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Tropical Diseases: An Unsolved Challenge

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Abstract: Tropical diseases are infectious diseases that are found predominantly in the tropics, where ecological and socioeconomic conditions facilitate their propagation. Climatic, social, and economic factors create environmental conditions that facilitate transmission, and the lack of resources prevents affected populations from obtaining effective prevention and adequate care. Tropical diseases are diseases of the poor, and investments in control and research to develop more effective intervention tools and strategies have been minimal. For some, however, effective intervention methods have been developed, and successful control has been achieved. This article focuses on tropical diseases such as Malaria, tuberculosis, leprosy, dengue and leishmaniasis. But from all these diseases Malaria, tuberculosis and leprosy yet not have effective means of control. Control strategies are being implemented at scale and have already achieved a major reduction in the burden of disease, and the causative agent has even been eliminated in some previously endemic areas. Those successes have not come easily, and much remains to be done to ensure complete and sustained control of the diseases. While dengue and leishmaniasis are serious diseases that the World Health Organization (WHO) characterizes as lacking effective control measures. All these diseases are targeted for elimination as a public health problem.
Key words: Tropical diseases, pathogens, drug molecules, drug targets, malaria, tuberculosis.

1. Introduction:
Tropical diseases are infectious diseases that are prevalent in or unique to tropical and subtropical regions where ecological and socioeconomic conditions facilitate their propagation. These diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation during the cold season. Insects such as mosquitoes and flies are by far the most common disease carrier or "vector". These insects may carry a parasite, bacterium or virus that is infectious to humans and animals. Most often disease is transmitted by an insect "bite", which causes transmission of the infectious agent through subcutaneous blood exchange. The tropics are more problematic for certain diseases for two reasons:
1) Tropical climates are more conducive to certain diseases.

2) Areas of poverty and primitive sanitation conditions are more common in the tropics.
World Health Organization (WHO) is most concerned with improving health in tropical countries.[1]

2. Factors responsible for tropical diseases:
The severity of diseases in tropical areas is due to widespread poverty and poor sanitation as well as climatic influences. Because of low national incomes, most developing countries cannot afford to buy vaccines to prevent poliomyelitis, measles, and yellow fever. Poverty is a condition that also leads to malnutrition, which makes people more susceptible to disease. Climate indirectly makes disease in tropical regions more severe by reducing agricultural production, which increases the risk of malnutrition. In a more direct way, hot weather and humid forests favor growth of the flies and mosquitoes that transmit

malaria, yellow fever, dengue fever, trypanosomiasis etc. It is possible also that higher temperature may favor the replication of pathogenic agents both inside and outside biological organisms. Socio-economic factors may be also in operation, since most of the poorest nations of the world are in the tropics. Climate change and global warming caused by the greenhouse effect and the resulting increase in global temperatures are causing tropical diseases and vectors to spread to higher altitudes in mountainous regions.[2]

3. Diseases Most Prevalent in the Tropics:

The most important diseases in the tropical regions of Southeast Asia, Africa, and South America are malaria, schistosomiasis, leprosy, filariasis, trypanosomiasis, and leishmaniasis, dengue fever, tuberculosis. Other diseases for which treatment is available but which are still common in developing countries include cholera, yellow fever, yaws, and amoebic dysentery. Additional neglected tropical diseases include buruli ulcer, dracunculiasis, treponematoses, leptospirosis, Strongyloidiasis, Food borne trematodiases, neurocysticercosis, scabies, hookworm, trichuriasis.[3] Malaria, tuberculosis, leprosy, dengue and leishmaniasis will be covered in this article.

