873	Southeast Asia	Nilechi *et al*., 2021
5	Hook worm	Ancylostomiasis	Angelo Dubini	1838	United States	Raji *et al*., 2020; Vance *et al*., 2015
6	*Echinococcus multilocularis*	Echinococcosis	Rudolf Virchow	1855		Leite, 2000
7	Anisakis	Anisakiasis	Van Thiel	1960	Netherlands	Hamidi *et al*., 2016
8	Angiostrongylus	Angiostrongyliasis	Pedro Morera, Rodolfo Cespedes	1971		Pokropivny and Skorokhod, 2007
9	Intestinal round worm	Ascariasis	Henry Ransom	1855	England	Hochella *et al*., 2015
10	Babesia	Bebesiasis	Smith & KilBorne	1888	Northeast & Upper Middle East	Sharma *et al*., 2015
11	Balantidium	Balantidiasis	Malmsten	1857	Tropical & Sub Tropical	Zaheer *et al*., 2020
12	Plasmodium	Malaria	Ronald Ross	1897	Secunderbad	Demirci *et al*., 2018
13	*Trichinella spiralis*	Trichinellosis	James Paget, Richard Owen	1835	London	Ceylan *et al*., 2021
14	Filarial worm	Elephantiasis	Demarquay	1863	Paris	Rossi *et al*., 2004

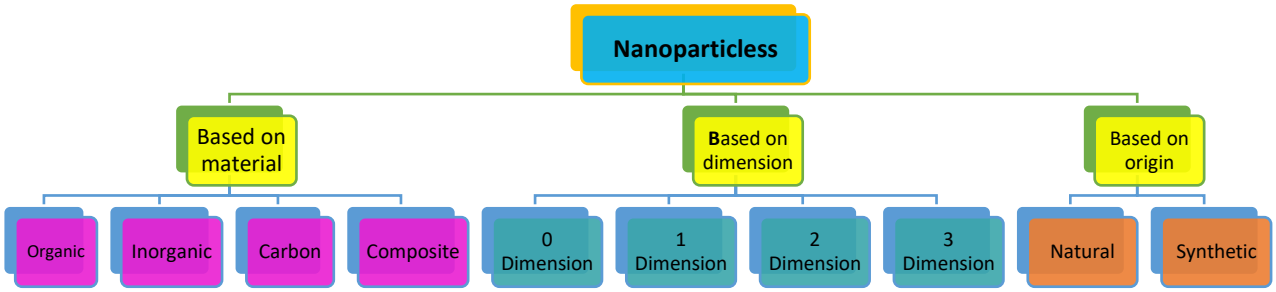

Fig. 1: Flow chart of NPs classification.

Characteristics of NPs: Nowadays, there is an increasing trend in the world towards the usage of nanoparticles. They are being used in various fields of life like:

- In MRI for color enhancement (Demirci *et al*., 2018)
- Pathogen detection (Ceylan *et al*., 2021)
- DNA probing (Rossi *et al*., 2004)
- Destruction of tumor by heat (Khater *et al*., 2020)
- Delivery system of drug (Pantarotto *et al*., 2003)
- Delivery of gene (Ali *et al*., 2021)
- Purification of biological molecules (Zaheer 2021)

In labeling as fluorescent (Gherbawy *et al*., 2013) and the list of applications goes on to almost every field of science. Nanoparticles are extensively used in fighting against the pathogens. These pathogens include various bacteria, viruses and protozoa. The effects of different nanoparticles on parasites are given in Table 2.

It is important to note that nanoparticles of both metallic and non-metallic origin have been shown to cause toxicity of different parasites at various life cycle stages. Moreover, the dosage and forms of nanoparticle administration vary in these studies. More research is required to declare the exact mechanisms of action of these nanomaterials within parasites.

The factors for NPs Choice: The action of NPs depends upon four different factors which are given in Fig. 2. For choosing a nanoparticle against a parasitic infection we must keep in mind the following four factors.

