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Review article

Road map to the treatment of neglected tropical diseases: Nanocarriers interventions

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ABSTRACT

Neglected tropical disease (NTD) is a set of 20 deadliest endemic diseases which shows its presence in most of the developing countries worldwide. Nearly 1 billion of the population are affected by it and suffered from poverty yearly. These diseases offer their own unique challenges and limitations towards effective prevention and treatment methods. Neglected tropical diseases are severe infections they may not kill the patient but debilitate the patient by causing severe skin deformities, disfigurement and horrible risks for several infections. Existing therapies for neglected diseases suffer from the loopholes like high degree of toxicity, side effects, low bioavailability, improper targeting and problematic application for affected populations. Progress in the field of nanotechnology in last decades suggested the intervention of nanocarriers to take over and drive the research and development to the next level by incorporating established drugs into the nanocarriers rather than discovering the newer drugs which is an expensive affair. These nanocarriers are believed to be a sure shot technique to fight infections at root level by virtue of its nanosize and ability to reach at cellular level. This article highlights the recent advances, rationale, targets and the challenges that are being faced to fight against NTDs and how the novel therapy tactics are able to contribute to its importance in prevention and treatment of NTDs.

1. Introduction

In spite of excellent increment in global pharmaceutical research and studies, still the large portion of world's population is affected by poverty due to the disaster of neglected tropical diseases. According to World Health Organization, nearly 1 billion of individuals are affected from NTDs yearly. The focus of developed nations are on the newer drug entities, molecules, latest techniques and innovative ideas for effective treatment and improvement of traditional treatment, therefore the patients has a reach to better and more specific treatments for existing diseases [1], while in low and medium income countries the millions of people are still waiting for the benefits of advancement of science. More than 70% of countries which reported to have presence of neglected diseases are low income and lower middle income economies. The deadly infectious diseases of poor people failed to arouse the interest of drug developers and pharmaceutical industries. Overlooking of neglected diseases is affecting the social and economic well-being of people in poor countries. Neglected Diseases include viral, bacterial, parasitic infections, acute respiratory infections and diarrheal infections of children common in Africa, Asia and some regions of America. WHO unique agenda for training and research in tropical diseases (WHO-TDR) outlines disease of poverty as diseases affecting the poor in developing countries into two modules; the first one includes three big diseases HIV/AIDs, Malaria and Tuberculosis which received worldwide considerable attentions and investment for their eradication while another class include neglected tropical diseases. As Per WHO neglected diseases are group of communicable diseases which are prevalent in 149 subtropical and tropical countries [2]. WHO identified 17 neglected tropical diseases,they include Buruli ulcer, Chagas disease, Dengue/severe dengue, Dracunculiasis, Food-borne trematodiases and fascioliasis (liver flukes), Human African trypanosomiasis, Human echinococcosis, Leishmaniasis, Leprosy, Lymphatic filariasis, Onchocerciasis, Rabies, Schistosomiasis, Soil-transmitted helminthiases, Taeniasis/cysticercosis, Trachoma, Yaws [3]. While, Disease group like mycetoa, chromoblastomycosis and other deep mycoses joined the group of NTDs along with scabies and other ectoparasitoses and snake bites lead to increase in the total of 20 disease groups by the WHO 2020. The suggestions were received in 10th conference of STAG (Strategic and Technical Advisory Group) in 2017 to add deep vein mycoses, scabies, chromoblastomycosis and snakebite envenoming and ectoparasites to

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the NTD portfolio. There are 35,000 deaths per day worldwide due to them. The people living in poverty in remote areas, urban slums, drinking unsafe water, living in close proximity with livestock, infectious vectors and with poor hygienic conditions without sanitation are mostly affected with those diseases. The children are most vulnerable targets. Some of neglected diseases are transmitted by vectors found in tropical regions where insect prevails and have access to drinking water due to lack of sanitization.

WHO estimates that diseases associated with poverty are 45% of total disease burden in developing countries. The poor people having a low profile, illiteracy, poor income status and unawareness are unable to caught attention from government agencies and public health sectors for many decades [4]. During the last few years there have been some initiatives and financial commitments by government agencies, non-profit global organizations and public private partnerships on the neglected diseases such as DNDi initiative (drugs for neglected diseases initiative), medicines for malaria venture, Bill and Melinda Gates foundation, but the efforts are insufficient to reach the treatment of neglected diseases to poor.

1.1. What after the intervention of different organizations including WHO, US-FDA, regulatory agencies, pharmaceutical companies, private-public, and international organizations?

The new chemical entities for treatment of global diseases like cancer, cardiovascular disease and neurodegenerative disorders, diabetes etc., has been remarkable discovered and being researched by big pharmaceutical companies and academics in last decades but there is a complete ignorance towards neglected disease due to lack of economic interest. The big pharmaceutical companies do not focus on such diseases as there is a small population affected in industrialized countries making it difficult for them to generate profit [5]. But after intervention of WHO, US FDA and international agencies pharmaceutical companies are beginning to see neglected diseases from a different perspective. The following table innumerates the initiatives taken by regulatory agencies regarding NTDs (Table 1).

1.2. The road map for neglected tropical diseases (NTD) 2021–2030

On the basis of prevention, elimination and eradication of neglected tropical diseases, WHO established a second blueprint for 2021–2030 [11]. It tracks the rules and guidelines of the first road map issued in 2012, to minimize the worldwide effect of neglected tropical disease through accelerating the effective work against the diseases. It also states the universal goals and milestones to 2020 for 17 different neglected tropical diseases including WHO's NTD portfolio. The primary goal for the new road map is to achieve sustainable development goals (SDG) and the diseases group those are ranked according to the WHO for speed-up in the advancement of prevention, elimination, controlling and eradication of 20 NTDs, as well as to maintain the alliance between state members and stakeholders for better future results [12]. The proper plan and strategies must be carried out by the disease expert, stakeholder, member states and implementers to overcome the disease and provide relief to the peoples that are exaggerated due to 20 diseases and groups by WHO's portfolio [13,14].

1.3. The NTDs prioritized by WHO: their devastating impact on impoverished communities

The road map of 2030 extensively affects the individuals living in deficiencies in tropical and sub-tropical regions and covers the therapeutics according to diseases and disease groups. More than 1 billion individuals of the world were facing problems like human, communal and financial which were executed by the NTDs, mostly the countries that generate low and middle income (Fig. 1). Figure 1Every year more than 2 lakhs individuals suffered and died from the snake bites, rabies

Table 1
Initiatives by regulatory agencies and private/governmental organizations.

Year	Regulatory body	Initiatives	Ref.
2000	WHO	191 united nations pledge together to meet millennium development goals by 2015 for combating the infectious diseases The pharma companies joined hands with WHO and started investing and donating in neglected diseases some of them include • MDR-TB Lilly partnership (Drug Discovery) • GSK pledged to eradicate lymphatic filariasis by supplying albendazole • Pfizer donated azithromycin for trachoma • Novartis invest in neglected diseases for treatment of leprosy and tuberculosis • Johnson and Johnson donated mebendazole for children without worms	[6]
2003	DNDi (Drugs for Neglected Diseases Initiatives)	DNDi is a Geneva Switzerland based non-profit organization founded by seven institutions- • Kenya Medical Research Institute (KEMRI) • Pasteur institute of France • Indian council of medical research (ICMR) • Malaysian Ministry of Health • Unique events for Research as well as Training in Tropical Diseases (TDR) • Medicines Sans Frontieres (MSF) • Oswaldo Cruz Foundation in Brazil with an aim of effective treatment for neglected diseases like chagas, Human African trypanosomiasis and malaria etc., Short and long term projects of delivering drugs through new drug discoveries or new formulations and combinations by 2014	
2008		A public institution (Farmanguinhos, Brazil) in partnership with DNDi launched second product artesunate-mefloquine fixed-dose combination (ASMQ) for treatment of malaria.	
2009	WHO	Based on the evidences of phase 3 clinical trials on stage 2 human African trypanosomiasis using combinational therapy of nifurtimox and eflornithine, WHO added the nifurtimox as an essential medicinal agent for the management of Human African Tripanosomiasis	[7]
2012	WHO	published a roadmap for prevention and eradication of 17 neglected diseases by 2020 13 pharmaceutical companies, government of UK, USA, UAE, Bill and Melinda Gates foundation, world Bank and other global health organizations signed London declaration on neglected tropical diseases pledging to eradicate 10 neglected diseases which includes guinea worm disease, lymphatic filariasis, leprosy, human African trypanosomiasis and blinding Trachoma	[8]
2020	WHO	WHO has drawn a roadmap for eradication of at least two neglected diseases by 2020	[9]
		Roadmap of WHO for eradication neglected tropical diseases ends in 2020 New road map for 2021–2030 focuses on integrated approach, collaborative	[10]

(*continued on next page*)

Table 1 (*continued*)

Year	Regulatory body	Initiatives	Ref.
		measures, development of new diagnostic tools and treatment strategies for prevention, control and eradication of the NTDs	

and dengue like infection, where millions of the individuals were disabled, hampered and discriminated against because lack of affordable treatment in the due time.

NTDs income generating authorities spend billions of US dollars each year in health systems, loss of productivity, decrease socio-economic and educational achievement. Due to NTDs, the patients and families were financially disturbed, e.g.: More than 40% of households annual income were spent by the rural societies in democratic republic of congo due to "Human African Trypanosomiasis" and nearby 75% families of Bangladesh, India, Nepal and Sudan were facing financial disaster during fighting against visceral leishmaniasis, although the charges were free for the tests and medicine [15]. The interventions for NTD are one of the biggest key factors in worldwide public health. It predicts that it's beneficial for the people who are invested in the prevention of diseases to get a profit of 25 US$ from 1 US$ and also 30% of annual rate return. Hence, contributions towards the health system and protective measures are affordable for individuals.

1.4. Action and progress against NTDs

The actions were taken against the NTDs to the idea by undertaking worldwide health analysis, which led to getting health services to all individuals and communities without sorrowing any financial poverty. The aim of SDG target 3.8 and the universal health analysis are the foundation of WHO's 13th general programme, 2019–2023. The steps against NTDs besides their monitoring and assessment strengthen each other which result in expanding the perspectives of health care systems for the individual by implementing the interventions regarding NTDs in most of the populations of the world. The treatment analysis of NTDs specify the worldwide health analysis, it can only be accomplished when the individual is suffering from a major risk factor or affected by NTDs having affordable high quality health facilities. Regarding health and economic benefits it is profitable to invest in the NTDs [16]. The effective approach from member states and the world-wide NTD community made a significant advancement to fight against NTDs. In the last 10 years, it shows the substantial improvement in the fight against NTDs i.e. advancement in the interventions and protective measures, new rules, tactics and guidelines along with collaboration, donor support and country promises [17]. Pharmaceutical firms donated more than 3 billion tablets to fight against the NTDs in the endemic countries to eliminate and eradicate the growth of NTDs. It provides safe, effective and affordable medicines by establishing public private companies [18]. Those accomplishments are the evidence to the long-term maintenance and devotion to the worldwide NTD community, in 2007 WHO organised the first council of NTD worldwide partners to call together the various disease inventiveness under one flag of NTD, pledges made in the meeting of worldwide partners in 2017 and London declaration on NDA 2012. They highlighted the massive prospective that can be revealed by working together in partnership to confirm that NTDs have a crucial key factor in worldwide health programmes.

1.4.1. Delivery of interventions and impact

- The peoples those who are at risk at 42% in 2012 in the endemic zones were led to 66% defensive reporting in 2019

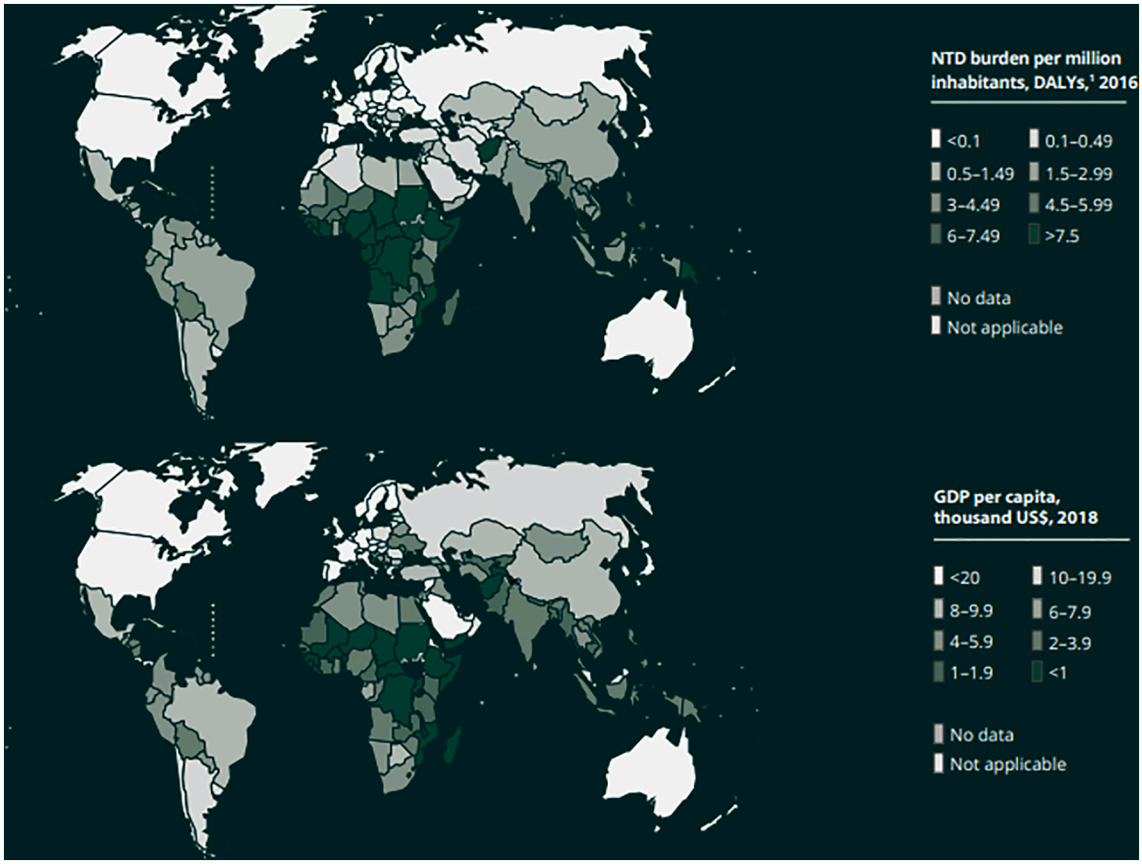

Fig. 1. Geographical spread of the NTD burden, by DALY (disability adjusted life year) and gross domestic product (Adapted from WHO, 2020).

- As compared to 2010, less than 600 million population need the intervention today to fight against NTDs
- From 2014, more than 1 million surgical preparation were given to the population for trachomatous trichiasis
- By the end of 2020, one of the neglected tropical disease should eradicate from 42 countries, territories and areas

1.4.2. Extension of overall scope and support for NTDs

- Disease group like mycetoa, chromoblastomycosis and other deep mycoses were joined the group of NTDs along with scabies and other ectoparasitoses and snake bites lead to increase in the total of 20 disease groups
- As of 2017, 1 billion US dollar committed by new donors.
- With the cost of hundreds of million US dollars, 11 pharmaceutical firms donate 3 billion tablets yearly in terms of safety, quality and affordability; meanwhile six additional drugs were available as drug donation promises

1.4.3. New interventions, tools and diagnostics

- New treatment tactics: eg:- combinational therapy for lymphatic filariasis i.e. Ivermecine, diethylcarbamaine and albendazol (IDA) [19], fexinidazole for the management of HAT, praziquantel (Paediatric) for schistosomiasis, Antibiotics were preferred instead of surgical application for Buruli ulcer and instead of i.v. benzathine benzylpenicillin, azithromycin were preferred for the management of yaws.
- New diagnostics: e.g.:- For the management of onchocerciasis, lymphatic filariasis, yaws and human African trypanosomiasis rapid and multiplex diagnostic test were performed; others in the row i.e. Assay of circulating cathodic antigen for *schistosoma mansoni* were performed, to diagnose the buruli ulcer the rapid diagnostic test of myolactone were performed
- New vector controlling tools i.e. cytoplasmic incompatibility method, sterile insect method and incompatible insect method along with population replacement methods with new traps and insecticides were implemented [20].