Malaria: Malaria is serious and sometimes fatal parasitic disease. The causative organisms of human malaria are transmitted by the bite of about 60 species of mosquitoes in the genus *Anopheles*. There are four types of the plasmodium parasite which can infect humans:[4] *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae.* The World Health Organization estimates that 300-500 million cases of malaria occur and more than one million people die from the disease each year.[5] Malaria infection is spread by the infected female Anopheles mosquito when the parasites are transferred from the salivary glands of the mosquito to the human who has been bitten. Incubation and replication occur in the liver cells of human host which in turn release the merozoite phase of the malaria life cycle into the blood stream where the red blood cells become infected. Mature gametocytes are found in the blood stream and are then transferred back to the mosquito host when an infected human is bitten to complete the life cycle.[6] It is the blood phases of the lifecycle which cause symptoms of disease like Fever, shivering, arthralgia (joint pain), vomiting, anemia (caused by hemolysis), convulsions and coma.[7]

Treatment: Early treatment of malaria will shorten its duration, prevent complications and avoid a majority

of deaths. Because of its considerable drag on health in low-income countries, malaria disease management is an essential part of global health development. Synthetic drugs include quinine, chloroquine, mefloquine, primaquine, proguanil etc.[8] Drug resistance occurs through spontaneous genetic mutations in parasite. When a patient is treated with a drug (e.g. chloroquine), parasites that are still sensitive to this drug are killed but other parasites have mutated genes they survive. The mutated parasites survive to reproduce and infect other mosquitoes and in turn another person. Hence the best available treatment, particularly for P. falciparum malaria, is a combination of drugs known as artemisinin-based combination therapies (ACTs) e.g. Combination of artemether-lumefantrine, artesunate-amodiaquine. Artemisinin has several characteristics that make it an excellent malaria medicine. It brings down the parasitaemia (the number of parasites in the blood) faster than any other antimalarial drug. No resistance to artemisinins has been reported. There are no effective alternatives to artemisinins for the treatment of malaria either on the market or nearing the end of the drug development process.[9] The development of resistance by the parasite against first line and second line antimalarial drugs, has underscored the importance to develop new drug targets and pharmacophores to treat the disease (Table 1).[10] Currently, work is progressing on the development of a malaria vaccine. Several vaccine candidates are now undergoing clinical trials for safety and effectiveness in human volunteers.[11]

Tuberculosis: Tuberculosis (TB) is a contagious disease. Like the common cold, it spreads through the air. When infectious people cough, sneeze, talk or spit, they propel TB germs, known as bacilli, into the air.[12] TB caused by mycobacteria, mainly *Mycobacterium tuberculosis.* Other mycobacteria such as *Mycobacterium bovis, Mycobacterium africanum, Mycobacterium Canetti, and Mycobacterium microti* also cause tuberculosis, but these species are less common.[13] Nearly one-third of the global population – two billion people – is infected with *Mycobacterium tuberculosis* (*M. tuberculosis*), more than eight million people develop active TB every year, and approximately two million die annually (World Health Organization, 2003).[14] Man is the primary host for *M. tuberculosis.* Infection is spread via airborne dissemination of aerosolized bacteria-containing droplet nuclei of 1–5 μm in diameter that carry *M. tuberculosis* droplets from an individual with infectious TB disease to an uninfected individual. The

infectious droplet nuclei are inhaled and lodge in the alveoli in the distal airways. *M tuberculosis* is then taken up by alveolar macrophages, initiating a cascade of events those results in either successful containment of the infection or progression to active disease (primary progressive TB).[15] It is associated with chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. When the disease becomes active, 75% of the cases are pulmonary TB. Symptoms include chest pain, coughing up blood, and a productive, prolonged cough for more than three weeks. Systemic symptoms include fever, chills, weight loss. The increasing emergence of drug resistant to TB, render individuals more susceptible to TB, pose further challenges for effective control of the disease.