Size: Physiochemical properties of NPs highly depend upon the size of NPs (Liz-Marzán, 2006). If the diameter of NPs changed their optical properties also changed (Haleem *et al*., 2022). The NPs of different sizes are distributed in the body differently and hence affects different parasites differently. The 60% liposomes of 100-200 nm are distributed in the blood after 4 hours of dose, while 20% of 250 nm (Chanzanagh *et al*., 2018). The nifurtimox NPs with size of 200 nm greatly increase the activity and circulation time for *Trypanosoma cruzi* (Haleem *et al*., 2022), Nifurtimox NPs of 50nm were present in liver in 60% concentration, while 100-250 nm or higher were in 25% concentration. It is also found that liposomes NPs of 100nm are the least present in spleen while NPs of higher size is mostly present in spleen. NPs of smaller size are easily excreted through urine instead of larger size NPs (Sun *et al*., 2019). Hence, we should be careful in choosing NPs for specific diseases and keep in mind their size for specific usage against a disease.

Shape: Properties of NPs also depend upon the shape of NPs (Burda *et al*., 2005). The Shape of Nanoparticles has a direct effect on the distribution rate and phagocytic activity of macrophages. It has been observed that cylindrical shape NPs were higher in number in liver than other body organs while the distribution of disc shape particles was higher in heart and lungs (Sun *et al*., 2019) and macrophages feel difficulty to gulp rod shape NPs and thus having longer life span than other shapes NPs (Geng and Discher, 2005). It has been found that the velocity of NPs and their phagocytic rate are inversely related to each other. Rod shape NPs have a longer life span than granular shape NPs (Chithrani and Chan, 2007). NPs having higher velocity are less phagocytosed by macrophages and vice versa. Therefore, for choosing a NP we should choose a specific shape according to their distribution rate and their life span in the body.

Table 2: Effects of nanoparticles on various parasites

Serial No.	Nanoparticles	Parasites	Mechanism of action	References
1	Silver	Fasciola	Silver NPs disrupt cell membrane function, damage DNA and electron transport chain	Brodaczewska *et al*., 2013
2	Chitosan	Trichinella	Improve bioavailability and absorption of albendazole and increased levels of ABZ-SO, which is a major metabolite of ABZ, in plasma	Abulaihaiti *et al*., 2015
3	Chitosan	*Echinococcus multilocularis*	Silver NPs disrupt cell membrane function, damage DNA and electron transport chain	Abbas *et al*., 2020
4	Silver	*Leishmania major*		Mohsin *et al*., 2021
5	Selenium and silver	*Leishmania major*		Sazgarnia *et al*., 2013
6	Gold	*Leishmania major*	Heavy electrostatic attraction, accumulation at cell surfaces, and interaction with cell membrane	Alshamiri *et al*., 2021
7	Nitazoxanide	*Cryptosporidium parvum*		Gaafar *et al*., 2014
8	Chitosan and silver	*Toxoplasma gondii*		Bakr *et al*., 2020
9	Zinc oxide	Hyalomma ticks	Zinc oxide accumulates inside cell and produces toxic H_2O_2, interferes with cell membrane,	Allahverdiyev *et al*., 2011
10	Tin oxide and silver oxide	Leishmania		Said *et al*., 2012
11	Silver, Chitosan and curcumin	*Giardia lamblia*		Saad *et al*., 2015
12	Copper Oxide and Silver	*E. histolytica, C. parvum*		Lan *et al*., 2021
13	Gold	*Giardia lamblia*		Allahverdiyev *et al*., 2011
14	Silver	*Leishmania tropica*		Ponarulselvam *et al*., 2012
15	Silver	*Plasmodium falciparum*		Mohapatra *et al*., 2010
16	Copper, LCu and LCuCl	*Plasmodium falciparum*		Tripathy *et al*., 2012
17	Chitosan tripolyphosphate with chloroquine	*Plasmodium berghei*		Nayak *et al*., 2010
18	Curcuminoids with lipids	*Plasmodium berghei*		Zaheer, 2022