1.4.4. Strengthening NTD structures and cross-sectoral alliances

- WHO's accomplishment worldwide on neglected tropical diseases gain the support from 45 alliance centres of WHO
- Establishment of network i.e. NTD NGO Network (NNN) to organised the work of the communities those are involved in the battle against NTD and other NTD collaborators
- Development of the association which aim to target scientific approach towards NTD as an operative research
- Stronger multi sectorial alliances e.g.: Foundation of 2015–2020 WASH plan to fight against NTDs worldwide, NTDs involvement in worldwide vector maintenance and one health tactics [21]
- Establishment of the ESPN i.e. Prolonged the use of unique scheme for the elimination of NTDs by providing effective chemotherapy in Africa which strong the WHOs capability's to target 5 NTDs

1.4.5. Creations of tactics, guidelines and resolutions

- Resolution WHA66.12 adopted on NTDs (2013)
- Resolution of 2 diseases i.e. snake bite envenoming in 2016 and mycetoma in 2016 [22] were approved by health assembly along with worldwide vector control response in 2017. However, resolution for 17 the 20 disease were approved by the health assembly.
- Currently, worldwide diseases strategies with 15 NTDs are available
- However, WHOs guidelines and booklets for diseases are accessible for 14 NTDs
- Development of integrated strategies e.g. for skin NTDs and vector control [23]
- National strategies to target NTDs were setup by more than 50 countries
- Number of countries in their health care resources mentioned the NTDs

1.5. Targets and milestone for 2030

This segment gives a summary of targets and milestones for NTDs (2030), which were held by the different organizations by consulting globally with members of states and United Nations along with scientific and research units, non-governmental management, implementing associates, donors and private administrators. The 13th general programme of WHO and SDGs (2019–2023) highlighted the overarching and cross cutting targets which followed the key point as management, impartiality, integration and country ownership for a number of diseases. The targets for divisions like WASH and vector control were dependent on established goals [24]. Disease based targeting (2030) and milestone (2023–2025) [25] were specified for each single disease among 20 diseases and groups for one of following:

(a) Eradication i.e., decrease in the ratio of particular pathogen worldwide permanently with cautious efforts without any threat of reintroduction
(b) Elimination (Interruption of transmission) i.e., decrease in the interruption of transmission chances of particular infection derived by pathogens in a definite geographical region with minimum threat of re-establishment which lead to cautious efforts and continuous preventive measure were required for re-establishment of transmission.
(c) Elimination: It specifies the infection as well as disease, a problem related to public health. It defines the aims and goals set by WHO to target the specific disease at accessible ratio.
(d) Control: It specifies the decrease in the incidence ratio, reduction in mortality and morbidity levels due to continuous cautious efforts along with continuity in newer interventions for the maintenance in reduction ratio

1.6. 1Overarching targets for 2030

- 90% reduction in individual those are dependable on interventions against NTD [26]
- 75% individual are going to recovered from disability's and increase life span against NTD
- Almost 100 countries having eliminated at least one NTD
- 2 diseases were eradicated

1.6.1. Cross-cutting targets for 2030:

1.6.1.1. Integrated approaches.

- Reduction in 75% death ratio from vector borne NTD (2016)- aim to attain worldwide target of WHOs vector control response
- 75% combined treatment analysis report for preventive chemotherapy
- Around 40 countries accept and implement the strategies to target skin neglected tropical disease

1.6.1.2. Multisectoral coordination.

- 100% access of basic needs in endemic domains like water supply, maintenance of hygiene and sanitization to achieve 6.1 and 6.2 milestones of SDG 6 for neglected tropical disease [27].

- 90% resources of countries implemented in national health tactics with neglected tropical disease.

- 90% savings of individual secure against disaster of poverty in health resources due to NTD, to accomplish the milestone 3.8 of SDG 3 [28].

1.6.1.3. Universal health coverage.

- 90% countries manage their resources in interventions, essential services and overall budget for NTD

- 90% countries with proper tactics indicate disability in national health system for the treatment of NTD

1.6.1.4. Country ownership.

- 90% of countries aware of the appropriate endemicity and reporting related to NTD

- 90% of countries record their data on neglected tropical disease which disaggregated by gender

1.7. Why is this the critical time to address the neglected disease with a newer angle of drug delivery (nanocarriers)?

According to The Lancet Global Health, a study by Belen Pedrique and colleagues showed that in past 10 years 850 new therapeutic products were registered and out of which only 36 has the indications for neglected diseases means only 4%, it indicates that how much neglected are the neglected diseases for research and development? And also it's a matter of crucial concern for Pharma fraternity that there is a strong urge to focus on the research and developments for the neglected diseases as the present efforts are insufficient [29]. It has been estimated that less than10% of global spending on health research is devoted to diseases or conditions that account for 90% of the global disease burden [30]. Newer drug developments as well as better access of existing drugs to the patients need to be addressed simultaneously. Existing therapies for neglected diseases suffer from the deficiencies like high degree of toxicity, side effects, low bioavailability and problematic application of affected populations sometimes [31]. But the fundamental problem is how to induce the pharmaceutical companies to invest in research and development for neglected diseases as the profit generation is less because the population affected is poor but on ethical considerations it is our duty as human beings to work for betterment of society even on low revenue generation. Due to lack of novel drugs, nanotechnology can be a great tool for treatment of neglected diseases. Nanocarriers have advantages of improved bioavailability, tailoring release profile, targeted approach and higher efficacy associated with less toxicity which could be helpful to treat neglected disorders [32]. Moreover, nanocarriers have a capability to encapsulate the drug molecule and provide sustained delivery as well as achieved therapeutic concentration at the disease site at specific time which is the most crucial factor while targeting neglected tropical disease. Nanocarriers also tailored the release profile to prolonged the effect of drug and minimize the dose administration. Combinational therapy might be essential while targeting NTDs due to limited chances of recovery or to act against chronic infection which is perfectly handled by nanocarriers drug delivery [33]. The era of 1975–1990 is an alarming situation for the NTDs, 10 drug molecules were listed to utilized against NTDs example, pentamidine for the management of HAT; nifurtimox and benznidazole for Chagas disease, ivermectin for the management of onchocerciasis, albendazole for soil transmitted nematodes, and halofantrine, pyrazinamide and mefloquine for malaria.praziquanteland oxamniquine for schistosomiasis [34]. Matter of fact is that all of the abovementioned drugs were developed nearly 40 years ago and they are continued to cater the patients of neglected diseases. The biggest fear was noticed in last few years, is the drug development which is quite critical in public as well as in private sector. Many of the drug molecules those are given currently for the treatment of NTDs are suffering from number of problems such as poor pharmacokinetic profile and minimal selectivity to target tissues and organs. The use of nanocarriers increases the pharmacokinetic characteristics of drug and reduced the treatment cost to populations. Nearly 1 billion of individuals are affected by NTDs stated by WHO. The mild cases of NTDs do not caused death but lead to life time disabilities and physically and mentally disturbance i.e., mental impairment, retarded body growth, reduced work efficiency, visual impairment or loss of eyesight [35]. Nanocarriers have two advantages the first one is improved pharmacokinetic profile due to entrapment of drug in nanosystem and another one is direct targeting to the cellular level due to nanoscale size and properties [36].

2. Nanocarriers

Neglected tropical diseases are parasitic infections which are difficult to combat and managed; as intracellular dissemination of parasites is a great challenge. Low drug payloads is poor reach of drug molecules to the intracellular level is a big problem and also dose dependent toxicities and extracellular degradation of drug molecules further complicate the situation [54]. There is limited number of drugs available for treatment of neglected diseases. Most of drugs administered for treatment of neglected tropical are administered orally or parenterally. Oral dosage forms include tablets, capsules, syrups, solutions, suspensions. The efficiency of abovementioned dosage form is limited due to low solubility, low bioavailability, and poor drug payloads at intracellular level and high drug dose requirements.

Fig. 2 (a) depicts the spherical nanocarrier i.e., solid lipid nanoparticles (SLNs) composed of various surfactant and formed the solid lipid core.Figure 2: Fig. 2 (b) depicts the colloidal carrier which is composed of non-ionic surfactant and similar to the liposomes. Fig. 2 (c) depicts the polymeric nanoparticles those are obtained from di or multi block copolymer like PLA, PLGA and poly ethylene which are biodegradable in nature. Fig. 2 (d) depicts the carrier which dispersed in liquid system through the accumulation of surfactant and molecules. Fig. 2 (e) depicts the colloidal carrier called as liposomes which composed tiny vesicles of lipid and aqueous compartment resulting from phospholipid and cholesterol. Fig. 2 (f) depicts the dendrimers those have unique architecture with internal core having a tree like branched appearance which is preferred for gene and drug delivery. Fig. 2 (g) depict the updated version of SLNs, known as Nanostructured lipid carriers (NLCs) composed the mixture of solid and liquid lipid and provide high loading and drug release profile. Fig. 2 (h) Polymerosomes are artificial vesicles made of blocked copolymers. 2 (i)Quantum dots are nanosized delivery systems able to track and image the drug. Fig. 2 (j) Carbon nanotube are one of the strongest nano delivery systems with greater tensile strength.

Colloidal drug carriers like liposomes, nanoparticles, nanoemulsions, nanosuspensions, solid lipid nanoparticles (Fig. 2) are of great potential due to their nanosize, as they have capability of intracellular delivery. During the last decade the focus of research towards nanocarriers has grabbed attention due to advantages of efficacy, specificity and improving therapeutic index of existing drugs for neglected diseases. Liposomes are vesicular lipid bilayers systems of nano size having ability to entrap hydrophilic and lipophilic drug and reducing their toxicity potential and targeting intracellular delivery [55]. Liposome has great potential for treatment of parasitic infections due to their capability of intracellular targeting. AMBisome; a liposomal formulation further substantiated the effectiveness of liposomes in treatment of parasitemia.

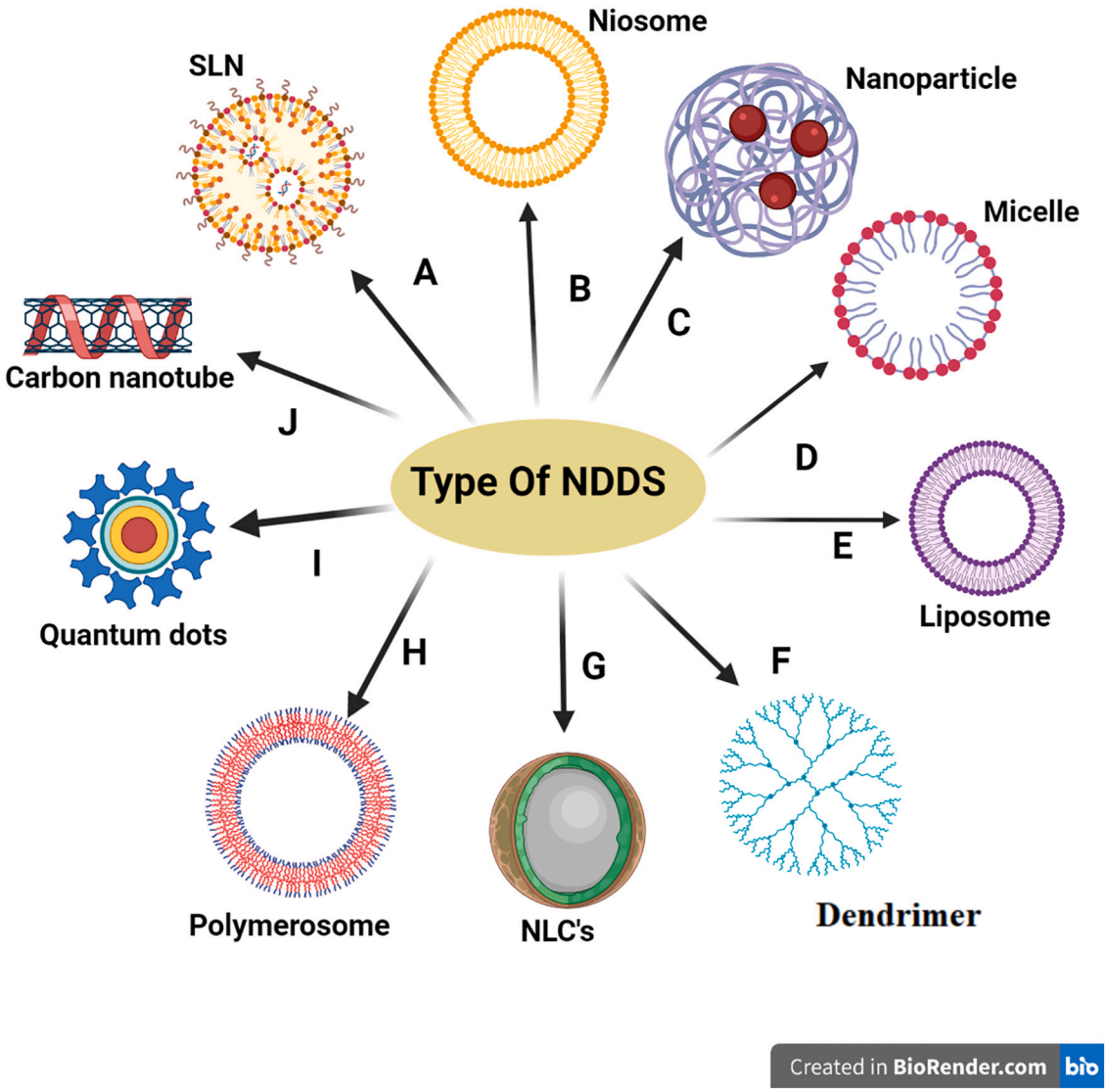

Fig. 2. Pictorial representation of various NDDS used as a nanocarriers (a) Solid Lipid Nanoparticle (SLN), (b) Noisome, (c) Polymeric nanoparticles, (d) Micelles, (e) Liposomes, (f) Dendrimer, (g) Nano Lipid Carriers (NLC), (h)Polymerosomes, (i) Quantum dots, (j) Carbon nanotubes.

Polymeric nanoparticulate drug delivery also has potential for better drug delivery at cellular level further it has better physiological stability and ability to withstand physiological stress; therefore they are being explored for oral delivery also which is not possible with liposomes. Solid lipid nanoparticles are second generation of colloidal carriers; they have combined advantages of liposomes, nanoparticles as well as emulsions and further have better stability as well as physiological compatibility. Solid lipid nanoparticles can be better targeted to intracellular delivery for treatment of parasitemia [56]. (Table 2).

The general physicochemical measures of the chemotherapeutic drugs used in the treatment of these neglected diseases like the poor solubility, low absorption; poor permeation brings forward the need of having delivery systems which would solve these problems [57]. Nanocarriers as drug delivery systems in the form of either nanoparticles or liposomes put forward the fact; they can effectively overcome the limitations of the conventional chemotherapy. This includes reducing the higher doses by making the optimized benefit of the dose loaded in the delivery system; increased solubility, permeability and enhanced bioavailability. Solid lipid Nanoparticles (SLNs) is the types of nano drug delivery systems which have lower immunity and toxicity due to the use of natural lipids. Also, SLNs have good control over the release profile of the entrapped drug with better stability and enhanced targeting ability leading to better therapeutic efficacy. In addition, the lipids when dissolved molecularly enhance the bioavailability of the poorly soluble drugs. SLNs are also useful to reduce the erratic absorption profile of entrapped drugs [58].

Nanocarriers can attach to bacterial cell membrane by electrostatic interaction and can lead to cell membrane disruption and induction of oxidative stress by free radical formation (Fig. 3). Figure 3Antibiotic resistant bacterial strains are crucial challenge for treatment of neglected tropical diseases. Killing of antibiotic resistant bacteria needs multi drug therapies which are expensive and has side effects. Drug loaded nanocarriers which may be called as nanoantibiotics can effectively kill drug resistant bacteria by cellular drug delivery [59] [60]. Figure 4 illustrates the mechanism of action of these nanocarriers (Fig. 4). The transcellular transportation of drug loaded nanocarriers is through lipid bilayer into the cell membraneFigure 4

This review highlights the endemicity of infectious diseases which fall under NTDs and a threat to mankind. It focuses on the present scenario of neglected diseases, current treatments available for the diseases. This paper explore the potential of nanotechnology derived system i.e., nanocarriers for the management of NTDs. Nanocarriers research done

Table 2
Neglected Tropical Disease categorised by WHO, Current drugs for Treatment/Prevention and Nano approaches for treatment.

