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Nanotherapeutics of phytoconstituents for parasitic diseases: a short review

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Abstract

The treatment of parasitic diseases is multifaceted. The control methods require a complex interplay involving experts in public health, government policies, education, and medical sciences. Several strategies used in the treatment of parasitic diseases are considered and they are based on the availability, effectiveness, affordability, and acceptability of the used drug. Other measures include effective elimination of vector, and animal reservoirs. Interestingly, new strategies and approaches for the treatment of parasitic diseases involve nanomedical encapsulation of drugs and active compounds. Furthermore, genome, cells, and signal pathways targeting have been used for preventing and treating parasitic diseases. These approaches are used for diagnosis, and treatments of disease and to gain increased understanding of underlying disease mechanisms. Phytocompounds such as flavonoids and others are used in nanotherapeutics for treating parasitic diseases as they prevent oxidation of a liable substrate in a system, among other beneficial properties. Therefore, the present review highlights the use of several phytocompounds in nanotherapeutics to treat diseases caused by parasites.

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1.0 Introduction

Parasites are organisms that can be found all over the world and can infect a wide number of hosts (Zapalski and Hubert, 2011). Parasites infect their host for food and living environment (Table 1). These organisms' present different stages of life making them have more than one host (Zapalski and Hubert, 2011). The vectors include arthropods, which are the first host of parasites before they are transmitted to other higher organisms such as man. Some of the modes of transmission of parasites are blood-sucking, ingestion of contaminated foods, exposure of wounds, among others (Zapalski and Hubert, 2011). The developing countries have a high prevalence of diseases induced by parasites and this leads to health problems (Zapalski and Hubert, 2011). Therefore, there is a need for public awareness and preventive measures to stop the spread of parasites through their hosts and the practice of basic hygiene measures. More so, diseases caused by parasites are still serious health issues despite the marked

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development in science and medicine (Zapalski and Hubert, 2011).

1.1 Global burden of parasitic disease

The global burden of disease (GBD) study is a comprehensive regional and global research program to assess mortality from major diseases caused by parasites, among other studies (Mathers, 2020). The study is a collaboration of over 3600 researchers from 145 countries and GBD for the parasitic diseases have been carried out to assess the financial and nonfinancial burdens caused by parasites (Murray, 1996). Parasites inducing diseases have shown dynamism in their mode of transmission, replication and survival rate. In addition, diseases caused by parasites have contributed to the high loss of lives and a global financial burden. Schistosomiasis is an example of diseases caused by parasite and it is common in the world's poorest countries, where there is poor access to safe water, basic sanitation, and hygiene education (da Paixão Siqueira *et al*., 2017). Previous reports have shown that there are over 200 million people infected with schistosomiasis and among them, about 40 million women of reproductive age are reported to have the disease. Furthermore, the mortality rate is estimated to approximately 280,000 yearly in Sub-Saharan countries (Cioli *et al*., 2014).

Table 1: Some parasitic diseases, causative organisms and hosts

S/No	Parasitic Disease	Causative organism	Family	Transmitting agent (vector/route)
1.	Malaria	*Plasmodium spp*	Protozoan	Mosquito
2.	Leishmaniasis	*Leishmania spp.*	*Trypanosomatidae*	Sand fly
3.	Chagas disease	*Trypanosoma cruzi*	*Trypanosomatidae*	Triatomid bugs
4.	African trypanosomiasis	*Trypanosoma brucei*	*Trypanosomatidae*	Tsetse fly
5.	Babesiosis	*Babesia spp.*	*Babesiidae*	Tick
6.	Toxoplasmosis	*Toxoplasma gondii*	*Felidae*	Parasite oocyst
7.	Trichomoniasis	*Trichomonas vaginalis*	*Trichomonadidae*	Genital contacts
8.	Giardiasis (beaver fever)	*Giardia* species	*Hexamitidae*	Feco-oral
9.	Cryptosporidiosis	*Cryptosporidium* species	*Cryptosporidiidae*	Oral transmission
10.	Amoebiasis	*Entamoeba histolytica*	*Entamoebidae*	Feco-oral
11.	Schistosomiasis	*Schistosoma spp*	*Schistosomatidae*	Snail
12.	Onchocerciasis *(river blindness)*	*Onchocerca volvulus*	*Onchocercidae*	Roundworm