Treatment: Although TB can be cured with chemotherapy, the treatment is exceedingly lengthy and takes 6–9 months. Apart from significant toxicity, the lengthy therapy also creates poor patient compliance, which is a frequent cause for selection of drug resistant and often deadly multidrug resistant TB (MDR-TB) bacteria. Currently, TB chemotherapy is made up of first-line drugs, isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB), given for six months. If the treatment fails as a result of bacterial drug resistance, or intolerance to one or more drugs, second-line drugs are used, such as para-aminosalicylate (PAS), kanamycin, fluoroquinolones, capreomycin, ethionamide and cycloserine, that are generally either less effective or more toxic with serious side effects. Current TB therapy, also known as DOTS (directly observed treatment, short-course) consists of an initial phase of treatment with drugs, INH, RIF, PZA and EMB, for 2 months daily, followed by treatment with INH and RIF for another 4 months, three times a week.[16] Resistance to first line anti-TB drugs has been linked to mutations in at least 10 genes; katG, inhA, ahpC, kasA and ndh for INH resistance; rpoB for RIF resistance, embB for EMB resistance, pncA for PZA resistance and rpsL and rrs for STR resistance.[17] Thus the complete genome sequence of *M. tuberculosis* provides an opportunity for a more focused and planned approach towards the identification of new drug targets such as:

1. **Genes involved in dormancy or persistence:** Recently, *pcaA* gene, which encodes a novel methyl transferase, has also been shown to be involved in the persistence in mice.[18]

2. **Genes involved in cell wall synthesis**: A variety of unique lipids like lipoarabinomannan (LAM), trehalose dimycolate, and phthiocerol dimycocerate which form non covalent anchorage with the cell membrane have been documented to play an important role in the virulence of *M. tuberculosis*.[19]

3. **Virulence genes**: Two gene clusters were identified and shown to be important for the growth of mycobacteria in the lungs during the early phase of infection.[20]

4. **Transcription factors**: Gene products that are involved in transcription regulation have long been used as target for drugs in a number of pathogens. For example rifampin, a well-known drug for tuberculosis, targets RNA polymerase.[21]

5. **Genes of other metabolic pathways:** These genes include, mgtc, which codes for a putative Mg+2 transporter protein. This protein has been shown to be essential for the survival of mycobacteria both, in macrophages and mice.[22]

Dengue: Dengue viral infections are caused by one of four single stranded RNA viruses of the family Flaviviridae. They can occur virtually throughout the tropics and are transmitted by their mosquito vector, *Aedes aegypti*. Female mosquitoes ingest the virus while feeding on viremic individuals, and after an 8- to 12-day incubation period they can transmit the virus to other humans during blood feeding. Thereafter, the female mosquito remains infective for life. Transmission of the virus from infected females to their progeny has been documented, but its epidemiological significance is not well understood Dengue virus is a small enveloped virus measuring 50 to 60 nm is size containing a single stranded positive sense RNA genome. Dengue virus has four serotypes, namely 1-4.[23] The geographical spread, incidence and severity of dengue fever (DF) and dengue hemorrhagic fever (DHF) are increasing in America, South-East Asia, Eastern Mediterranean and the Western Pacific. Some 2500 million people - two fifths of the world's population are now at risk from dengue and WHO currently estimates that there may be 2.5-3.0 billion people who remain at risk globally.[24] Disease is presently endemic in more than 100 countries. WHO has classified signs of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) into various grades (Table 2):[25]

Treatment: [26]
Currently there are no antiviral treatments available for dengue fever. But standard treatment protocol is shown in Table 3.
Dengue vaccines are in clinical development but problematic because: [27]

• With four closely related viruses that can cause the disease, the vaccine must immunize against all four types to be effective.

• There is limited understanding of how the disease typically behaves and how the virus interacts with the immune system.

But dengue is still lacking adequate control measures, so that there is need to identify potential drug targets. Novartis Institute of Tropical Diseases has one dengue target in assay development (NS5 methyl transferase), two in lead finding (NS3 helicase, NS3 protease) and two lead optimization projects.[28] Dengue virus contains seven non structural proteins from which NS3 is a multifunctional protein with an N-terminal protease domain (NS3pro), RTPase, an RNA helicase, and an RNA-stimulated NTPase domain in the C-terminal region.[29] Thus the dengue virus NS3 plays a crucial role in viral replication and represents an interesting target for the development of specific antiviral inhibitors/drugs.[30]