Disease	Source	Treatment	Novel Approach	Drugs in Clinical Trials
Buruli ulcer	*Mycobacterium ulcerans*	Combination of Rifampicin with -streptomycin -clarithromycin -moxifloxacin	Topical nano-particulate delivery: -Liposomes[37] -Lipid nanocarriers[38]	–
Chagas disease	*Trypanosoma cruzi*	-Benznimidazole -Nifurtimox -Ibandronate -Pamindronate -Allopurinol	liposomal formulation[39] using stearylamine and egg yolk phosphatidylcholine	Under Phase II: E1224 a prodrug of ravuconazole
Dengue/severe dengue	*A. aegypti or Aedes albopic*	Antipyretics and Analgesics	mosquitocidal silver nanoparticles -PLGA nanoparticles[40]	Approved:USFDA Dengvaxia® (2019) only for Europe and US endemic areas
Dracunculiasis	*Guinea-worm*	No treatment	Water treatment using: -Nanofiltration -Biosorption -Nanoadsorption -Ultrafiltration	–
Food-borne trematodiases and fascioliasis (liver flukes)	*O. felineus Fasciola hepatica*	-Praziquantel -Triclabendazole	Chitosan based nano capsules and nanoemulsion[41]	–
Human African trypanosomiasis	*Tsetse flie*	-Pentamidine -suramin -melarsoprol -eflornithine -nifurtimox	-PLGA Nanoparticle[42]	Approved: Fexinidazole (2018)
Leishmaniasis	*L. donovani* *L. mexicana* *L. tropica* *L. major* *L. aethiopica*	-Sodium stibogluconate -amphotericin B -deoxycholate -Pentamidine -isethionate -Milfetosine -ketoconazole -itraconazole -fluconazol	-PLGA Nanoparticle[43] -Carbon Nanotubes -Pegylated nanoparticle	Under Phase II: 18-Methoxycoronaridine and Glucantime
Leprosy	*Mycobacterium leprae*	-Rifampicin -clofazimine -dapsone	-Nano-Liposomes -Nano polymeric micelles	–
Lymphatic filariasis	Spread of filarial parasites through mosquitoes	-Diethylcarbamazine (DEC) -Ivermctin -Doxycycline	-Self-nanoemulsifying DDS -Liposomes[44] -PLGA Nanoparticle[45] -Lipid based system	–
Onchocerciasis	*Onchocerca volvulus*	-Ivermectine	-Microemulsion[46] -Lipid based system	–
Rabies	Spread of rabies virus to people through bites or scratches	4 doses of rabies vaccine	-Dendrimers[47] -Silver Nanoparticles[48]	Under phase IV: -Chloroquine, Atovaquone and Proguanil, Doxycycline Biological: Rabies Vaccine
Schistosomiasis	Intestinal schistosomiasis: -*Schistosoma mansoni, Schistosoma japonicum, Schistosoma mekongi, Schistosoma guineensis and related S. intercalatum* Urogenital schistosomiasis: – *Schistosoma haematob*	Praziquantel	-Lipid Nanocapsules[49] -Nanoemulsions[50]	–
Soil-transmitted helminthiases	Roundworm: *(Ascaris lumbricoides)* Whipworm: *(Trichuris trichiura)*	-Albendazole -Mebendazole -Ivermectin	-Liposomes -Microemulsion[51]	–
Taeniasis/cysticercosis	-*Taenia solium* -*Taenia saginata* -*Taenia asiatica*	-Praziquantel -Niclosamide		–
Trachoma	*Chlamydia trachomatis*	Azithromycin	-Liposomes[52] -PLGA nanoparticles[53]	Under Phase IV: Azithromycin mass treatment and Azithromycin targeted treatment
Yaws	*Treponema pallidumm*	-Azithromycin -Benzathine penicillin		–

so far and the future prospects of nanocarriers to be explored to widen the horizons of treatment of neglected diseases for the benefit of mankind as well as how it is successfully developed by researchers and co-workers like as lipid based nanocarriers for Buruli ulcers, nanoparticles of benzimidazol for chagas disease, nanosuspension for cysticercosis, magnetic nanoparticles for dengue, solid lipid nanoparticles for echinococcosis, microemulsion and microcapsules for Foodborne Trematodes, liposomes for leshmaniasis, nanoemulsion for leprosy, PLGA nanoparticle for Lymphatic Filariasis and so on.

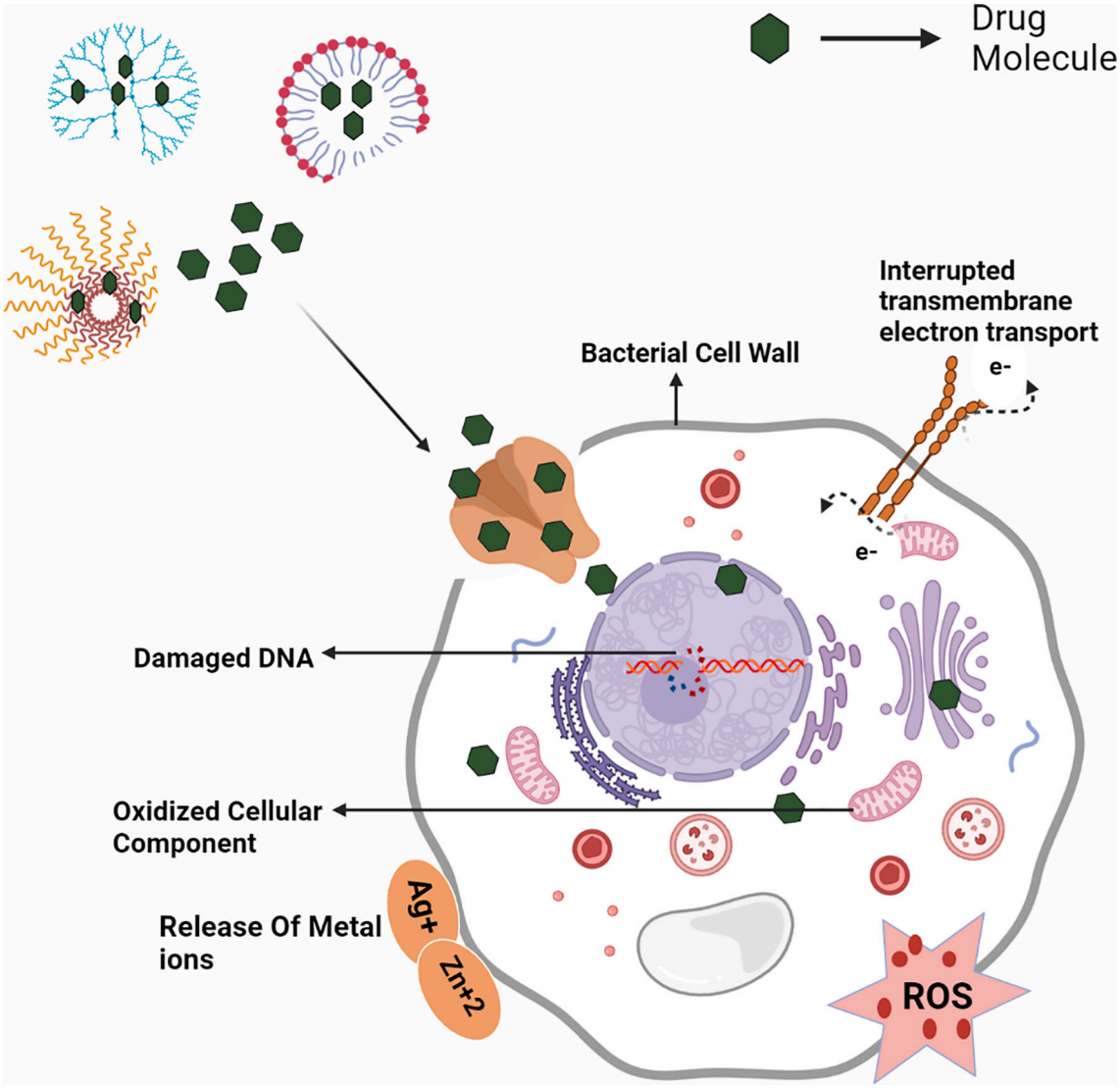

Fig. 3. Nanocarriers shows better transmembrane transport through the cell due to nanosize leading to mitochondrial damage.

3. Individual diseases addressed with a view point of nanocarriers interventions

3.1. Buruli ulcer

Buruli ulcer is chronic necrotic infection of skin. It is the third most dangerous mycobacterial infection after tuberculosis and leprosy [61]. It is mainly abundant in tropical regions of Africa, Japan and Australia, affecting the children of age 5–15 years. Largest number of endemic cases occurs in rural central and West Africa such as Ghana, Congo, Cameroon, Nigeria etc. It is caused by mycobacterial ulcerans, the disease starts with simple dermal papule leading to extensive necrotic ulcer in few weeks. Buruli ulcers damage nerves and blood vessels as well as invade bones. Metastatic lesions can occur in the skin, soft tissue, or bone and may spread through the lymphatic circulation or vasculature. The mycobacterium releases an exotoxin named mycolactone, a soluble polyketide which is cytotoxic leading to fast dramatic destruction of cells and extensive coagulating necrosis without inflammation and fever. The mycolactone inhibits translocation of protein in endoplasmic reticulum, leading to defect in protein metabolism, cell detachment, and AT2R receptor activation causing hypoalgesia, neurite degeneration and cell death. Almost 90% of ulcerative lesions occur on lower extremities and limbs. World health organization (WHO) in 1998 classified it as neglected infectious disease. As per WHO reports, Buruli ulcer is reported in 33 countries in Africa, Asia, the Western Pacific and America. Democratic Republic of the Congo and Ghana, Benin and Cameroon report the majority of cases. The major endemic countries outside Africa are Australia and Japan [62].

3.1.1. Current treatment

Until 2004, the treatment of Buruli ulcer was exclusively relied on surgery, extensive incisions and skin grafting. Although this treatment goes well only with early lesions, it is impractical with large lesions leading to amputation of limbs. From 2004, while considering endemic disease, WHO mentioned the 2 month first line therapy for the management of Buruli ulcer i.e., daily subcutaneous injection of streptomycin and oral administration of rifampicin [63]. The treatment can promote healing without relapse, arrest the disease and able to reduce surgical excisions. The classes of antibiotics those are highly preferred as the treatment strategy against buruli ulcers are aminoglycosides, rifamycins and fluoroquinolones. Furthermore, wound care is also desirable for lesion, the topical chemical treatments like clays, phenytoin powders, and nitrites, physical treatments like application of heat for healing after surgery and hyperbaric oxygen are currently used. The major challenge with current treatment of Buruli ulcer involves long hospital stays (average of 3 months), antibiotic resistance, and surgical

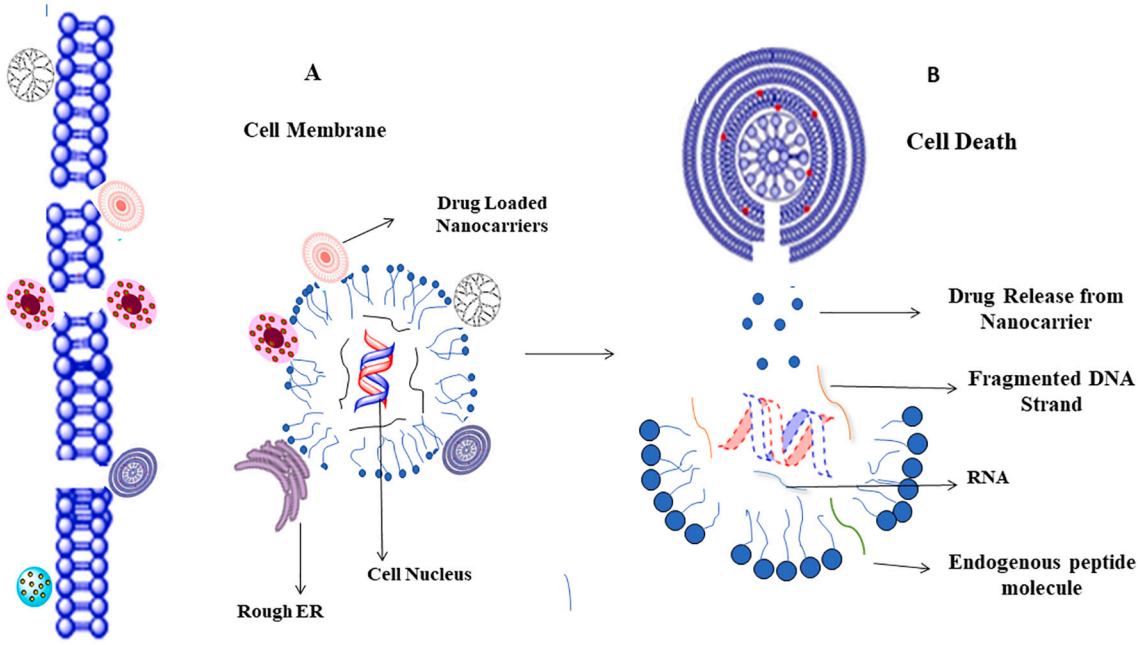

Fig. 4. Mechanism of action of drug loaded Nanocarriers.
Fig. A; illustrates the transcellular transportation of drug loaded nanocarrier through lipid bilayer into the cell membrane. Fig. B; illustrates the release of drug molecule from nanocarrier and enter in the nucleus via nuclear pores. While, nucleus consist of genetic component the DNA and RNA. Drug molecule binds to the base pair of DNA lead to development of mismatched base pair which result in fragmentation of DNA and death of the cell.

procedures leading to patient discomfort and inconvenience. Another challenge to overcome buruli ulcer is its early detection and diagnosis. As per WHO, the research priorities include developing diagnostic kits for early detection of disease and development of vaccine or the improved treatments for patient convenience [64].

3.1.2. *Nanocarriers for buruli ulcer*

As the existing treatment of Buruli ulcer is lengthy and relies on drugs for tuberculosis, it has drawback of not being effective against severe lesions and associated with adverse effects and cumulative toxicity due to high doses. Further, the conventional drug delivery systems are not able to provide sufficient drug concentration and targeting at cellular level leading to inefficient therapeutic response. The antibiotics has demonstrated high in vitro antimycobacterial activity against *M. ulcerans* but do not result into therapeutic benefits when administered in humans due to poor reach to the deep necrotizing tissues where M ulcerans proliferates and/or obstruction of deep penetration due to irreversible tissue damage. Despite clinical efficacy the severe side effects of ototoxicity, nephrotoxicity and hepatotoxicityadvocates for alternative treatments.

In a review published in 2017, a comparative study for evaluation of effectiveness of antibiotic regimen of streptomycin – rifampicin based on clinical trials was performed, on patients of all ages taking antibiotics and those without antibiotics and surgery treatment for Buruli ulcer. The search strategy of database was aimed at finding both published and unpublished trials between 1990 and upto 2014. Evidence indicated from the systemic review suggests that surgery remains necessary for some lesions if they are not early detected. Early diagnosis of disease with antibiotic treatment has a good success rate [65]. A diagnostic test established by a researcher from Harvard university in collaboration with WHO for the detection of mycolactone toxin produced from bacteria leading to tissue damage which if can be detected in early stages can help in cure of Buruli ulcer by combination of antibiotics, Although, in another preliminary trials in Benin and Ghana discovered that test is highlydelicate than microscopic studies and it is easy to performed by the operators even those having basic training experience at district level labs and hospitals. WHO officials said that this diagnostic kit can play as game changer as early diagnosis will be able to cure Buruli at early stage with the help of antibiotics [66].

Recently researchers have identified a highly bactericidal compound pyrazolo [1,5-a] pyridine-3-carboxamide, TB47 against *mycobacterium ulcerans* in mouse model with less toxicity [67]. Currently scientists are focused to understand the Buruli ulcer at genetic level, which may lead to a hope for development of vaccine in coming decade, recently a genome wide association study of Buruli ulcer performed to understand role of LncRNAs and autophagy pathways in rural Benin [68].

Wound care is also an important aspect in treatment of Buruli ulcer. Topical Nano-formulations can play effective role for treatment of lesions in Buruli ulcer as wound care is also desirable for lesions. Nanoformulations provide drug targeting, low dose efficiency and intracellular delivery leading to drug accumulation. For topical route also nanoparticulate drug delivery has advantages of improved permeation. Liposomes affects subcutaneous skin permeation of drug molecules either the molecules penetrates through the skin barrier associated with intact liposomes or they crosses after liposome disruption through skin thereby facilitating the drug transport across skin by hydration of layers or other physicochemical changes. In 1980 Mezei and Gulasekharan first reported that Triamcinolone acetonide loaded liposomes have higher accumulation within dermis and epidermis with low systemic circulation [69]. Lipid nanocarriers are being explored for topical delivery of drugs for treatment of lesions in buruli ulcer [70]. Clay compositions for topical application are being investigated for lesion treatment in buruli ulcer. Antibacterial Clay compositions were patented in USA in 2016 for treatment of buruli ulcer. Antimicrobial composition is prepared from calcium bentonite, sodium bentonite, pyrite and water. Dry clay is mixed with water and applied as paste or poultice to the skin lesion of patient.