1.2 Epidemiology

The World Health Organization (WHO) estimated that the global burden of parasitic infections is approximately three billion report cases to one million death per year (Piperaki and Tassios, 2016; Pisarski, 2019). The differences in the life cycles of parasites are associated with geographic and socioeconomic factors (Smith Darr and Conn, 2015; Leiby *et al*., 2019). Factors such as malnutrition, contaminated food, natural disasters, the occurrence of war, poor health status, and others contribute to the transmission, dissemination, and the growth of parasites and increase the incidence of diseases leading to significant morbidity and mortality among vulnerable populations (Smith Darr and Conn, 2015; Torgerson *et al*., 2015; Leiby *et al*., 2019).

1.3 Current strategies

The treatment of parasitic disease is multifaceted. The control methods require a complex interplay involving experts in public health, government policies, education, and medical sciences (Watkins, 2003). Several strategies used in the treatment of parasitic diseases are considered and they are based on the availability, effectiveness, affordability, and acceptability of the used drug. Other measures include effective elimination of vectors and animal reservoirs (Watkins, 2003). Interestingly, new strategies and approaches for the treatment of parasitic diseases involve nanomedical encapsulation of drugs and active compounds (Figure 1).

Molecular medicine aims to understand and comprehend the molecular basis of the pathogenesis of the parasites and employ such data to design specific diagnostic methods,

effective prophylactics, and therapeutic options (Singh, 2020). Recombinant DNA technology and cloning techniques are used as conventional tools for studying molecular profiles of parasites. These molecular techniques involve targeting genomic DNA, signaling pathways of the parasites, among others, to provide effective targets for managing parasites, which will results in improved human health (Singh, 2020). The aforementioned targets involve the use of the CRISPR-Cas9 system, engineered meganucleases, RNA interference, immune cells, and stem cell-based therapy, immune checkpoint therapy, immunomodulators, immunotherapeutic approach, and recombinant proteins/cytokine therapy. Genome, cell, and signal pathways targeting have been described in several studies for preventing and treating parasitic diseases. In particular, genome editing has been used in malarial parasite treatment for *P. falciparum* and *P. yoelii* (Wagner *et al*., 2014; Ghorbal *et al.*, 2014).

As earlier mentioned, the nanomaterial is another field of biomedicine with diagnosis and treatment options for parasitic diseases. The application of nanomaterials has received considerable attention in recent decades for their usage against parasitic diseases (Singh, 2020). The reported application includes the use of chitosan nanoparticles and nanosuspension, gold nanoparticles, iron oxide nanoparticles, silver nanoparticles, and polymeric vaccines. In addition, a study reported that the use of silver alone or in a combination with chitosan as nanoparticles was effective against toxoplasma, exacerbating serum IFN-γ level and decreasing burden of the parasite (Gaafar *et al*., 2014). In another study, a combination nanotherapy involving the combination of chitosan, silver, and curcumin nanoparticles has been reported to be effective in clearing parasites causing giardiasis from intestine and stool without any adverse effects (Said *et al*., 2012). Furthermore, Cryptosporidium oocysts were cleared using chitosan as nanosuspension (Ahmed *et al*., 2019).