Leprosy: Leprosy, a chronic infectious disease caused by Mycobacterium leprae, was identified by G.H.A Hansen in 1873. Leprosy, also known as Hansen's disease that primarily affects the skin, the peripheral nerves, the upper respiratory tract, and the eyes. The causative agent is an acid-fast bacterium, *Mycobacterium leprae*.[31] Leprosy now remains a major public health problem in only 10 countries of the world. There are approximately one-two million people worldwide who are permanently disabled as a result of leprosy.[32] For chemotherapeutic purposes leprosy is classified according to the number of skin lesions and may be described as:[33]

• Paucibacillary (borderline-tuberculoid, tuberculoid, and indeterminate), when there are 5 or fewer lesions.

• Multibacillary (lepromatous, borderline-lepromatous, and borderline leprosy), when there are more than 5 lesions, or skin smears positive (any site).

Signs and symptoms associated with skin lesions which may be single or multiple usually less pigmented than surrounding skin. Sometimes lesion is reddish or copper colored. Sensory loss is a typical feature of Leprosy. Skin lesion may show loss of sensation to pin prick.[34]

Treatment: The major goals of the leprosy control program are (1) early detection of patients; (2) appropriate treatment; and (3) adequate care for the prevention of disabilities and rehabilitation. There are several effective chemotherapeutic agents against M. leprae. Dapsone (diaphenylsulfone, DDS), rifampicin (RFP), clofazimine (CLF, B663), ofloxacin (OFLX), and minocycline (MINO) constitute the backbone of the multidrug therapy (MDT) regimen recommended by WHO. Other chemotherapeutic agents, like Levofloxacin (LVFX), sparfloxacin (SPFX), and clarithromycin (CAM) are also effective against M. leprae.[35] For many years dapsone was the only effective antileprotic drug available. Its long-term use as monotherapy led to selection of dapsone-resistant M. leprae.[36] World Health Organization (WHO) has specifically introduced multi-drug therapy (MDT) to prevent the emergence of drug resistance and to produce good clinical responses.[37] Prevention of leprosy by vaccination would provide a valuable public health tool. However there is currently no specific vaccine effective against leprosy.[38] The Bacille Calmette-Guerin (BCG) vaccine was originally aimed at prevention of tuberculosis but is actually more effective against leprosy.[39]

Leishmaniasis: It is also known as "Kala azar". It is caused by protozoan parasites that belong to the genus *Leishmania* and is transmitted by the bite of certain species of sand fly. More than 20 Leishmania species are pathogenic to humans, and more than 30 species of sand flies are proven vectors. It is estimated that 12 million people worldwide are infected. The different species of Leishmania cause illness of differing severity. Visceral leishmaniasis (VL), caused by species of the *L. donovani* complex, is usually fatal if untreated. Mucocutaneous leishmaniasis, caused by the *L. braziliensis* complex, is highly disfiguring and mutilating, and it can be fatal because of secondary complications. Cutaneous leishmaniasis (CL), caused by the *L. major*, *L. donovani*, and *L. braziliensis* complexes, may be a simple, self-limiting skin ulcer, but it can be disabling when numerous lesions occur. Diffuse cutaneous leishmaniasis, caused by the *L. mexicana*.[40] Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. The sandflies inject the infective stage, metacyclic promastigotes, during blood meals. Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophage and transform into amastigotes. Amastigotes multiply in infected cells and affect different tissues, depending in part on which Leishmania species is involved. These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sandflies become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes. In the sandfly's midgut, the parasites differentiate into promastigotes, which multiply, differentiate into metacyclic promastigotes and migrate to the proboscis. The symptoms of leishmaniasis are skin sores which erupt weeks to months after the person affected is bitten by sand flies. Other consequences include fever, damage to the spleen and liver and anaemia.