An open-label, non-inferiority, randomised (1:1 with blocks of six) multicentre, phase 3 clinical trial was carried out, where oral dosing of RC8 to RS8 in patients with initial, restricted Buruli ulcer lesions was compared. Although, oral rifampicin 10 mg/kg with intramuscular streptomycin 15 mg/kg once daily for eight weeks (RS8) is very efficacious, streptomycin injections are unpleasant and possibly toxic. For treatment of early Buruli ulcer lesions, they wanted to study the

effectiveness and tolerance of oral rifampicin 10 mg/kg + clarithromycin 15 mg/kg extended release once day for 8 weeks (RC8) to that of RS8. Lesions were cured without recurrence in 144 (95%, 95% CI 91 to 98) of 151 patients treated with RS8, compared to 140 (96%, 91 to 99) of 146 patients treated with RC8 at week 52 after starting treatment. The difference in the amount of cases with cured lesions, −05 (95% CI –52 to 42), was not statistically higher than 0 ($p = 0.59$) The upper limit of the 95% confidence interval for the difference of 42% is less than the non-inferiority margin of 12%, indicating non-inferiority. Lesion healing in category I (5 cm) lesions took 16 weeks (IQR 6–28) in the RS8 group, compared to 28 weeks (16–38; $p = 0.0001$) in the control group. Category I lesions healed at a median of 13 weeks (IQR 6–24) in the RC8 group, compared to 20 weeks (12−32) in category II ($p = 0.031$). The kind of lesion (ulcer vs. non-ulcerated lesions at presentation: nodule, plaque, or oedema) had no effect on healing duration. Ulcers healed in the RS8 group in 20 weeks (IQR 8–28) versus 24 weeks (6–35) in non-ulcerated lesions ($p = 0.31$). Ulcers healed at a median of 12 weeks (IQR 8–24) in the RC8 group, but non-ulcerated lesions healed at a median of 20 weeks in the non-ulcerated group. The tudy concluded that a fully oral antimicrobial treatment with rifampicin and an extended release version of clarithromycin (RC8) for early, localised Buruli ulcer was non-inferior to a treatment with rifampicin and injectable streptomycin (RS8). Despite the fact that both treatments were generally well tolerated, the safety results for RC8 treatment were in favour. Eight people who received streptomycin experienced side effects symptoms that were related to the medicine. Their findings support the use of RC8 as a first-line treatment for early, circumscribed Buruli ulcer lesions when fully oral treatment is available [71].

3.2. Chagas disease (trypanosomiasis)

Chagas disease was identified with the name of American Trypanosomiasis. It was discovered by Brazillian physician Carlos Chagas in 1909.The disease is big health problem in Latin America as it is endemic in Latin American countries affecting 10 million of economically active people. Centre for disease control (CDC), America has classified Chagas disease as one of five neglected parasitic diseases. It is caused by flagellate protozoan Trypanosoma cruzi, transmitted to human by haematophagous riduvidae bugs like triatomainfectcans, triatomadimidiata, triatomasanguisuga via faeces of bugs, ingestion of uncooked infected food, infected blood transfusion, contaminated food and congenital route. Acute phase is asymptomatic; nearly 40% of people develop symptoms after chronic infection for many years when intracellular Amastigotes (multiply in host cells to release trypomastigotes to blood) causes irreversible damage to heart, oesophagus and colon of patients. Heart is the main organ affected; symptoms include thromboembolism and cardiomyopathy leading to cardiac failure and death. Chagas is non ischaemic cardiomyopathy is most important manifestation of disease.

Chagas disease can be caused by a sudden, transient illness (acute) or a long term (chronic) disorder. Symptoms might range from mild to severe, although many people who are affected have no symptoms and are ignorant that they are infected. One-third of infected people will have cardiac damage, which can lead to progressive heart failure or even death, with symptoms appearing years, if not decades, later. In persons living with HIV/AIDS, Chagas disease is a severe parasitic infection that causes meningoencephalitis and myocarditis [72,73] Unfortunately, the treatment for chagas disease is limited, a few compounds are in phase III clinical trials and the drug discovery efforts are limited.

3.2.1. Current treatment

In the past decades minimal amount of research was focused towards discovery of new drugs for treatment of neglected diseases, even though some medicines were discovered lately but unfortunately none of them were for Chagas disease. Furthermore, recently the studies towards understanding of *T cruzi* genome are performed but still there is lack of vaccine for chagas disease. The London declaration on neglected tropical diseases anoounced for eliminating or controlling 10 neglected diseases by 2020 including chagas disease but less than 1% of chagas infected population is treated [74]. Current treatment includes two nitroheterocycles; Nifurtimox and Benznidazole for last 45 years. Currently biphosphonates; Pamindronate and ibandronate (Pyrophosphate metabolism inhibitors), Alloprurinol (purine salvage inhibitor), K777 (cysteine Protease inhibitor), Thioridazina (inhibition of reductive metabolism) and Posaconazoles (ergosterol biosynthesis inhibitors) are parasitological cures in acute and chronic infections. Biphosphonates inhibit parasite growth by inhibition of protein prenylation but long term use of Biphosphonates lead to ocular inflammatory reactions, nephrotic syndrome, renal failure and osteonecrosis of jaws as well as impaired access to targets, high plasma concentration and toxicity.

3.2.2. Nanocarriers for chagas disease

In order to minimize the above mentioned side effects of conventional therapy there is a need of reduction of dose and frequency of medicines. Also, the main challenge of Chagas disease is to eradicate intracellular parasite and to cross the barrier to reach the sufficient amount of drug to the intracellular site. The selective and massive delivery of drug to the host cells would minimize the side effects and improve the therapeutic efficiency of treatment. [75]. Circulating accessible Typomastigotes and intracellular Amastigotes are the potential targets for the treatment.Nanocarriers provide active drug targeting via. Surface modification with ligands i.e., proteins, peptides, aptamers, polysaccharides and small molecules which provide site specific delivery by binding to a specific receptor (Fig. 5). Nanodrug delivery based products are a great tool to cross anatomical barriers and improve access to the cellular target of drug.First nano based drug delivery system of chagas disease was liposomal formulation using stearylamine and egg yolk phosphatidylcholine. The liposomal formulations were studied on *T. cruzi* infected HELA cells. Stearylamine loaded liposome are able to destroy the forms of T.cruzi i.e., 50% of trypomastigotes within 12 min and 50% of epimastegotes within 310 min. Over 99% of trypomastigoteswere killed within 60 min. It was found that SA liposomes can kill the T cruzi cells efficiently even without entrapping any drug, this finding suggests that how nanocarriers can dramatically treat chagas disease [76].

In another study, Trypanocidal drug Nifurtimox was encapsulated in poly-ethyl cyanoacrylate (PECA) nanoparticles.Nanoparticulate Nifurtimox exhibited IC50 values 21 and 13 times lesser than that of free drug when tested against trypomastigotes and intracellular amastigotes [77].

Benzimidazole is the drug of choice for treatment of chagas disease but it has severe side effects like polyneuritis, lymphadenopathy and bone marrow depression on long term use in chronic patients, therefore patient fails to comply with the treatment; which causes the treatment to be discontinued. Also high doses of drug are needed to elicit desirable therapeutic response which is again an issue in chronic patients. The targeting of drug to tissues where amastigotes colonies are prominent like hepatic tissues can be addressed by nanomedicine (Fig. 6). Morilla et al. formulated multilamellar liposomal formulation of antichagasic drug benzimidazole and studied the in vitro protein binding behaviour of liposomal formulation [78]. Further they studied the selectivity of benzimidazole to hepatic tissues after incorporating them in the liposomal vesicles. The pH-sensitive fluorophore 8-hydroxypyrene-1,3,6-trisulfonate (HPTS) loaded liposomes were incubated for 10,20, 30and 40 min with murine macrophage cell line J 447 for the study of endocytosis and fate of liposomes by fluorescent microscopy, after 40 min of incubation the internalization of fluorescent liposomes confined to endolysosomes were confirmed. 0.2 mg/kg dose of benzimidazole solution and liposomal formulations were administered intravenously, Subcutaneously and intramuscularly to male wistar rats ($n = 3$), The rats in first subgroup were bled at 0.5, 1, 2 and 3 h and sacrificed at 4 h. The rats in second subgroup was bled at 5, 6, 7 and 8 h and sacrificed at 9 h. A final blood sample, liver, kidney, heart spleen, and tissue around injection site immediately after sacrifice were collected and stored at −80 °C. The

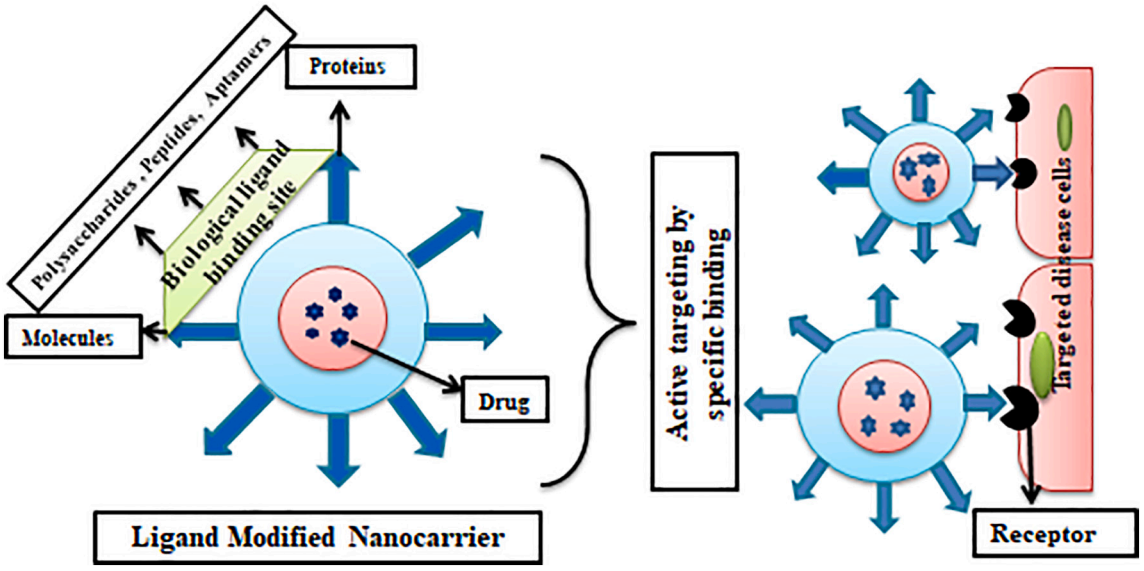

Fig. 5. Surface modified nanocarries.

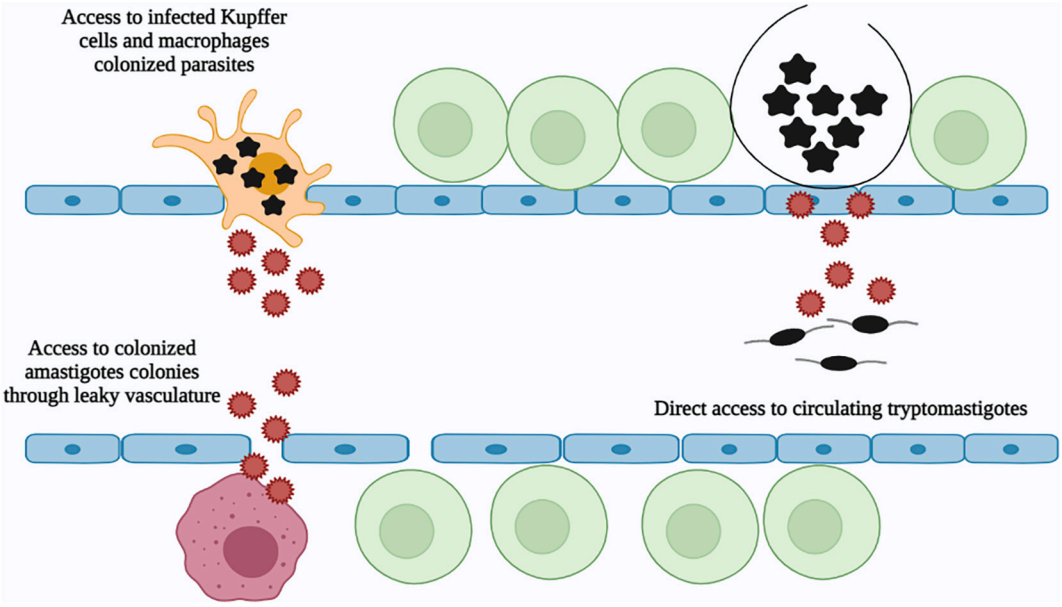

Fig. 6. Nanocarriers directly target the drug to colonized amastigotes, have direct access to circulating tryptomastigotes and access to colonized parasite in macrophages and Kupffer cells leading to complete eradication of parasite.

drug was extracted from rat tissues, quantified and followed by HPLC separation and UV detection at 324 nm. It was shown that liposomal formulation has maximum liver accumulation which is the site for parasite colony after 4 h and it was 3 fold higher than the free drug [79].

Marcela and co-workers formulate the nanoparticles of benzimidazole. The IgG titres specific to *T. Cruzi* were significantly reduced in mice when serum samples were analyzed by ELISA and after administration of Benzimidazole nanoparticles [80].

Garcia and *co*-workers formulated oral multiparticulate based drug delivery system using polymethacrylate interpolyelectrolyte complexes as carrier system. The results confirmed a reduction in liver damage as there was reduction in De Ritis index (the ratio of plasma levels of serum glutamate oxaloacetate transminase (GOT) and serum glutamate pyruvate transaminase (SGPT) in comparison to reference. Also, it was found that multi-kinetic BZ-loaded MDDS are efficient to override the parasitemia and interestingly [81].

3.3. Dengue/severe dengue

Dengue fever is a serious arthropod-borne viral infection spread by the female mosquito *Aedes aegypti*, which nests primarily in man-made containers containing stored water in metropolitan settings. It has recently become a major international public health concern, as approximately 25,000 people die each year as a result of it. Dengue fever has now been discovered in over a hundred countries across Africa, the Americas, Southeast Asia, the Western Pacific, and the eastern Mediterranean. According to a study published in 2019 on the existing and future global transmission of dengue virus, around 53% of the world's population (between 3.45 and 4.09 billion people) is at risk of infection. [82]. The transmission of disease is prevalent in urban and sub urban areas of tropical and subtropical regions worldwide. As per reports of WHO, the incidences of dengue outbreaks were severely increased within Eastern Mediterranean region since 2000. Dengue infection

symptoms involve the flu like illness, life threatening hemorrhagic fever, severe headache and even death of patients. Severe dengue is further complication due to plasma leaking, respiratory distress, fluid retention, severe bleeding, blood in vomit and organ impairment and decrease in body temperature. Dengue virus is a Flaviviridae virus with a single-stranded enclosed RNA genome (genus: Flavivrus) [83]. There are four serotypes of dengue virus (Den-1, Den-2, Den-3, Den-4) causing full spectrum of dengue illness. The immunity to one kind of dengue virus for the rest of life is achieved once a person have been infected with it [84]. Four days after being struck by an infected mosquito, a person will develop viremia, or a high level of dengue virus in the body. Clinical signs include a sudden onset of high fever, severe headache and retro-orbital pain, myalgia, arthralgia, a maculopapular rash, and minor hemorrhagic fever [85].

3.3.1. Current treatment

There is no specific treatment of dengue presently; the class of antipyretic and analgesic were preferred for the treatment of dengue globally. Severe dengue fatality rates are reduced to less than 1% with early detection of illness progression and access to adequate medical care. If significant dengue infection is not detected and treated early, the case fatality rate might be as high as 5–10%. Dengue fever has been treated with repurposed drugs such as chloroquine and statins [86]. However, in 2019 US Food and Drug Administration permited the use of Dengvaxia for the treatment of dengue under some restriction to licensing in Europe and dengue endemic affected areas of United States (US) only. After the positive laboratory reports Advisory Community on Immunization Practice (ACIP) access, the use of Dengvaxia on June 2021 for children between the ages of 9–16 years. Meanwhile, the prevention is dependent on control measures of vector by combating the growth of mosquitoes.