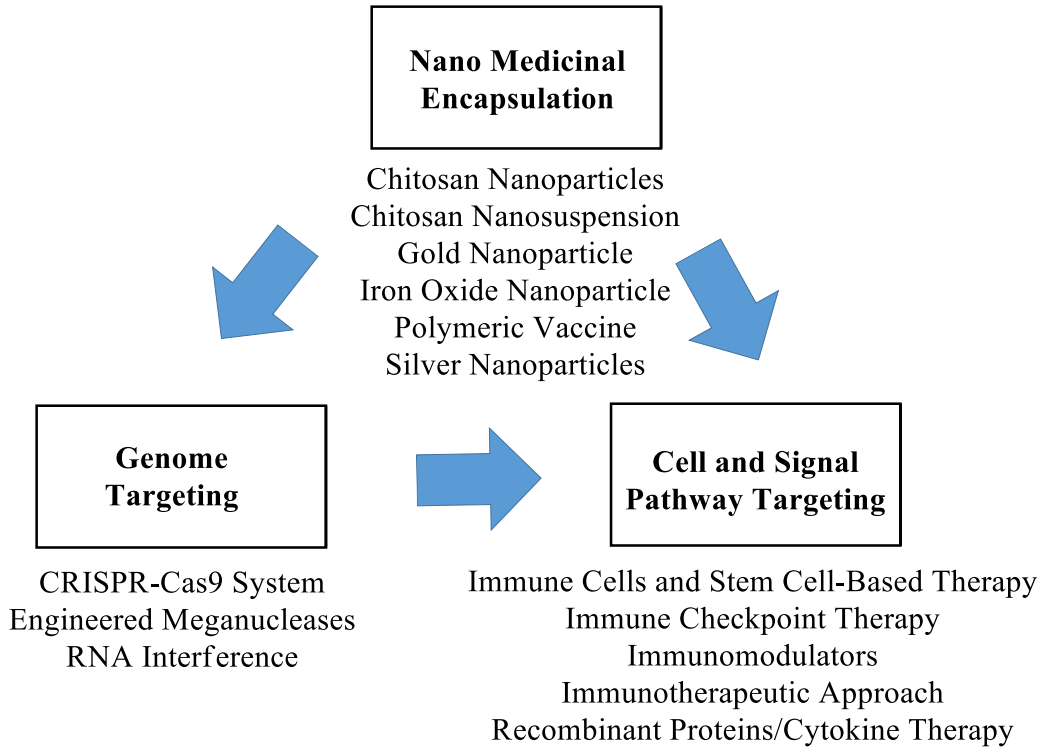

Figure 1: Nanoparticles approach against parasitic diseases

2.0 Phytoconstituents

Plants are still the predominant part of foundations for novel natural therapeutic agents (Schmidt *et al.*, 2012). Countless drugs for the management of several serious ailments have been provided directly or indirectly by compounds from plants. Plants constitute an extensive variety of secondary metabolites including flavonoids, tannins, alkaloids, and terpenoids (Tijjani *et al.*, 2018) with remarkable activity against parasites (Thirumurugan *et al.*, 2018) (Figure 2).

The use of plant secondary metabolites in the fight against diseases caused by parasites has been practiced for so long and it is also used in recent time (Singer *et al.*, 2012). These plants can equally be used to control vectors carrying the parasites causing diseases, including Leishmaniasis and Chagas (Schmidt *et al.*, 2012; Richardson et al., 2015).

Mostly, secondary metabolites are known for their numerous biological properties including antiparasitic and antimicrobial, immunosuppressive, antitumor actions, among others (Thirumurugan *et al.*, 2018). In addition, the existence of parasites in the gut of herbivorous animals like sheep is controlled by secondary metabolites after ingestion of plants. This helps to control the spread of parasites causing diseases such as leishmaniasis and Chagas (Singer *et al.*, 2012; Richardson *et al.*, 2015). Several plants have been tested against the parasites causing malaria and trypanosomiasis. However, such information is still speculative in terms of other parasitic diseases. *In vitro* and *in vivo* models are used to validate the antiparasitic potentials of several plants and their products (Wink, 2012).

Artemisinin is a sesquiterpene lactone with antiprotozoal activity and it is known for antimalarial activity (Maude *et al.*, 2010). Artemisinin was reported to trigger cell-cycle arrest and apoptosis and exhibited parasiticidal activity with IC_{50} values of 160 and 22 µM against pro- and amastigotes respectively (Sen *et al.*,2007; Schmidt *et al.*, 2012).