Treatment: There are two common therapies containing antimony (known as pentavalent antimonials), meglumine antimoniate and sodium stibogluconate. It is not completely understood how these drugs act against the parasite; they may disrupt its energy production or trypanothione metabolism. Unfortunately, in many parts of the world, the parasite has become resistant to antimony and for visceral or mucocutaneous leishmaniasis[41] but the level of resistance varies according to species.[42] Amphotericin is now the treatment of choice.[43] Miltefosine is a new drug for visceral and cutaneous leishmaniasis. The target for chemotherapy of leishmaniasis is intracellular amastigote that survives and divides in tissue macrophages, whereby causing the disease. There are some validated and potential antileishmanial drug targets:

1. Trypanothione metabolism: Validation of trypanothione reductase as a drug target suggested by genetic experiments.
2. Glycolysis: Glycolysis is considered essential, many enzymes enclosed in glycosomes.
3. Protein kinase: Cyclin-dependent kinases essential to parasites.
4. Microtubules: Tubulin validated as a drug target.[44]

Table 1: Summary of drug targets and candidate molecules against the malaria parasite:

Target	Enzyme\ receptor	Candidate molecule
Cell Cycle	CDK	Quinolinones, oxindoles
Apcicoplast	Fab I	Tricpyrazoles
Apcicoplast	FabA/Z	NAS-21, NAS-91
Apcicoplast	Fab H	Thiolactomycin analogues
Apcicoplast	DOXP	Fosidomycin
Food vacuole	Haemozoin	-
Food vacuole	Proteases, Peptidases	1,4-Bis(3-amino propyl) piperazine derivatives
Membrane	Phospholipid. Haemozoin	Bis quaternary ammonium and bisthiazolium salts

Abbreviations: CDK, cyclin-dependent kinases; DOXP, 1-deoxy-D-xylose-5-phosphate;FabI,enoyl-ACP reductase; FabH,□-ketoacyl-ACP synthase III; FabA/Z, □-hydroxy acyl-ACP dehydratase.

Table 2: Classification of DHF and DSS
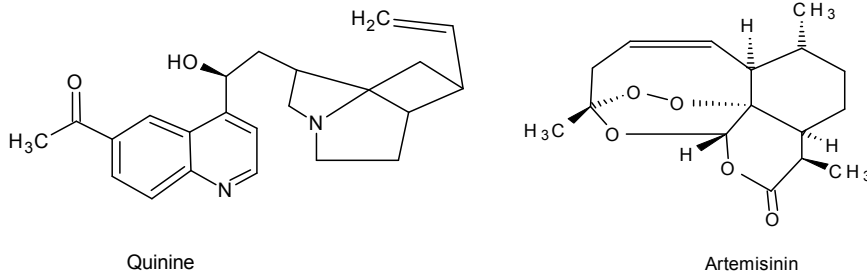
Grade I	In presence of heamoconcentration, fever, and nonspecific constitutional symptoms, a positive tourniquet test is the only haemorrhagic manifestation
Grade II	Grade I + spontaneouos bleeding
Grade III	Above signs + Circulatory failure, pulse pressure less than 20mm Hg but systolic pressure is still normal
Grade IV	Profound shock, hypotension, or unrecordable blood pressure

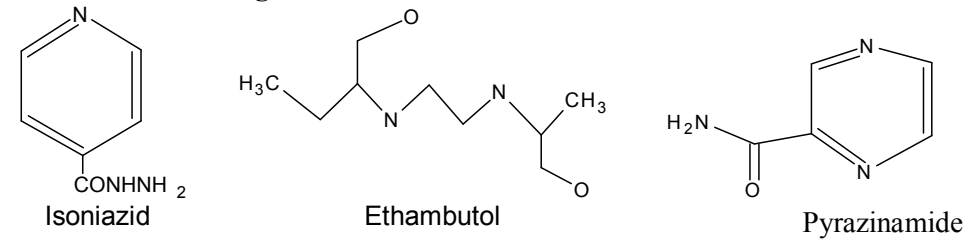**Table 3: Standard treatment protocols for dengue**