3.3.2. Nanocarriers for treatment of dengue

Silver nanoparticles were reported using Moringaoleifera seeds extract. The formulated nanoparticles showed antiviral activity against Den-2 infected cells. Most of the nanoparticles for treatment of dengue are developed against the vector mosquito *aedes aegypti* [87]. The mosquitocidal silver nanoparticles were formulated by Murugan and co-workers using extract of Artemesia vulgaris against the larvae and pupae of mosquitoes [88]. There are constant efforts by scientists for development of vaccine against dengue. So far, one vaccine, Dengvaxia CYD-TDV a tetravalent live attenuated vaccine from Sanofi Pasteur is registeredand others are under late phase of clinical trials but none is efficient in protection against all four serotypes. It has shortcomings of less effectiveness and is effective only on the children above age of 9 years. The other vaccines in clinical trial includes TV003/TV005 and DEnVax (TDV). Durbin and co-workers in 2005 performed a study of immunogenicity of live attenuated virus Den 4 in phase 2 clinical trials. The vaccine was found to be safe and immunogenic. The live attenuated vaccine has the limitations of unbalanced responses to viral serotypes. Metz and co-workers has formulate a recombinant vaccine as well astetravalent DENV protein subunit vaccine via utilizing recombinant envelop protein which going to adsorbed on the surface of PLGA nanoparticle for immunogenicity in mice [89]. Reginald et al. 2018 explains that a successful dengue vaccine must be able to impart neutralising antibodies as well as must be able to elicit cell mediated immunity, which can be achieved by designing B, CD8+ and CD4+ multi epitope peptide vaccines [90]. Cationic gold nanoparticles containing siRNA complexes can infiltrate vero cells and significantly inhibit dengue virus serotype 2 (DENV-2) multiplication and infectious virion release. Metal nanoparticles (copper, silver, gold, and selenium) have also been examined for their larvicidal effectiveness against the dengue virus vector. Metal nanoparticles were shown to have the ability to inhibit the growth of the mosquito vectors of dengue illness, according to the research (genus Aedes) [91].

3.4. Dracunculiasis

Dracunculiais is Guinea worm infection which is parasitic disease. A person becomes infected when it drinks water contaminated by water flea that host guinea worm (Dracunculusmedinensis also known as fiery serpent) larvae. However, water fleas were died after the ingestion and get digested by the body which led to release of larvae (Stage III) and eventually penetrate the stomach and intestinal wall of the host and further entered into the abdominal region as well as retroperitoneal spaces. After maturation (60 to 90 days) mating takes place and male worm dies after mating and absorbed in the body while female worm migrate to subcutaneous tissue in the leg and after 72 h blister ruptures and worm comes out with symptoms of vomiting, fever and dizziness. The suffering patient often immerse burning lesion in water, when submerged in water the female worm releases thousands of stage 1 larvae to the water. The young form of worm survives out of human body for three weeks. Meanwhile it is eaten by water fleas; the larvae inside water fleas survive upto four months. Dracunculiasis is diagnosed by seeing the worm emerging out from the subcutaneous lesion on legs of patients. The infection does not create immunity so infections can be repeated and simultaneously many worms can emerge from patient. And the infected host remains unaware of infection until painful blister emerges. Secondary infections around blisters are another problem.

Transmission of Guinea worm occurs through contaminated unfiltered water, drinking water from ponds and stagnant water in rainy season. In 1986, dracuncluliasis was endemic in 20 countries of Asia as well as Africa, with nearly 3.5 million people affected but a great work has been done in this regard and in 2010 it reduced to 2000 cases in 6 villages of Africa There is no vaccine or treatment for guinea worm which further dropped to 1060 cases only in sudan, Mali, Ethiopia and Chad. According to WHO reports 2018, 21 human cases were reported in Chad, Sudan and Angolabut 999 cases of animal infected with worm has been reported. Mali has reported last case in 2016 and Ethiopia is free from guinea worm in 2017. Global Dracunculiasis Eradication Program is now near its goal to achieve and it's a hope that it will be successful in near future.

WHO certifies a country free from dracunculiasis if there are no records of indigenous cases for 3 consecutive years and they maintain adequate surveillance nationwide. 192 countries and territories had been certified free of dracunculiasis in 2012. The treatment of dracunculiasis includes extraction of worm with stick by winding it and pulling it out.it is painful and may take several weeks as it is extracted centimetre only. The secondary infections are treated by antibiotic ointments. Anthelemintic drugs were not effective against dracunculiasis and still there is no vaccine against dracunculiasis [92]. The water treatment for decontamination and disinfection of contaminated water by using nanotechnology for biosorption and nanoadsorption of removal of contaminants, nanofiltration and ultrafiltration is being developed recently.

3.5. Food-borne trematodiases and fascioliasis (liver flukes)

Intestinal flukes, Liver flukes and lung flukes are known as food borne trematodes. Liver flukes (*Fasciola hepatica*, *Opisthorchis felineus*, *Clonorchissinensis*, *Fasciolagigantica*, and *Opisthorchis viverrini*), intestinal flukes (e.g., *Echinostoma*spp, *Fasciolopsisbuski*, and the heterophyids) and lung flukes (*Paragonimus* spp.). The infection in human occurs due to ingestion of contaminated freshwater fish, shellfish, water plants and raw and uncooked aquatic products; hence it is called fish borne and plant borne trematodiasis. Trematodes possess the property like oral and ventral sucker and lacking the respiratory as well as circulatory systems. Due to ventral and oral sucker, flukes were attached to the host bile duct, intestine and lung parenchyma.

Clonorchiasis is also known as Chinese liver fluke disease. It is a common infection of dogs and other fish eating carnivores which are reservoir final hosts. Humans may substitute reservoir final hosts if they

eat raw, salted, smoked, uncooked or improperly cooked fish as they ingest metacercariae larvae reaching to intestine and bile ducts. The infections can be acute and chronic. The acute infections are asymptomatic and the chronic may lead to fibrosis and destruction of liver parenchyma, carcinoma and fatal cancer of bile ducts.

The only drug recommended for Clonorchiasis is Praziquantal. Diagnosis of disease is done by stool tests and immunological assay to identify antibodies.

Fasciolasis is caused by two parasitic trematodes *Fasciola hepatica* and *Fasciola Gigantica*, it mainly affects liver. The infection is cused by leaf shaped worms which are visible by naked eyes. The infection starts when infected animals like cattles, sheeps, buffaloes, goats horses donkeys, defaecate in fresh water. As the worm lives in bile ducts of those animals the eggs and larvae comes out in faeces and are ingested by water snails which are intermediate hosts. Further larvae are release from snails and swim and attach to the aquatic plants like water mint, water cress and many salad vegetables which are again source of infection when ingested. In acute phase worms penetrate intestinal walls and peritoneum and liver cells and cause internal bleeding, fever, nausea, abdominal pain. While chronic infection leads to anemia, jaundice, liver fibrosis and pancreatitis.

WHO estimates that no continent is free from fasciolasis there are 2.4 million people are infected in more than 70 countries. An area of high transmission includes highlands of South America, Nile valley, Caspian Sea basin and countries of south East Asia.

WHO and Novartis signed an agreement in 2018 for (2019–2022) for providing donation of Triclabendazole to countries where fasciolasis is endemic. Triclabendazole is the only medicine recommended by WHO for the treatment of fasciolasis.

Daniel and co-workers has developed chitosan based nanoformulations of triclabendazole which is the only medicine recommended for fasciolasis and clonorchiasis (liver flukes). The drug entrapped chitosan nanocapsules and nanoemulsions were successfully uptaken by caco 2 cells [93]. A number of species of trematodes of genus paragonimus (P. westermani, P. heterotremus and *P. philippinensis*) causes the lung fluke disease or paragonimiasis.It is most commonly found in China, Asia, korea, phillipines, Thailand, Vietnam and other east asian countries Paragonimus is the parasite of crustacean eating mammals like dogs, domestic cats, tigers, mongoose, leopards and monkeys which are the final reservoir hosts. The adult lung fluke lay eggs in the lungs which are either swallowed and defecatedor expectorated in sputum. The infection in human being occurs due to swallowing of uncooked crustaceans. The symptoms of lung fluke disease include rusty sputum; cough lasting for more than three weeks and symptoms similar to tuberculosis.

Infections caused by digenetic trematodes, such as schistosomiasis and fascioliasis, are a threat to people in low income generated countries of the tropics, causing severe morbidity and mortality in people as well as significant global losses in cattle productivity. As a result, there has been a worldwide hunt for new control measures for the disease's snail vectors. As a result, the molluscicidal efficacy of a new medication, curcumin and nisin poly lactic acid (PLA) encapsulated nanoparticles (CurNisNp), was tested against adults (> 2 months old) of Biomphalaria pfeifferi, Bulinus globosus, and Lymnaea natalensis vector snails. After 96 h of exposure at various doses, mortality was measured. The molluscicide was shown to be highly toxic to snails of the species *L. natalensis* (LC50 323.6 ppm). This study adds to the appeal of curcumin-nisin polylactic acid (PLA) nanoparticles as a molluscicide, indicating that they may be feasible option molluscicides for the selective management of fascioliasis. More pharmacological optimization, on the other hand, could result in a higher molluscicidal potency [94].

3.6. Human African trypanosomiasis

Human African trypanosomiasis, also known as sleeping sickness, is a parasitic disease spread by mosquitos. Approximately 60 million people worldwide are at risk of contracting the disease. Human pathogenic parasites are being spread to humans through bites of blood sucking tsetse flies (genus Glossina) that have acquired their infection from humans or animals harbouring human pathogenic parasites [95]. The infection caused by *Trypanosoa bruceei gambiense* lead to develop gambiense human African trypanosomiasis (gHAT) and almost 98% of all HAT cases reported from it. Human was badly affected by gHAT and this parasite abundantly found in animals. gHAT found to be a chronic disorder which categorised in two stages i.e., haemolytic stage which shows the symptoms like headaches, pain in joints, fever and enlargement of lymph nodes. While other one is neurological stage, symptoms like sleep disturbance, changes in behaviour, confusion, sensory and motar disturbance. These disabilities were occurred when parasite crosses the BBB. The main vehicle of spreading of HAT is the bite of infected tsetse fly of genus glossina. However, transfer of infection from mother to child is also a mode of transmission [96].

The various tactics and interventions were utilized to overcome the infected parasites i.e., supply of safe and purified water to minimize the direct contact with tsetse flies (WASH), vector control baits and traps with permeated screens, treatment of poultry animals like cattle and pigs and controlled the use of insecticides. The medicinal treatment including pentamidine, eflornithine and nifurtimox and fexinidazole act against gHAT and the cases were detected based on active and passive screening, in active screening-survey of infected peoples those are visiting in the endemic villages and screening of entire population. While in passive screening those are suspected in clinical test going to attend the health resources [97].

The infection occoured by trypanosoma brucei rhodesiense caused rhodesiene human African trypanosomiasis (rHAT) and almost 2% of entire cases reported through it. However, rHAT were least affected to human compared to gHAT and know to be zoonosis (occoured from wild and domestic animals). Short term infection were rapidly caused by rHAT when parasite exist in CNS through BBB i.e., headache, pain in joints, fever, cardiac and renal disorders (haemo lymphatic stage) as well as disturbance in sleep, behavioural changes, confusions and motar and disturbances (neurological stage). Similarly, rHAT is spread through the bit of infected tsetse fly of genus glossina and spreading through mother to child is also a mode of transmission of parasite [98].

The interventions and strategies to overcome this infection via., supply of safe and purifies water and decrease contact with tsetse flies (WASH), spreading of insecticide and vector control tactics using baits and traping of permeated screens, treatment of poultry animals like cattle and pigs, medicinal treatment including suramin and melarsoprol and detection of infected individual by passive screening [99]. There is no HAT immunization available, and it is unlikely that a vaccine will be developed any time soon. The primary reason is the parasite's ability to escape antigenic variety from the human immune response by modifying the significant surface glycoprotein possess on its surface to avoid antibody-mediated reactions [100]. Few drugs have been recommended for the treatment of HAT based mostly on disease stage and infecting sub-species. Pentamidine and suramin are used as 1st line agents in the early stages of *T. brucei*, but pentamidine is extremely toxic. Melarsoprol and eflornithine were used in the stage 2 of gambiense. These drugs have been developed between 1920 and 1949, and their mode of action is still unknown. Under specialized entitlements, another medicine, nifurtimox (released in 2009), is administered in combination [101]. Fexinidazole, a newer medication, is an orally administered medicine that is used to treat both phases of *T. brucei* gambiense [102]. In 1975, the World Health Organization designated trypanosomiasis as one of the neglected illnesses in order to encourage endemic countries to find more effective medications. There are still no new medications that have been found and licenced for the treatment of HAT [103].

3.6.1. Nanocarriers for human African trypanosomiasis

Today, the WHO recommends pentamidine, suramin, melarsoprol, eflornithine, nifurtimox, and fexinidazole as therapeutic choices for

HAT, depending on the parasite sub-species implicated and the stage of illness development. Since its discovery in 1940, pentamidine was used to treat the early stages of gHAT. It's an aromatic diamidine with a slew of negative side effects, including glucose homeostasis issues, leukopenia, and hypotension, as well as a cumbersome delivery route (intramuscular). Furthermore, it has a low permeability of the blood-brain barrier (BBB), implying that it is ineffective in the treatment of late-stage HAT. Suramin was introduced to the market in 1920 and is still one of the therapy options for the first step of rHAT. The most prevalent side effect is urticarial rash (which affects around 90% of the patients). Nephrotoxicity, pyrexia, and nausea are some of the reversible side effects. In T.brucei, as a monotherapy treatment, nifurtimox is efficacious against both beginning and at the end of Gambian infections, although it has a very inconsistent cure rate (30–80%) and severe toxicity with long-term use. Clinical studies for Oxaborole SCYX-7158 for HAT treatment are presently underway. The positive results of SCYX-7158 in animal models have led the relevant researchers to assume that late-stage HAT could be a viable therapy option. Two more oxaborole compounds, SCYX1608210 and SCYX-1330682, also exhibited good efficacy in animal models of the condition. The study found that the medicine penetrates the BBB swiftly, making it a promising choice for late-stage HAT treatment, while some side effects, such as gastrointestinal problems and headaches, have been reported. In 2017, a phase II/III research to examine the efficacy and safety of SCYX-7158 as an oral treatment for adult gHAT patients was initiated based on these findings [104]. In the current era, nanoparticle gained the attention of researchers to go in depth in nanotechnology and drug delivery across biological membranes for treatment against NTD. Nanoparticulate drug delivery systems of lipid, polymer, or metal composition have emerged as a promising field of research, as experimental findings suggest that they can improve the ability to directly target pathogens, penetrate host barriers allowing the drug to reach pathogen residence areas, and reduce toxicity by reducing the amount and frequency of dosing. Franco and *co*-workers were developed polymer derived nanocarrier and colloidal liposomes of pentimidine for the treatment of human African trypanosomiasis and compared the drug permeation across biological membrane from both the nanocarriers. The physico-chemical and preformulation studies were performed for proper selection of components. Cytotoxicity was done on mouse brain endothelioma cells for 96 h and cell monolayer integrity and transportation were performed for 24 h. While comparing pentamidine loaded polycaprolactone (PCL) with mean size of 267.58 nm and drug loading of 0.16 mg/mg, pentamidine liposomes shows excellent characteristics with mean size of 119.61 nm and drug loading of 0.17 mg/mg. In terms of drug release studies, PCL shows 12.13% release and liposomes shows 22.21% release after 24 h. Meanwhile, 87%, 66% and 63% of dose of liposomes, PCL and free pentamidine transported across BBB and liposomal preparation of pentamidine show excellent properties among them [105]. Combination therapy, such as eflornithine-nifurtimox, is now being utilized to treat Trypanosoma. Infections with brucei are of special interest, as is the potential use of SLNs to enhance the healing qualities of certain treatments.