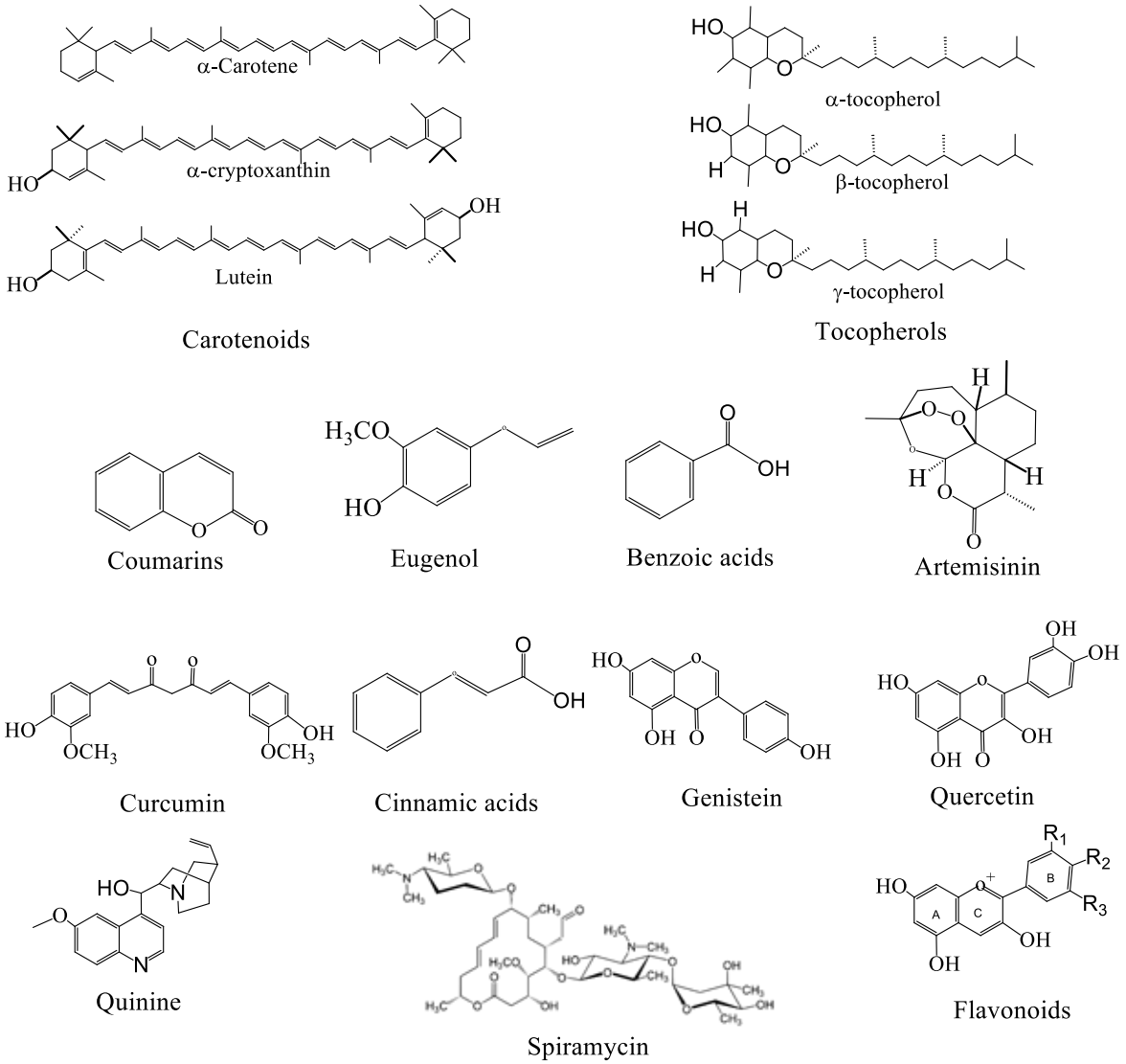

Figure 2: Secondary metabolites with antiparasitic properties

3.0 Phytoconstituents nanoformulation/ nanotherapeutics

Nanotherapeutics are emerging fields involving the use of nanotechnology principles to fight against diseases (Noh *et al.,* 2012; Mahato *et al.,* 2016). Also, nanotechnology involves the use of nanoparticles with different ranges of sizes (Bharali and Mousa, 2010; Ventola, 2012). Nanotherapeutics and nanomedicine are aspects of nanotechnology used in medicine for better diagnosis and treatment (Mahato *et al.,* 2017). Therefore, biological molecules conjugated with nanostructures provide more benefits in disease diagnosis and treatments. Some of the uses of nanotherapies against parasitic diseases are discussed in the subsequent sections.

Also, the increasing rate of drug resistance and adverse side effects of conventional therapies is alarming and resulting to a global health burden (Singh *et al.,* 2017). Diseases induced by protozoans are predominant in the humid regions of the world (Schmidt *et al.,* 2012). Among the seventeen illnesses, which are considered as "Neglected Tropical Diseases" by WHO are Human African Trypanosomiasis, Chagas disease, and Leishmaniasis. Malaria is another serious disease caused by a parasite and seen in poor environments, but it is not regarded as a neglected tropical disease by WHO (Schmidt *et al.,* 2012). Parasites are destroyed to avoid the spread of diseases caused by them. Several methods are used to control parasites and this includes the use of insecticides, draining of stagnant waters, refuse and sewage disposal, and others (Van Wyk and Wink, 2004).