Condition	Tests	Drugs (dosage type and time)
Dengue fever (DF)	Complement fixation test	Analgesics and Antipyretics like paracetamol: 3–5 days
	Neutralization test (NT)	
	ELISA for IgG and IgM	
	Isolation of the virus	
	Haemagglutination inhibition (HI) test	
Dengue hemorrhagic fever (DHF)	Clinical signs and symptoms	Analgesics and Antipyretics like paracetamol Fluid replacement
	ELISA for IgG and IgM	Whole blood/platelet/plasma /replacement
	Isolation of the virus	
Dengue shock syndrome (DSS)	Clinical signs and symptoms	Antipyretic like paracetamol Fluid replacement
	ELISA for IgG and IgM	Whole blood/platelet/plasma /replacement

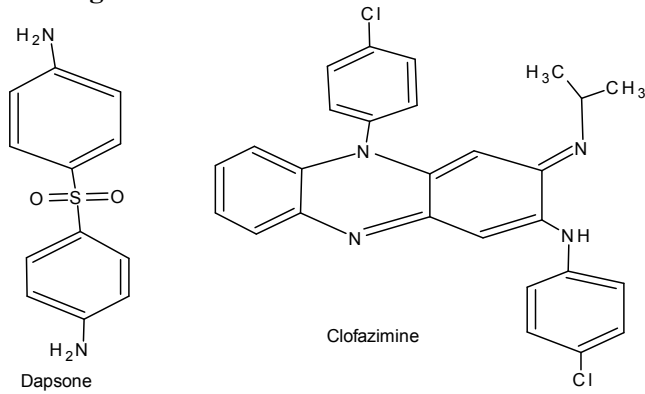Structures of some antimalarial,antitubercular, antileprotic and antileishmanial drugs are shown in fig no. 1.

Antimalarial Drugs:

Quinine

Artemisinin

Antitubercular Drugs:

Isoniazid   Ethambutol

Pyrazinamide

Antileprotic Drugs:

Clofazimine

Dapsone

Antileishmanial drugs:

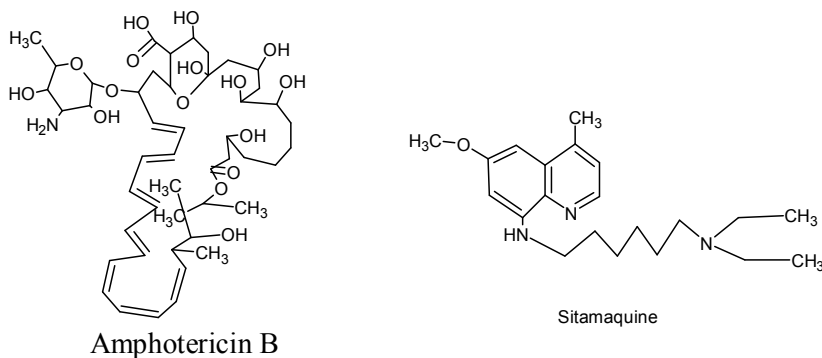Sitamaquine

Amphotericin B

Fig No 1: Structures of some important antimalarial, antitubercular, antileprotic antileishmanial drugs.

Future scope:

The future scope lies in the study of mechanism of drug resistance, search for newer targets and newer molecules which can selectively inhibit them. Although there is obviously great progress in controlling tropical diseases to be made through the use of biotechnology, there remains a need to continue more traditional research approaches in parasitology, infectious disease natural history, and basic biomedicine. The control of mosquitoes and other vectors has been a successful route of disease control in certain geographic areas for several diseases. Vaccine development is another focal over of research.

Conclusion:

Tropical diseases are basically most affecting the poor population. The research on these diseases is also limited .The government agencies and scientific communities most focus on the research activities in this specific area. Though some drugs are available, the problem of drug resistance still persists. Hence there is always a need to search for newer targets .The systematic application of target for drug design and QSAR can lead to search of better lead molecule. Apart from this the up to date study of the biology of vectors causing these diseases is also needed.

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