In another study, Ben Zirar and co-workers created a poorly soluble drug melarsoprol nano suspension with poloxamer 188 or 407 and mannitol 72. The wavelengths measured were 324 ± 88 and 407 ± 45 nm, respectively. The size of the nanosuspension is affected by poloxamer 188 and increases with melarsoprol concentration. They were placed after a freeze-drying point, preventing the development of aggregation events. To prevent melarsoprol hydrolysis and the generation of melarsenoxide, the nanosuspension of melarsoprol must be delivered soon after reconstitution. The distribution to multiple organs in mice revealed robust reticuloendothelial pathway targeting, with a 5-to-9-fold higher concentration in the liver than the free drug. The brain concentration was 3–5 times lower than when the substance was unbound. Their large size, which makes crossing the BBB difficult, could explain these results. Melarsoprol microparticles were produced with PCL using either the suspension-in-oil-in-water (S/O/W) solvent evaporation method or the complexation of melarsoprol with methyl-cyclodextrin followed by the water-in-oilin-water (WCD/O/W) solvent evaporation method. 161 mg/g of melarsoprol were incorporate within S/O/W Microparticle and showed 50% drug release after 2 h and 80% after 7 h in PBS 7.4 containing 30% PEG solution and only 2.89 mg/g of melarsoprol microparticle were incorporate in WCD/O/W nd showed the fully faster drug release. No further tests on HAT-infected animals were conducted due to the substantial drug release reported. Furthermore, because melarsoprol is exceedingly hazardous, it is best to avoid using it with drug delivery systems [106]. Pentamidine-loaded polymeric PEGylated-chitosan nanoparticles coated with a single-domain antibody (nanobody) generated from camel heavy-chain antibodies that targets *T. brucei*'s interface Pentamidine enters trypanosomes via endocytosis when put into this nanocarrier rather than traditional cell surface transporters. The therapeutic dose of pentamidine-loaded nanobody-chitosan nanoparticles was 100 times lower than pentamidine alone in a murine model of acute African trypanosomiasis. Importantly, due to changes in the surface transporter aquaglyceroporin, this novel formulation had no effect in vitro or in vivo against a trypanosome cell line that had become resistant to pentamidine [107].

3.7. Echinococcosis

In human being echinococcosis happens due to contaminations caused by taeniidcestodes. The prominent ones of this cestode are caused by the larval stages of the genus Echinococcus. From the known genus Echinococcus- granulosus, multilocularis and vogeli/ oligarthrus causes the three prominent types of infections known as the cystic, alveolar and polycysticechinococcosis, respectively. The life cycle of this parasitic disease revolves around the canids like dogs which are known hosts for them. The prominent types are known to be of more public health concern which has issues of being tagged as the re-emerging diseases. Alternatively known as the cystic hydatid disease (CHD) in humans, the hydatid cysts are visible as water-filled tumors in the abdominal region which are caused due to Echinococcusgranulosus.

3.7.1. Current treatment

Being one of the most common and widespread among the infected parasitic disease, it has issues of being the costliest treatment in terms of public health. The generally available treatments include surgery, PAIR (puncture-aspiration-injection-respiration) technique and chemotherapy. Surgery till date is the most preferred treatment of choice as it is able to remove the cysts from the body. However, in cases where the infection has spread to multiple organs surgery cannot be performed at multiple sites in the body. In addition, surgery has serious drawbacks of the patient falling for an anaphylactic shock and chances of mortality is also high for patients who have undergone major invasive multiple surgeries. Lastly, not to forget that the chances of recurrence of the disease after surgery is always there. The current chemotherapy regimen for treating patients with cystic echinococcosis (CE) include the albendazole and mebendazoleof the benzimidazoles.

As per the dose approvals of WHO, albendazole is administered orally as tablets (twice a day) to 10 to 15 mg/kg of body weight for a 28-day cycle. The tablets are to be taken with meals to a maximum daily dose of 800 mg. After undergoing chemotherapy for 12 months; 50 to 70% of the patients have shown a reduction of cysts both in terms of size and numbers. Whereas, only a fraction of 10–30% would show a pure cure meaning complete removal of the infection and 14 to 25% of patients show relapses after chemotherapy.

Chemotherapy with these drugs is also done before and after the surgery to minimize the spread of the infection. However, many serious side effects including hepatotoxicity, leucopenia or thrombocytopenia are seen with this drug which needs a better treatment.

To avoid adverse reactions patients are given steroids and

anticonvulsants. The first week of the therapy being the toughest as the patient is trying to adjust to the chemotherapy, oral or intravenous corticosteroids are given to avoid cerebral hypertensive reactions.

3.7.2. Current initiatives by the government

After intervention of WHO for gathering data from Europe, Asia and USA it is clear that human echinococcosisis more prominent in the northern hemisphere. Since then, this infection being lethal has been declared as a public health problem. The WHO and informal working groups of WHO working on Echinococcosis have prepared a manual to present all important aspects of the infection like life-cycle of the causative organism, epidemiology, diagnosis, treatment and the prevention methods. The governments of individual countries are concern to provide current knowledge to be clubbed with the modern techniques.

3.7.3. Nanocarriers for echinococcois

In humans, albendazole (ABZ) is one of the most preferred chemotherapeutic agents against cystic echinococcosis (CE).The hepatic enzymes convert ABZ into its active metabolite albendazole sulfoxide (ABZSO) after oral administration. Both these drugs are poorly water soluble. To overcome the drawbacks associated with the conventional chemotherapy using ABZ; Soltani et al. (2017) took both forms ABZ and ABZSO to encorporate into SLNs and examined their ability to infertile hydatid cysts. The drug (ABZ or ABZSO) was dissolved in the lipid melt containing comprisal 888 ATO and both tween-80 and PVA were used under stirring to get SLNs using the micro emulsification technique by high shear homogenization method. The final dispersion containing SLNs were freeze-dried to enhance their stability by storing in vials at 4 °C. The nanoparticles so obtained were of size <180 nm. The drug loading was low in both drugs; 6.1% for ABZ-SLN and 6.3% for ABZSO-SLN. However, the entrapment efficiency of the loaded amount was ~90% for both. Membrane permeation studies were performed using the hydatidcystsof the livers of infected sheep. The intra-cystic drug concentrations showed that the in vitro permeability study revealed that both ABZ-SLN and ABZSO-SLN had significantly higher concentration of drugs into the hydatid cysts. Among the two nano systems, the ABZSO-SLNs had better permeation across the cystsdue to increased diffusion or better solubility than ABZ [108].

The other benzimidazole derivative-mebendazole (MBZ) is the other choice of drug in treating alveolar echinococcosis. This drug too has poor solubility issues leading to lower bioavailability. Since the treatment lasts for 1–2 years with another 5–7 years needing monitoring as the drugs treatment might lead to relapse, even recurrence causing death of the patient.The solubility issues of the drug were resolved by converting into solid dispersions using the nanocrystal techniqueusing polyethylene glycol (PEG) [109]. Such developed polymer crystals of MBZ exhibited a 32-fold rise in drug solubility in vitro and 2.12-fold rise in the bioavailability of the drug studied in rabbits. The presently available drugs poor bioavailability has all the chances for causing a recurrence in the patient and may sometimes also be responsible for even the death. It was concluded by this study that such nanocrystal formulations of MBZ would be efficaciously suited as a safer treatment of human echinococcosis.

Another benzimidazole anthelmintic compound flubendazole (FLBZ) is also useful in echinococcusgranulosus; especially in nematodiasis and treatment of hydatid cysts. Although FLBZ effectiveness has been reported to be better than ABZ particularly in secondary hydatid cysts [110,111]. In mice; its efficacy is still not understood well in human cystic echinococcosis. The main reason cited for this is the drug's hydrophobicity which makes it poorly available in the blood circulation and the cysts [112]. Hence, to maintain the required amount of drug in the desired site of action, a much higher dose is given by the conventional dosage forms frequently which subsequently increases the chances of dose related side effects. Amphiphilic di block copolymers like methoxy polyethylene glycol-polycaprolactone (mPEG-PCL) have been reported to effectively entrap the hydrophobic drugs and enhance their bioavailability. In this context to enhance the uptake and improve the bioavailability of FLBZ it was loaded in mPEG-PCL nanoparticles by nanoprecipitation method to a mean particle size of 101.41 ± 5.14 nm [113]. The *E. Granulo protoscoleces* were taken from infected sheep's liver hydatid cysts and maintained in vitro in RPMI medium. The mortality rate of metacestodes of E.granulosuswas 100% with a 15 days treatment by FLBZ-NPs reflecting. This protoscolicidal effectwas most effective at a concentration of 10 μg/mL in NPs and was much better than the plain drug FLBZ.

The scolicidal agents cause infertilization and inactivation of the parasites leading to their death. Silver nitrate, hypertonic saline, mannitol, chlorhexidine gluconate, or ethanols are some of the examples of scolicidal agents. These agents are better than the invasive surgeries as they do not require the surgically removal of the cycts of the protoscolices. However, most of the scolicidal treatments have consequences of causing necrosis of the liver or fibrosis of the biliary tract in addition to some serious adverse effects, low efficacies and toxicities [114]. With an aim to put forth novel scolicidal materials with low adverse effects; Rahimi et al. (2015) used green silver nanoparticles having scolicidal activity against *E. granulosus*. The scolicidal efficacy of the synthesized green silver nanoparticles were investigated in-vitro on protoscolices of CHD. The authors used the hydatid cysts of *E. granulosus* from infected sheep and asepticallytransferred them to settle down and collected the protoscolices. Other than being economic method the rationale suggested for the use of preparing green silver nanoparticles (AgNPs) was their eco- friendly nature with benefits of using natural resources (yeast extract). In this study the supernatant of the aqueous aerial extract of *Penicillium aculeatum* to 1 mM aqueous $AgNO_3$ solution led to formation of AgNPs with a mean particle size of 80.42 nm. After 60 min, the mortality rate was 80 and 79% with AgNPs treatment by using the strengths of 0.1 and 0.15 mg/mL respectively, indicating a very high significant difference form as compared to the control group. The maximum scolicidal effect from the AgNPs (0.15 mg/mL) was 90% mortality of the *E. granulosus* in 120 min. This was a note worthy achievement both in terms of efficacy (of the treatment) and safety (of the patient). The mechanism of action by which the AgNPs exhibited this scolicidal effect was reported to be due to electrostatic interaction between the nanoparticles and the parasite. The AgNPs has a positive charge whereas the charge on the parasite (*E. granulosus*) was negative which formed a complex on its surface [115].

3.8. Leprosy

Leprosy is a chronic infectious disease caused by mycobacterium laprae. *M laprae* multiplies slowly, its incubation period is 5 years and sometimes symptom occurs after 10 days. It mainly affects skin, mucosa, peripheral nerves, respiratory tract and eyes. The disease is transmitted through droplets from nose and mouth during frequent contact. Leprosy is curable by multi drug therapy, if it is left untreated, it can lead to permanent disability to skin, limbs and eyes. Symptoms of leprosy include skin lesion with sensory loss with thickened nerves.

There were 2,16,108 cases registered globally in 2016 as per WHO in 145 countries. In 2016 WHO launched its Global Leprosy Strategy 2016–2020 towards a leprosy free world.

Multi-drug therapy with antibiotics iscurrent treatment of leprosy. Dapsone is bacteriostatic. Rifampicin is combined with dapsone for paucibacillary leprosy. Rifampcine, clofazimine and dapsoneare combined for treatment of multibacillary leprosy. Single dose of bacillary laprosy can be cured by rifampicin, ofloxacin and minocycline.

But the problem associated with current treatment is resistance due to antibiotic treatment and hypersensitive reactions. The nanotechnology based formulations are under study presently by researchers across the world. Hong Zhi Li et al. 2017 formulated PLGA nanoparticles of dapsone and clofazimine for simultaneous delivery which were further stabilized using chitosan. The nanoparticles have slow and

sustained drug deliveryin comparison to plain drugs which ensures prolonged stay of drug in systemic circulation thus decrease in progression of bacterial growth [116]. Vierra et al. 2016 developed surface functionalized solid lipid nanoparticles of dapsone for targeting intestinal M cells so as to improve therapeutic efficacy of drug for treatment of leprosy. The nanoparticles were surface coated with mannose [117]. Further, vierra et al. 2018 developed mannosylated solid lipid nanoparticles for selective delivery of Rifampicin to macrophages for treatment of tuberculosis, rifampicin is also drug of choice for treatment of lepsosy [118]. Kanwar et al. 2018 developed solid lipid nanoparticles using lactonic glycolipids for antileprotic drugs rifampicin and dapsone [119]. Joubert H 2016 developed nanoemulsion of clofazimine for topical drug delivery using Avacado oil for mycobacterium infections. It was found that emulgels were more efficient in delivery the drug to the layers of skin [120].Burger et al. 2018developed topical nanoemulsion for delivery of clofazimine, artemisone and decoquinate for treatment of topical tuberculosis which is also a mycobacterium infection [121]. Lipid nanoparticles are one of the most prevalent ways used to improve the oral administration of poorly hydrophillic medicines. Solid lipid nanoparticles, in particular, are the most promising delivery strategies for improving hydrophobic medication oral bioavailability. Using the heat homogenization-ultrasonication process solid lipid nanoparticles based system was formulated using precirol ATO 5 and tween 80. In vitro cytotoxicity tests demonstrated that when CLZ is loaded in the SLNs, gastric and intestinal cells withstand it better than when it is free in solution. The tailored nanoparticles offer a promising oral CLZ delivery system. Through a Plackett–Burman design, CLZ incorporated into polymeric nanoparticles of poly(lactic-*co*-glycolic acid) (PLGA) displayed an in vitro gradual release profile of CLZ. CLZ must be released continuously in order to avoid recrystallization in the intestinal lumen and within the cells. In addition, CLZ loaded in polymeric nanoparticles was capable of penetrating Caco-2 cellular membranes significantly after 8 h. The use of PLGA nanoparticles to administer CLZ reduced medication intrinsic toxicity and improved intestinal permeability. [122].

3.9. Rabies

Rabies is a viral disease which is spread by infected animal bite or scratch. Rabies caused nearly 17,400 deaths worldwide in 2015. It is a RNA virus of rhabdovirus family; the virus enters the peripheral nervous system directly and migrates to brain or it replicates in muscle tissues from where it enters to neuromuscular junction. After entering into brain the virus produces acute inflammation of brainleading to coma and death. Further consequences include either hydrophobia or hyperactivity in patient or paralysis.

Rabies is most common in countries where stray dogs are prominent like countries in Asia and Africa other animals like bats, foxes and racoons also spread rabies. The virus is passed though saliva of infected dog either due to bite of animal or if saliva gets into an open wound or through mucus membrane such as eye or mouth. It cannot pass through intact skin.

The symptoms of rabies include uncontrolled movements and excitement, violent movements, fear of water, confusion and loss of consciousness further leading to death.

Animal control and vaccination are the current treatments for rabies. Rabies vaccine and rabies immunoglobulins are effective in preventing the disease if person receives the treatment before start of symptoms. Washing the lesions and scratches by water and detergent or povidone prevents the transmission of virus. There are two types of vaccinations for the rabies, one is pre-exposure vaccination, and other one is post exposure vaccination. The pre exposure vaccination is done to persons who are at high risk of exposure to animals. Rabies vaccines are cell culture vaccines or embryonated egg vaccines used for pre exposure and post exposureprophylaxis. Rabies immunoglobulin is only used for post exposure purpose. Pre-exposure rabies vaccination is made up of three full intramuscular (i.m.) doses of embryonated-egg-based or cell cultured vaccine given on 0, 7 and 21 or 28 days. For post exposure purpose, Human Rabies immunoglobulin (HRIG) or equine Rabies immunoglobulin are used for severe exposure as passive immunization. While cell culture and embryonated egg vaccines are used for active immunization.

Intervention of nanotechnology is the need of hour to fight rabies, as it is fatal disease and patient is difficult to survive, once the symptoms appear. Use of nanoparticles as adjuvant for vaccine will improve the immunogenicity of vaccine while it also reduces the undesirable side effects. Nivedh et al. 2016 developed nanoparticles based vaccine using PLGA and Chitosan as polymer. Rabies whole attenuated viral antigen is entrapped in PLGA nanoparticles by emulsification solvent evaporation method and in chitosan nanoparticles by ionic gelation method which were further suface functionalized by biocompatible polymers like acacia, casein, ovalbumin etc. The nanovaccines were assessed for in vitro immunogeneity, phagocytosis assay, blood compatibility and genotoxicity, no toxicity was reported for the nanoparticles [123]. Asgary et al. 2016 studied the use of silver nanoparticles as adjuvant in rabies veterinary vaccines which were developed by green synthesis using the plant eucalyptus procera [124]. The researchers at university of Georgia 2015 reported thedevelopment of a new vaccine where the protein from rabies virus is inserted into parainfluenza virus the vaccine is named PIV5, they claimed that the vaccine is effective in rescueing the mice even after much long time of infectionwhich was previously impossible.