The development of an active agent for controlling diseases caused by parasites is very challenging because the parasite and its host are eukaryotes (Winks, 2012). The available conventional drugs used for treating these parasites pose several serious adverse effects (Schmidt *et al.,* 2012). Additionally, there are problems of resistance. Due to all these challenges, there is a need for the development of new, safer, affordable treatment strategies (Wink, 2012).

Nanotechnology involves the use of particles with dimension(s) that fall within the nanometer range (10^{-9}) (Parboosing *et al.,* 2012) and the field describes nanoscience in relation to biological systems, while nanomedicine, which is similar to nanobiotechnology, involves the application of nanostructured molecules to diagnose, treat and prevent diseases (Singh *et al.,* 2017; Rezaei *et al*., 2019). The area of nanomedicine is gaining recognition in the control, diagnosis, and treatment of diseases induced by microorganisms (Singh *et al.* 2017).

In different bioimaging applications and *in vitro* diagnostics, quantum dots have been lately applied owing to their large stoke shifts, high photostability, and tunable narrow-emission spectral features. This luminous quality of quantum dots shows their application as a strong fluorophore to label microorganisms (comprising intracellular organelles), genes, red blood cells, and proteins. The use of quantum dots as a probe for anti-malarial drug screening is also possible (Kareem, 2019).

Nanoparticles exhibit unique physical properties that have related benefits for drug delivery and these are principal as a result of small size (that influence the circulation time and bioavailability), big surface area (solubility is relatively promoted than bigger particles), and tunable surface charge of the particles with the likelihood of large drug payloads and encapsulation. These characteristics, which are different from bulky materials, make nanoparticle drug distribution systems better candidates to achieve and/or increase therapeutic purposes (Singh *et al.,* 2017).

Numerous metal nanoparticles (MNPs) are produced to control the growth of microorganisms surrounding wound infection, via chemical methods which offer numerous advantages like desired shape, high purity, and structure (Boomi and Prabu, 2013). MNPs have emerged as reasonable options to inhibit bacterial infections and accelerate wound-healing processes (Boomi *et al.,* 2020).

Nanobiotechnology is a unique field has witnessed excellent progress in developing nanomaterials and utilizing them for extensive biotechnological applications (Mahato *et al.,* 2016). Currently, nanomedicine, a field under nanobiotechnology, involves the application of nanomaterials in therapy and diagnosis (Baranwal *et al.,* 2018). Nanoparticles have numerous applications in diverse fields but there are limitations in their usage for biomedical purpose due to some degree of harmful or detrimental effects (Shah *et al.,* 2015). For these limitations to be overcome, the biosynthetic pathways and precursors used in the process of production of the nanoparticles are essential and should be considered (Geethalakshmi and Sarada, 2012). From another part, gene and drug delivery, bio-imaging, antimicrobial medications are some of the applications of AgNPs, a type of nanoparticle (Ahmed *et al.,* 2016). Another importance in the use of nanoparticles with therapeutic actions is that they are less expensive compared to conventional drugs. Plant extract mediated production of nanoparticles is most desired among several other biosynthetic approaches, because they have phytochemicals in abundance, and are readily available. Also, the development of a drug takes several years and it involves multiple steps which makes it normally an exhaustive procedure. Furthermore, among these drugs, some have limited scale effects on parasite as well as the presence of cytotoxicity to host cells by the agents (Zahir *et al.,* 2015). However, nanoparticles like AgNp have reports of no phytofabrications. Therefore, phytofabrication possibly will be a method that might offer a direct method to synthesize highly potent nanotherapeutic agents and minimize the above-mentioned problems (Baranwal *et al.,* 2018). Altogether, Baranwal *et al.* (2018) revealed that specific inhibition of *Leishmania donovani* by an AgNPs is effective and shows no harmful effects to the host organism. Also, their work tends to provide a better method for the production of highly effective

nanotherapeutic agent against *L. donovani* that is less harmful towards non-target cells, which is among the important conditions for the marketable capability of every nanotherapeutic agent. The biosynthetic procedure illustrated by Baranwal *et al.* (2018) could be adopted in pharmaceutical industries for large-scale production of nanotherapeutic agents that could be used as an effective antileishmanial agent.