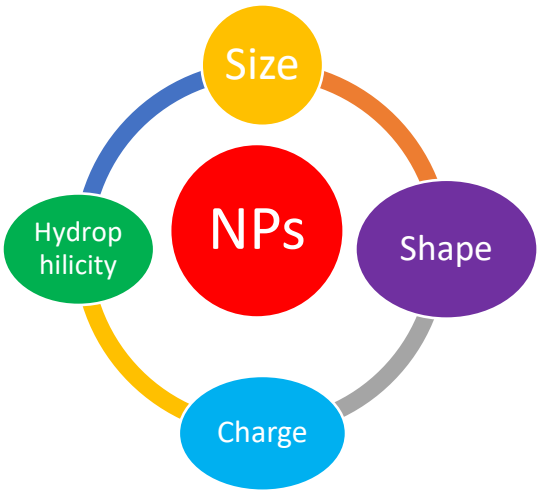

Fig. 2: Factors for Nps Choice.

Hydrophilicity: The Surface Hydrophilicity of NPs has also great impact on the life span of NPs and their bioavailability. Hydrophilicity of NPs is directly related to the PEG, by modifying the PEG we can change the hydrophilicity and hence protein binding properties can be altered. Studies have revealed that PEG modification can prolong the half-life of drug within the body (Fülöp *et al*., 2018; Abbas *et al*., 2014). We achieved knowledge that liposomes with modified PGE have much higher life span than those having no PEG (Jalil *et al*., 2021). As for parasitic infections, we need long-term usage of drug, so we should use PEG-modified NPs for the higher life span in the body.

Charge: The effect of NPs their half-life and their metabolism depend upon the surface charge of NPs. The charged NPs have a higher distribution rate and shorter life span than that of neutral NPs. Negatively charged NPs have a higher clearance rate and shorter life span (Aziz *et al*., 2021). Studies have revealed that positively charged NPs cumulated with negatively charged serum proteins and negatively charged NPs are found in liver in higher concentrations than that of neutral NPs and macrophages phagocyte the negatively charged NPs in liver (Degla *et al*., 2022). Toxocariasis of muscles is treated by negatively charged liposomes as they are accumulated in the muscles (Lu *et al*., 2017). Hence, the surface charge of NPs highly affects the properties of NPs like metabolism, distribution rate and their half-life.

Rationale of Using NPs: Most of the antiparasitic drugs are still a good choice for veterinary practice and it includes tablets, capsules, injections etc. Some drugs are degraded by enzymes like ivermectin and praziquantel, they also cannot cross some tissue and cell membrane barriers. Some drugs are poorly absorbed or are degraded by the GIT like benzimidazole (Sarangi *et al*., 2018; Silva *et al*., 2016). In case of intracellular parasites, like Leishmania, most of antiparasitic drugs cannot cross transmembrane barrier so have little therapeutic effects (Štrbac *et al*., 2021). There is an increasing toxicity and resistance in parasites due to large doses and over usage of antiparasitic effects (Youssef *et al*., 2020). Treatment prices are also increasing day by day due to increasing dearness and it is also a problem in developing and under-developed countries in treatment of parasitic infection (Navarrete-Vazquez *et al*., 2011). New resistant strains are emerging and for treatment of those resistant strains we need an effective treatment against infection, in this regard NPs show good results and effective treatment (Santos-Magalhães and Mosqueira, 2010). It is because NPs like Ag, Au, Si, Cu, Ti and other metals and metallic oxides showed effective treatment against parasites (Abd El-Azeem *et al*., 2019; Tammam *et al*., 2020).

Nowadays, NPs are mostly used because they show effective results and fewer side effects and are also used in vaccines against various parasites (Hozyen *et al*., 2019). Moreover, the intra-nasal nanovaccines are also being researched for otherwise difficult to tackle pathogens of the respiratory tract.

Conclusions: Anti-parasitic drugs are used to control parasitic infections, with the passage of time parasites became resistant to the drugs and drugs show low or no effect against that parasite. Nanoparticles show good results for parasitic infection treatment because they enhance the bioavailability and biodistribution of drugs. The safety of using nanoparticle from broader perspective still needs to be probed and well established. Another avenue for nanoparasitology is the effort on making nanomaterial production more facile and cost-efficient.

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