Further monoclonal antibodies can be explored for treatment of rabies.

Another investigation on the adjuvanticity effect of G2 dendrimer in veterinary rabies vaccination was reported. The toxicity of a nonlinear globular G2 dendrimer containing citric acid and polyethylene glycol 600 (PEG-600) was investigated in vitro using the J774A.1 cell line. The dendrimer's adjuvanticity impact was next examined using rabies virus as a model in NMRI mice. A fast fluorescent focus inhibition test was used to monitor the increase of neutralising antibodies (RFFIT). Finally, using a standard NIH test, the relative potency of the produced formulation was determined, and the results were compared (and analyzed) with the commercially available rabies vaccine. When data from the in vitro toxicity experiment is compared to the control group, no substantial harmful effect is seen in the cells. The in vivo assay revealed that mice given a specific formulation had a better survival rate due to the adjuvanticity action of dendrimer, which was also verified by RFFIT. Unfortunately, when comparing to the alum-containing rabies vaccine, the relative efficacy of the prepared formulation does not provide the desired results. Data show that nanoparticles can boost immune responses in the right way [106]. A rabies vaccination and immunocontraception using an adjuvanted hydrogel-based pDNA nanoparticulate vaccine was reported. In comparison to the Th1 type in their earlier pDNA investigation, researchers saw an immune reaction leaned towards a Th2 type in vivo. The IgG2a/IgG1 ratio (1) and the cytokine expression profile of IL-4 and IFN- were used to confirm the finding. For rabies vaccination and GnRH antibody-based immunocontraception, the humoral immune response is critical. Anti-GnRH antibody titers were discovered four weeks after immunization in mice and remained for 3 months after the animal trial ended. Future research testing prevention against rabies challenge and animal breeding prevention could benefit from the adjuvanted pDNA nanoparticulate vaccination [125].

3.10. Schistosomiasis

Schistosomiasis is a disease caused by flatworm parasites schistosoma known as blood flukes. The parasite lives in the veins draining to urinary tract and intestine which is transmitted to fresh water by defaecation and through urine from where eggs are hatched and larvae reach to water snails and again come to the human by contaminated drinking water and on contact with skin. The symtoms for urogenital

schistosomiasis include heamatouria, vaginal bleeding etc. .the symprtoms for intestinal schistosomiasis include intestinal bleeding, blood in stools, diarroea, abdominal pain etc. Praziquantal is the most commonly used drugwith other anthelmintics like Ivermectin and Avermectin, previously oxamniquine was the first line drug but its resistance was the main problem.

Praziquantel (PZQ) is a well-known schistosomiasis medicine that has been approved by the World Health Organization (WHO). It has a low efficiency in patients during the early stages of infection. As a result, numerous researchers set out to find new alternative medications for the management of schistosomiasis. Frezza et al. 2013 developed liposomal formulation of praziquantel for treatment of schistosomiasis to combat the tolerance and resistance developed due to drug so as to improve the existing treatment, it was found that the liposomal formulation was better targeted to liver [126]. Torabi et al. 2018 developed albendazole and praziquantal antihelmintic drugs loaded chitosan nanoparticles by ionotropic gelation methodfor enhancing the bioavailability [127]. De Souza et al. 2014s tudies further the effect, toxicity and permeation, of praziquantal loaded nanoparticles on schistosomamansoni cultures, it was found that praziquantal loaded SLNs were more effective leading to death of parasite cells [128].

The effect of various doses of calcium silicate (CS) containing 5% copper oxide [CS-5% CuO] on golden hamsters infected with *Schistosoma mansoni* and Schistosoma haematobium (Egyptian strains) was studied in vitro and in vivo. In vitro and in vivo tests for both Egyptian Schistosoma strains revealed that CS-5% CuO displayed excellent anti-schistosomal activity. After 6 h, 10 gmL of CS-5% CuO showed the most potential effect, with substantial activity of (P value = 0.001). As a result, CS-5% CuO could be a novel treatment for schistosomiasis [129].

Khalil et al. investigated the effects of iron nanoparticles on adult *Schistosoma mansoni* worms at 30 and 60 mg/L concentrations. Their findings showed that the concentration of 30 mg/L had activity on worms, with mortality rates of 15%, 20%, and 100% following incubation periods of 2, 3, and 12 h, respectively. After incubation periods of 1, 2, 3 and 48 h, it recorded 55%, 65%, 77%, and 100% for the concentration of 60 mg/L, respectively [130]. Luz and *co*-workers evaluated the anti-schistosomal effectiveness of curcumin coupled with poly (lactic glycolic acid) (PLGA) nanoparticles in vitro with a 100% death rate at 50 and 100 50 M after 12 and 24 h of incubation, respectively, in 2012. After 12 h of incubation at 40 M and 30 M, it resulted in a decrease in motor activity. Furthermore, after 48 h of incubation, partial modifications in adult integument, presence of modification, and structural vesicles were observed at doses of 40 M curcumin loaded with PLGA nanoparticles [131].

3.11. Leishmaniasis

One of the NTDs exacerbated by the bacterial pathogens parasite Leishmania species (Protozoa, Trypanosomatidae) is leishmaniasis [132]. Sand flies (mostly female Phlebotomus and Lutzomyia) harbored the parasite, which was transferred to humans by the bite of infected sand flies. Sand flies breed in damp soil, forests, caverns, and rodent burrows, and feed on diseased animal reservoir hosts or people. Humans can potentially spread the parasite within themselves through blood transfusions or sharing needles. Each year, 1.5 to 2 million new cases are reported worldwide, 350 million people are at risk of contracting the disease, and 70,000 people die from leishmaniasis [133]. In 2017, 20,792 new cases (94%) of the 22,145 reported to WHO existed in seven countries: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan (World Health Organization, 2018). Brazil is responsible for 96% of these cases (57,582). From 1990 to 2018, the overall incidence of Leshmaniasis increased by 52.9% in this country alone, for an even greater increase in the kids below the age of one year [134].

Leshmaniasis consist of two broad domains i.e., cutaneous and visceral leshmaniasis. Cutaneous leshmaniasis (CL) is occurred by the protozoan leshmania parasites, which is spread through female phlebotomine sandflies. The disease will developed to only 10–25% those are affected by leishmania parasite. According to the WHO, over 85% of new CL cases occurred in ten countries in 2018: Afghanistan, Algeria, Bolivia, Brazil, Colombia, Iran (Islamic Republic of), Iraq, Pakistan, the Syrian Arab Republic, and Tunisia. Annually, 600,000 to 1 million new cases are predicted to be reported worldwide [135]. Mucosal leishmaniasis (ML) destroys or partially destroys the mucous membranes of the nose, mouth, and throat [136]. Over 90% of mucosal leishmaniasis (ML) cases occur in Bolivia (Plurinational State of), Brazil, Ethiopia, and Peru [137]. Serological tests have limited validity for both CL and ML, and clinical manifestation is being used to confirm the treatment.

Cutaneous leshmaniasis develop unpredictable changes on skin, it causes disabilities and long term scares, skin lesions (ulcers), young girls faces the problem of stigmatization and mental health problems and severe mutilations on face due to mucocutanious leishmaniasis. Various reasons like improper immune system, poor housing, malnutrition and lack of economic resources which are associated with CL [138]. Core strategic tactics to overcome CL i.e., WASH- insecticide spraying along with insecticide treated net and maintainance of envornmental hazards, vector rodent control and the treatment depends on the particular parasite species, pathological reports and type of disease. Pentavalent antimonials, paromomycin, cryotherapy and thermotherapy such tools to act as local treatment against CL. Systemically availaibale treatment of liposomal amphotericin B, mitefosine and rapid diagnostic test are performed for the leshmaniasis [139]. Visceral leishamaniasis (VL) is occoured by the protozoan leshmania parasite which is spread through female phlebotamine sandflies. The disease will develop only to 10–25% those are infected by the parasites. Weight loss, spleen and liver enlargement, fever and occurrence of anemia are the symptoms was shown in VL, meanwhile in 95% cases VL found as deadly disease [140]. The treatment of HIV-Lesmaniasis is most difficult to treat and have fewer chances of diagnosis. The 5–15% of patient was suffered from post kala azar dermal leshmaniasis (PKDL) which develop rashes for 2–3 years even after treatment of VL. Patient who are suffering from PKDL have major chances of VL infection. Weak immune system, malnutrition, poor housing and lack of economic resources are associated with VL like as CL.

3.11.1. Nanocarriers for leshmaniasis

Any novel medicine for the treatment of leishmanial illnesses is a significant undertaking. Nanoscience/nanotechnology has recently been used to re-modify current anti-leishmanial medications into nanoparticle-based drug delivery systems, which is a potential method for leishmaniasis management [141]. Ideally, nano engineered carrier materials containing conjugated/encapsulated medicines have superior biocompatibility, effective biodegradability, and nonimmunogenic properties, making them an ideal alternative for anti-leishmanial targeted therapy [142]. Natural and semi-synthetic polymers are generally preferable to synthetic counterparts when considering features such as biocompatibility, biodegradability, increased drug loading capacity, extended circulation, toxic solvent free-formulation, and availability. Semi-synthetic polycaprolactone biopolymer (PCL) nanoparticles, for example, have been produced with Amphotericin B nanoprecipitation loading for the management of dermal leishmanial diseases [143].

The study performed by saqib and co-workers reveled that the predicted IC50 of the produced nanoparticle formulation was found to be much lower than controlfree Amphotericin B and AmBisome® for both L. *tropica* KWH23 and L. *donovani* amastigotes, demonstrating maximal parasite suppression [144]. Although, The biopolymer, chitosan, has also been produced with Amphotericin B nanoparticles for the management of cutaneous leishmaniasis (CL) [145]. Amphotericin B-loaded nanoparticles demonstrated in vitro activity against L. *major* intracellular amastigotes with comparable activity to unencapsulated Amphotericin B but drastically reduced toxicity to KB-cells and red blood cells [146]. Liposomes improve the stability and efficacy of the active anti-

leishmanial drug, as well as reduce toxicity by promoting penetration into infective tissues/cells/macrophages and preventing release from the targeted site. Berberine-loaded liposomes, for example, for the treatment of L. infantum-infected BALB/c mice. Berberine loaded liposomes were produced and increased their selectivity index by around 7fold by decreasing their cytotoxicity to macrophages [147].

To administer Amphotericin B (AmB) and Paromomycin (PM) orally for the management of visceral leishmaniasis a 2-hydroxypropyl—cyclodextrin modified solid lipid nanoparticles (m-DDSLNs) were reported. In vitro anti-leishmanial activity of m DD SLNs (1 g/mL) demonstrated the greatest inhibition of L. *donovani* amastigote production (96.22%). In L. *donovani*infected BALB/c mice, mDDSLNs (20 mg/kg 5 days, p.o.) significantly reduced the liver parasite load (p 0.01) compared to miltefosine (3 mg/kg 5 days, p.o.). The results showed that SLNs may be sent to precise locations [148].

In another study, Sarwar and co-workers emphasized the novel strategy to act against leshmaniasis by increasing permeability, oral bioavailability and anti-parasitic prospectives of amphotericine-B using mannose thiolated chitosan (MTC) based nanocarrier. The ex-vivo evaluation identified the parasitic burdens in bone marrow derived macrophages using transgenic leshmania donvoni which was expressed as red fluroscent protein DsRed2. The production of TNF-alpha and IL-12 were higher in MTC based nanocarrier compared to control, which activate the macrophages to impart immune response in cytokine estimation studies. The study also reveal that the MTC based nanocarrier showed specific permeation across Caco2 cell lines while compared to amphotericine —B. As well as, the oral bioavailability and half-life of MTC based nanocarrier where 6.4 and 3.3 folds higher than oral amphotericine –B. Although, acute oral evaluation revelead that MTC based nanocarrier were less toxic than amphotericin-B [149]. Hence, the MTC nanocarrier seems to be effective approach in oral absorption and bioavailability of amphotericine-B in treatment of leshmaniasis.

Leishmanial parasites are an internal parasite that primarily targets macrophages. They can prevent phagosome maturation, allowing them to survive and reproduce within macrophages [150]. Macrophage targeted drug delivery systems may be able to solve several of the associated issues, such as drug toxicity, resistance, and stability. Another study looked at the effectiveness of orally administered paromomycin (PM)-loaded mannosylated thiomeric nanoparticles (MTC-PLGA-PM) for targeted distribution to diseased organs against VL treatment. Ex vivo permeation data revealed that PM penetration with MTC-PLGA-PM was 12.73 times higher than free PM. Flow cytometry study of the L. *donovani* contaminated macrophage model revealed increased macrophage uptake and parasite killing activity [151].

3.12. Lymphatic filariasis

Lymphatic filariasis (LF) is occurred due to infection caused by the species of filarial parasites i.e., *Brugia malayi*, Wuchereia bancrofti and Brugia timori. The species of mosquito were responsible for the spread of the infection from genera anapheles, mansonia, culex and aedes. Adult parasites infect the lymphatic vessels which lead to sickness and released of microfiliaria in blood. Hence, due to improper functioning of lymphatic vessels, lymphoedema (swelling of lymph), hydrocele and acute appearance of adenolymphangitis were noticed. Peoples those are suffering from LF, have shorter life span with disabilities and mental health disorders [152].

To overcome the spread of infection, WHO recommended the preventive chemotherapy as an mass drug administration (MDA) including treatments of diethylcarbamazine, ivermectine and albendazole. The proper hygiene of injured limb should maintain for the disease management (WASH). Progress and maintenance of sanitization can effectively reduce the vector breeding in particular region. Based on parasite and vector species, vector controls minimize the spread of transmission (eg: Insecticide treated nets were utilized in regions were anopheles vector act as primary vector). Although, skincare routine, proper exercise and maintenance of hygiene can effectively reduce the development of lymphoedema and surgery for the treatment of hydrocele [153].

3.12.1. Nanocarriers for Lymphatic filariasis

Devineni and co-worker established the combinational therapy of liposomes (LP) and microneedles (MNs) for the treatment of filariasis using ivermectin (IVM) an antifilarial drug. *In- vitro* studies on pig ear skin reveal that microneedles array increase the permeation of IVM-liposomes across the biological membrane. The optimized formulation containing IVM-LP was formulate and incorporate in the dissolving MN array, the increased in permeation of IVM were identified by assistance of MNs. IVM-LP containing transdermal patch have prepared and solid MNs were tested to assist the amount of IVM penetrate from IVM-LP. In vitro skin permeation studies were carried out using franz diffusion cell assembly for 24 h and found IVM-LP was effectively permit skin membrane and suitable for lymphatic uptake due to less than 100 nm mean size. While, dermatokinetic studies revelead that the delivery of IVM was higher from procin skin with permeability coefficient of 0.798 ± 0.009 cm/h for MNs. To conclude, IVM-LP assisted MNs were effectively delivered IVM as a transdermal preparation and single dose regimen could be effective to target lymphatic filariasis [45], [154]. The antifilarial efficacy of poly (lactic-*co*-glycolic acid) nanoparticles encapsulating ivermectin (nano-IVM) against the human lymphatic filariid Brugia malayi in the rat host *Mastomys coucha* was investigated. The nanoprecipitation approach was used to prepare and optimise Nano-IVM. The nano-IVM (F5) that was chosen had a uniform spherical morphology with 96 nm diameter and 74.12% entrapment efficiency, and when used at a suboptimal dose of 100 g/kg body weight, it totally eradicated filarial parasites from blood circulation 60 days after infection in B. malayi-infected animals. In instance, coadministration of nano-IVM (F5) with the usual filaricide diethylcarbamazine (DEC) was proven to be effective in suppressing microfilaria and completely eliminating microfilaria 45 days after therapy. Meanwhile, Nano-IVM (F5) was also proven to be useful against adult phase parasites, producing 36.67% worm death when used in combination with DEC, and 75.89% when used alone; nevertheless, female sterilisation was found to be nearly same. As a result, the combination of encapsulated IVM and DEC outperformed any single formulation or medication combination in terms of microfilaricidal efficacy and marginally improved macrofilaricidal efficacy [155].