Plants are a rich source of phytochemicals with numerous biological activities. The medicinal properties of plants are determined by the presence of secondary metabolites present in them and this includes terpenoids, phenolics, alkaloids, and flavonoids (Tijjani *et al*., 2018). Flavonoids are example of secondary metabolites with several therapeutic properties viz anticancer, antiviral antioxidant, and anti-inflammatory actions (Swargiary *et al.,* 2016; Tijjani *et al*., 2018). These plants are used as raw materials for the synthesis of conventional drugs (Lima *et al.,* 2020) in the treatment of diseases including those caused by parasites. A review by Newman and Cragg (2016), explains that large fraction of drugs newly approved within the last 25 years are impressively from plant source.

Higher biological activity has been observed in the presence of antioxidants and several phytochemicals. For instance, plants with antioxidant action showed activity against *Paramphistomum sp*. (Swargiary *et al.,* 2016). Thus, several plants have been reported to display anthelmintic activity (Swargiary *et al.,* 2016). Furthermore, *Hibiscus sabdariffa* extract and its phytochemicals were reported to possess antiparasitic action (Hassan *et al.,* 2015). In an *in vivo* study, *H. sabdariffa* mitigated altered heamatological parameters and tissue morphology in rats infected with *Trypanasoma congolense* (Hassan *et al.,* 2015).

4.0 Nanodelivery

Nanodelivery systems are among emerging platform in the treatment of parasitic diseases and the technology is applied in different forms (Norouzi, 2017). Some are to improve the bioavailability of drugs while some improve the delivery of drugs to their target regions (Table 2). Target drug delivery is a phenomenon used by therapies to be able to bind, detect or recognize molecules that are highly exposed on the cell surface of specific cells thereby inhibiting particular genes or cell surface proteins responsible for causing diseases (Norouzi, 2017; Tayo *et al.,* 2020). Several targets were discovered on cell surfaces, which are vital for engineered drug loaded nanoparticles for targeting. An example is seen in the case of the nicotinic type of acetylcholine receptor and acetylcholine esterase which are found predominantly on the surface of male schistosomes tegument (Tayo *et al.,* 2020). Other major surface proteins found on the tegument, which can be targeted, include aquaporins, tetraspanins, tetraspanins, glucose transporter and dynein, among others (Norouzi, 2017; Tayo *et al.,* 2020). These molecules found on the tegument surface can serve as the essential molecular targets for the development and design of novel vaccines and drug molecules against *Schistosoma* parasites (Tayo *et al.,* 2020).

Nanomaterials were used by researchers to overcome the problems of biological and chemical agents for the management of diseases (such as parasitic diseases), some of which include lipids, modified biomacromolecules, polymers, and also in order to improve the potentials of drugs that have been proved to be effective and promising (Holthof *et al.,* 2012; Xu *et al.,* 2016; Soriano *et al.,* 2018). Their major qualities include improving water solubility, prolonging drug action, high bioavailability, rapid clearance, and enhancing *in vivo* stability of drugs and others (Hui *et al.,* 2020). Based on these potentials, the bioavailable nanomaterials are in the forms of liposomes, dendrimer, micelles, polymeric micelles, polymeric nanoparticles, metallic nanoparticles, nanocrystals, and nanotubes (Tayo *et al.,* 2020). They are used for monitoring, preventing, treating, and controlling diseases such as those caused by parasites (Tayo *et al.,* 2020).

The toxicity of nanomaterials is an aspect of nanotechnology which has to do with the safety of nanomaterials and this area is still speculative (Yu *et al.,* 2015). They are generally associated with the size, surface charge, chemical composition, and functionalization of the nanoparticles (Hui *et al.,* 2020). However, other factors like the route of exposure and excellent clearance could also contribute to the toxicity of nanomaterials in organisms (Dolman *et al.,* 2010).