3.13. Onchocerciasis

A parasitic disease i.e., onchocerciasis or river blindness occoured due to infection caused by the *onchocerca volvulus* (worm). Various disabilities like permanent loss of eyesight, visual impairment, itching and disfiguring of skin were happen during onchocerciasis. Simulium blackflies spread the infection through continuous bites and release the parasites in human. According to WHO, by the end of 2019, 1.8 million of individual worldwide didn't required interventions for the treatment of onchocerciasis and verified to eliminate transmission from four countries [156].

To overcome the onchocerciasis, the preventive therapy of MDA (mass drug administration) of ivermectine (IVM) in between one to two year should achieve for 10 or more years. Maintainance of hygiene and spraying of insecticides at parasites of black fly and larva generating sites (WASH) as well as new tactics for removal of foliage from rivers. Medicinal treatment of ivermectin which progressively reduces the symptoms of illness and doxycycline to cure the disease while maintaining visual loss [157]. Onchocerciasis is in co-endmic phase and to tackle the issue, new tactics and strategies still under process.

3.14. Yaws

Yaws is a childhood chronic disease occurred due to infection caused

by spiral bacteria i.e., *Treponema pallidum*. The various deformities, skin infection and damage of bones and cartilage were affected due to it. Transmission of infection through skin contact (scarpes and cuts) were affected the populations. In 1950s, the yaws was the first NTD which targeted to eradicate worldwide, whereas the transformed efforts for eradication of yaws was started in 2012 [158]. To eradicate and eliminate the yaws, the preventive chemotherapy concluded with the use of single dose of azithromycin (macrolide antibiotic) as an first line treatment in the management of yaws and benzathine benzylpenicillin as an second line drug treatment for the patient those are showing resistance to azithromycin, maintenance of personal hygiene (WASH) and the patient was advised for the check-up after 4 weeks of the dose treatment, 95% case were completely recovered [159].

3.15. Taeniasis/cysticercosis

Taeniasis is tapeworm infection. The most common taeniasis is caused by taeniasolium (pork tapeworm) and taeniasaginata (beef tapeworm). The disease is generally asymptomatic but severe infection leads to weight loss, diarrhoea, abdominal pain, dizziness, headache, nausea etc. Cysticercosis is a type of taeniasis caused by ingestion of eggs of taeniasolium, through contaminated food and water.Neurocysticercosis is infection of central nervous system; the symptoms include dizziness, occasional seizures, hypertension etc.Taeniasis is contracted by uncooked and raw pork and beef containing larvae. The disease is common in Asia, Africa, latin America on farms in which pigs are exposed to human excreta, and where beef and pork are eaten. Oral antiparasitic drug praziquantal, niclosamide, albendazole are the drug of choice for the treatment.

3.16. Trachoma

Trachoma is an eye syndrome which is occurred due to infection caused by bacterial *chlamydia trachomatis*. Continuousincidence of infection was badly affecting the eyelids and develops the eyelashes as well as trichiasis (due to rubbing of eye surface). Trachoma can severely damage the corneal sites and develop the intense pain which result in complete blindness or irreversible visual impairment. Primary reason for the transmission of infection is personal contact among individual and by the flies contact in nasal or oral cavity. Improper hygiene, crowded places, lack of sanitisation and water may cause the major risk in transmission of infection. Almost 3–8 billion US$ economic burden facing by the populations, communities and organizations due to trachoma [160].

According to the WHO safe strategy, the combinational eye ointment therapy of azithromycin and tetracycline as a mass drug administration (MDA) progressively minimizethe infection caused by *C. trachomatis* as preventive chemotherapy. Proper face wash and maintenance of environmental hygiene (WASH), advancement in sanitization, access of clean water and behavioural changes must implement. Although, reduction in breeding of muscid flies which is primary vector for infection of ocular *C. trachomatis* [161].

In recent years, peptide-based vaccinations have developed as viable options for the treatment of infectious illnesses. Ganda and co-workers reveled the antimicrobial efficacy of a dendrimer-based carrier system for peptide-based vaccine administration is demonstrated in a mouse model of *Chlamydia trachomatis*. The suggested carrier system includes generation 4 hydroxyl-terminated polyamidoamine (PAMAM) dendrimers (G4OH), to which a peptide mimic of a chlamydial glycolipid antigen—Peptide 4 (AFPQFRSATLLL) was attached via an ester bond. After subcutaneous vaccinations, Pep4 coupled to dendrimer elicited Chlamydia-specific blood antibodies. Furthermore, this novel vaccine preparation considerably reduced infectious loads and tissue (genital tract) damage in inoculated animals after vaginal challenge with infectious *Chlamydia trachomatis*. Pep4 coupled to G4OH or just combined with peptide gave better protection than Pep4 and adjuvant (i.e. alum), indicating that the PAMAM dendrimer may have an adjuvant effect. These findings show that the hydroxyl-terminated PAMAM dendrimer is a potential polymeric nanocarrier platform for peptide vaccine delivery [162]. The quick nasolacrimal outflow of the medication and the low permeability of the corneal epithelium contribute to the low bioavailability of ocular drops. As a result, there is a desire to develop a system to enhance drug permeability and bioavailability. Salimi and co-workers goal of this work was to develop and describe a novel microemulsion system as an intraocular delivery system for azithromycin, as well as to assess its physicochemical properties and rabbit corneal permeability, in order to improve drug penetration. The results revealed that MEA-7 (12.87%) and MEA-2 (0.909%) had the highest and lowest percentages of drug permeated through rabbit cornea, respectively. The partitioning, flow, and permeability coefficient of rabbit cornea dramatically increased by all ME formulations with varying compositions and features. Azithromycin flux (Jss) in MEA-7 was 11.958 mg cm-2 h-1, which was 39.86 times greater than control [163].

3.17. Mycetoma, chromoblastomycosis and other deep mycoses

The numerious bacterial and fungal microorganisms are the reason of development of “Mycetoma” a granulomatous infection. Classification was based on the causative agent i.e., fungal mycetoma called as eumycetoma and bacterial mycetoma called as actinomycetoma. Actinomycotic mycetoma wasoccoured due to filamentous bacteria i.e., *Nocardia brasiliensis, Actinomadura madurae, Actinomadura pelletieri, Streptomyces somaliensis*, etc., and eumycotic mycetoma was occurred due to fungi i.e., *Madurella mycetomatis, Trematosphaeria grisea, Falciformispora senegalensis, Falciformispora tompkinsii,* etc.The increase in morbidity and mortility rate of disease lead to development of deformities and various disabilities along with long term infection of skin, connective tissues, bones and muscle [164]. Men are more prone to affected from this disease compare to women of all ages mainly those poor individual that are working in the domain of agriculture unit i.e., farming or animal breeding. Meanwhile, WHO characterized mycetoma as a neglected tropical disease in the year 2017.

The preventive chemotherapeutic approach was utilized to overcome the spread of mycetoma by maintaining personal hygiene and avoid secondary infection by taking self-care need of affected limb (WASH). While the medicinal treatment depend on the causative agent like., for bacterial infection, chronic therapy of antibiotic combinations were recommended and for fungal therapy combined antifungal majorly itraconazole and terbinafine were recommended as well as surgery for local excision [165]. Cleaning and dressing of infected wounds with proper disinfection and wearing of protective cloths needs to take care.

Patra and co-workers 2021, performed the novel treatment using linezolid on a Indian girl who is suffering from the infection of actenomycotic mycetoma. Initially she was treated with dose of amikacin 15 mg/kg IV daily and cotrimoxazole 2 tablet twice daily. They have use amikacin instead of gentamycin due to effective drug profile and daily one time dosing. After continuous 1 month of treatment, the dose regimen did not respond and no improvement was noticed in lession. Therefore, doxycycline table 100 mg daily was given instead of the amikacin injection with the dose of cotrimoxazole. Therapy was performed for 2 months, but the lession was turned out to be more intensed, inflammatory and increased in size.

Due to lack of response given by cotrimoxazole and doxycycline. The patient was started with the dose of linezolide an oxazolidinone antibiotic (600 mg tab) twice daily. The study found that, lession was responded to linezolide within first 2 weeks of therapy. The blood count and liver function test was found to be normal and the treatment was continued for 3 months until the lesion was completely recovered [166].

Chromoblastomycosis (CBM) known as chromomycosisis a long-lasting fungal infection which progressively damaged the skin and subcutaneous tissues via, number of fungal species. Majorly three fungal species i.e., Fonsecaea pedrosoi, Cladophialophora carrionii and

Phialophora verrucose along with other skin mycosis those are affecting the skin of individual in certain countries known as paracoccidioidomycosis (PCM) caused by the species of paracoccidioides and sporotrichosis (ST) caused by the species of sporothrix. The wounds caused by CBM are clinically frequent in nodular, verrucous and tumorals. However, the wound caused by ST was skin abrasions which are single nodule and ulcer or a chain of nodule. PCM damage the respiratory tract along with lymphatic system, skin and mucous tissues which are the simplest pathways for administration in blood stream of healthy people. Spreading of CBM, PCM and ST was a painful inoculation of microorganism through disaggregated skin layer. Almost 10,000 cases of CBM, PCM and ST was reported worldwide since 1940s, while the precise spread were unknown but expected to be higher, CBM and ST are spreading worldwide, while the spread of PCM were noticed in the counties of America. Meanwhile, the excess spread was found to be in the tropical and subtropical areas of Africa, Asia and latin America. The highest cases of CBM were reported by the Madagascar and Brazil. The preventive chemotheraphy was highlighted to overcome the spread of disease by using pet control strategies for sporotrichosis to prevent the spreading of microorganism in humans. Currently, no specific gold standard treatment protocol exist for CBM, medicinal treatment option of itraconazole (antifungal) with or without terbinafine along with immune and physical therapyand surgery was performed for minor abrasions. However, itraconazole is the drug of choice for the treatment of PCM and ST [167] [168]. Protective measure should be taken by using clothes and shoes and avoid the direct contact with feral cats (ST).

3.18. Scabies and other ectoparasitoses

Sarcoptes scabieivar hominis a microscopic bug caused the infection and lead to development of scabies and other ectoparasitoses. The spreading of infection in humans via, direct skin contact of female bug and lay down the eggs which elevate the immune chain which caused intense itching and rashes. Infection caused due to bacterial species may lead to thwart the disease, which caused serious events of septicaemia, kidney disease, heart failure and soft tissues infection [169].

The preventive treatment strategies to overcome the spread of disease by providing mass drug administration (MDA) of oral ivermectine and use of topical scabicides. Maintainance of proper hygiene which is helpful in outbreaks and minimize the risk of secondary infection in infected peoples (WASH). Topical treatment of permethrine, benzyl benzoate, malathion and sulfur ointment are considered as a topical scabicides for the diagnosis of scabies [170]. In some countries, the data reported the use of ivermectin was discontinued it lead to development of lymphatic filariasis and onchocerciasis.

Dahlizar and *co*-worker developed the topical gel spray formulation of ivermectine using low molecular weight gelling polymer i.e., palmitoyl glycine histidine (Pal-GH). Rheological studies was performed using propylene glycol and shows excellent rheological behaviour (Thixotropic behaviour) with higher spreading ability. Compared to oral administration of ivermectine in humans, the topical gel of ivermectine was found to be achieved higher concentration of 0.1% ivermectine containing Pal-GH when study performed of hairless rats. Hence, the conclusion found out to be topical administration of ivermectine containing Pa-GH gel spray was effective alternative to oral formulation in the management of scabies [171].

3.19. Snakebite envenoming

Snakebite envenoming in NTD lead to a complex composition of various toxins i.e., Venom. It occurred due to the bite of venomous snake or other species of snake venom spread into the eyes. The numerious variety of snakes those contain dangerious venomes are categorised in two subsets i.e., Elapidae and Viperidae. While, kraits, cobras, mambas and sea snakes comes under the class of elapidae and true vipers, pit vipers, and Lamprophiidae come under viperidae. The toxins secreted by those species in humans lead to a chances of disabilities like as paralysis, reduction in blood pressure, loss of breathing, bleeding(caused fatal haemorrhage), kidney injury and tissue damage (chances of permanent disabilities), rhabdomyolysis and death due to respiratory paralysis along with physical and psychological imbalance [172]. While observing such disaster WHO categorised the snakebite envenoming as a neglected tropical disease in 2017.

To overcome snakebite envenoming health care workers provides the high quality, safe and effective antivenoms in the rural areas individuals those are affected. Ancillary treatment such as surgery, wound care, secondary infection, control of infection and shock therapy were improvised. House hold management using bed with bed nets to avoid sleeping on floor, by sealing gaps and cracks in wall, roof and doors and using of footwear and light outdoors to avoid the risk [173]. Although, proper health care strategies should maintain by avoiding any unproven harmful firs aid treatments. Polymer-based nanoparticles have emerged as a promising vehicle for increasing vaccination efficacy. Fatima et al. looked at a novel approach for preventing snake envenomation using PLGA nanoparticles containing *Cerastes cerastes* venom as an intranasal vaccine delivery system. The size, shape, distribution, and venom-nanoparticle interactions of the particles were studied using a double emulsion solvent evaporation method. An intranasal immunization trial was conducted in mice to assess the immune response, reactogenicity, and protective efficacy of this nanovaccine. Immunization with Cc-PLGA NPs induces a systemic innate and humoral immune response and confers protection against *Cerastes cerastes* venom (Cc) at concentrations more than 6 LD50, with cross-protection against *Vipera lebetina* venom (Vl) at concentrations greater than 5 LD50. Cc venom was nano-encapsulated to minimize its toxicity and the tissue changes it caused. The Cc-PLGA NPs nano-formulation is a strong adjuvant system that improves the humoral immune response and protects against excessive lethal dosages of viper venoms, according to the findings [174].

In another study, Silva and colleagues developed small, narrow-sized cationic *Crotalus durissus cascavella* (CDC) venom-loaded chitosan nanoparticles (CHNP) capable of inducing anti-CDC venom antibody responses. The ionic gelation approach produced stable and slightly smooth spherical nanoparticles (160 nm) with a protein loading efficiency of more than 90%. The in vitro release behaviour of proteins from nanoparticles was substantiated by the relationships between venom proteins and CHNP evaluated by FT-IR spectroscopy. The vaccination animal model utilizing BALB/c mice showed that CDC venom-loaded CHNP was more efficient than aluminium hydroxide, a traditional immunoadjuvant. As a result, CHNPs loaded with CDC venom showed promise as a biotechnological immunotherapy method [175].

4. Future prospectives of nano formulations in the treatment of NTDs

The development of nano-metric pharmaceutical dosage form highlighted the modern steps towards prevention, treatment and chemotherapeutic actions and to inhibit the unwanted biological and chemical adverse effect of drugs and medicines. Nanotechnology is going to gain the attention of researchers and scientist due to their numerious benefits and new insight to approached against the neglected tropical disease. Meanwhile, the major demerits of this delivery system is physical and chemical instability along with low encapsulation property, particle aggregation, precipitation etc., possesses bad impact on release profile of drug which ulter the bioavailability and biological properties. Working with bio and nano materials in a nanometric scale for drug delivery may result in undesirable side effects, due to such nanomaterials are in the size range of bio-macromolecules and cells and may interact and affecting normal cellular functions. To conclude, more strategies are needed to prevent and detect both environmental impact and side effects in living organisms based on the working of nanomaterials and use of nanocarriers for particular NTDs, respectively.

5. Conclusion

2020 was an important year for worldwide response to address neglected tropical disease which sets the new targets and goal for the road map of 2021–2030 and renewed by London Declaration commitments. In the upcoming years, the focus will be kept on new worldwide health and development tactics, alliance with health care organizations and attention on NTDs resources and minimize the poverty among the population due to spread of NTDs through 2030. In current time we are still lagging behind in the development of novel nanointerventions, in enhancing the basic knowledge and experience as well as in generating the evidences based result in laboratory. In this paper we highlighted the treatment strategies, novel interventions and advance machinery to tackle the growth of NTD. WHO confirmed the mass drug administration is a crucial step to control the spread of NTD. However, there are still many demerits i.e., discover, diagnosis, treatment and to tackle the spread of transmission of some NTDs. Meanwhile, development of new drug moiety is one of the key steps to overcome these issues. In the current era, delivery of drug through newer approaches is more suitable than development of new drug moiety due to expensive and time consuming process. Nanotechnology-based drug delivery systems gain the attention of researcher and scientist to counteract NTDs. Regarding various merits like enhancement in cellular uptake, increase in absorption profile, aqueous solubility and bioavailability studies as well as decreasing the drug toxicity while targeting NTDs. Moreover, nano particulate system or nanocarriers has been applied in the delivery of drugs and vaccines as delivery system for prevention of NTDs.

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