Nanotechnology uses a specific mechanism designed for several types of nanoparticles that enable them to reach their target organs without being degraded (Roscigno *et al.,* 2017). Nanoparticles have overcome the limitations shown by other agents (Roscigno *et al.,* 2017). Several targets were identified on the surface of the teguments, which are essential for designing drug-loaded nanoparticles to target organs

Table 2: Nanodelivery systems in treatment of parasitic diseases

S/No	Type of Nanoparticle	Parasitic Disease	Type of Organism	Reference
1.	Nano-Nitazoxanide	*Cryptosporidiosis*	*Cryptosporidium parvum*	Sedighi *et al*., 2016
2.	Albendazole–chitosan microspheres	*Echinococcosis*	*Echinococcus multilocularis*	Abulaihaiti *et al*., 2015
3.	Copper oxide, Silver NPs	Entamoeba	*Entamoeba histolytica* *Cryptosporidium parvum*	Saad *et al*., 2015
4.	Silver NPs	*Fasciola*	*Fasciola hepatic*	Gherbawy *et al*., 2013
5.	Silver Chitosan Curcumin	Giardiasis	*Giardia lamblia*	Said *et al*., 2012
6.	Gold NPs	Giardiasis	*Giardia lamblia*	Bavand *et al*., 2014
7.	Amphotericin B incorporated into poly(D, L-lactide-co-glycolide)	Leishmania	*Leishmania*	Venier-Julienne *et al*., 1995
8.	TiO_2 Ag_2O	Leishmania	*Leishmania*	Nayak *et al*., 2010
9.	Chitosan	Leishmania	*Leishmania infantum*	Salah-Tazdaït *et al*., 2015
10.	Gold NPs	Leishmania	*Leishmania major*	Sazgarnia *et al*., 2013
11.	Silver NPs	Leishmania	*Leishmania major*	Karimi *et al*., 2015
12.	Selenium Silver	Leishmania	*Leishmania major*	Jameii *et al*., 2015
13.	Silver	Leishmania	*Leishmania major*	Karimi *et al*., 2015
14.	Silver NPs	Leishmania	*Leishmania tropica*	Allahverdiyev *et al*., 2011
15.	Silver NPs	Leishmania	*Leishmania tropica*	Khosravi *et al*., 2011
16.	Chitosan–tripolyphosphate conjugated chloroquine	Plasmodia	*Plasmodium berghei*	Tripathy *et al*., 2012
17.	Curcuminoids-loadedlipid	Plasmodia	*Plasmodium berghei*	Nayak *et al*., 2010
18.	Copper(II) nanohybrid solids ($LCu(CH_3COO)_2$ and $LCuCl_2$)	Plasmodia	*Plasmodium falciparum*	Mohapatra *et al*., 2010
19.	Silver NPs	Plasmodia	*Plasmodium falciparum*	Ponarulselvam *et al*., 2012
20.	Chitosan Silver	Toxoplasmosis	*Toxoplasma gondii*	Gaafar *et al*., 2014
21.	Chitosan	Trichinellosis	*Trichinella spiralis*	Brodaczewska *et al*., 2013

5.0 Challenges and Limitations

Generally, the treatment of parasitic diseases has challenges, which is different from other diseases. Some of the challenges are associated with metabolism, distribution and excretion of the therapeutic agents. More so, the processes involved in the discovery of drugs for treating parasitic diseases are expensive, as well as their validation and clinical trials. For example, the cost of the antimalarial drugs from discovery to market is estimated to be about US$300 million (Nwaka and Ridley, 2003). Resistance to available drugs is another major challenge, and others include poor efficacy and side effects (Mukherjee *et al*., 2016). Moreover, inadequate attentions are given to most of the diseases caused by parasites and this includes filariasis, leishmaniasis, trypanosomiasis, and others (Mukherjee *et al*., 2016).

6.0 Conclusions and future perspectives

Parasitic diseases affect the quality of life and their treatments cast a serious health burden. In addition, drugs resistance to major conventional agents used in treating them is a global threat to their control and elimination and this may result in limited therapeutic options for treating these parasitic diseases. Phytocompounds such as

flavonoids and others are used in nanotherapeutics for treating parasitic diseases as they avoid oxidation of a liable substrate in a system, among other beneficial properties. In this sense, protecting the efficacy of the compounds (phytoconstituents/phytoantioxidants) for treating parasitic diseases is highly recommended especially in endemic countries. Thus, more studies are recommended in this area of phytocompounds and nanoparticles for the design of effective and safe molecules in treating diseases caused by parasites.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

All authors have read and consented to the submission of the manuscript.

Availability of data and material

Not Applicable.

Competing interests

All authors declare no competing interests.

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