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Opinion Article

DRUGS FOR NEGLECTED TROPICAL DISEASES: A PRIORITY OFTEN OVERLOOKED

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Introduction

Rural poor and disadvantaged urban populations are targets of majority of the tropical infectious diseases. **[1]** Many of them are labelled as Neglected Tropical Diseases (NTDs) by World Health Organization (WHO). Majority of those affected people, live in tropical, sub-tropical, under developed or developing countries. Their living conditions are mostly sub-standard, and have inadequate health care infrastructure. Further, their close proximity to domestic animals also help in transmission of many zoonotic NTDs. WHO has identified 17 priority NTDs caused by viruses, Parasite (protozoa, and helminths), bacteria. According to WHO (2018) about a billion people are affected with one or more NTDs in 149 countries, and approximately 35,000 deaths occur every day due to NTDs worldwide.**[2]** Though they are the root cause of severe socio-economic burden for the countries yet, strategic research to develop intervention of NTDs is scarcely funded.**[3]**

Southeast Asia is one of the hotspots for NTDs. India, has the largest absolute burden of 11 major NTDs.Out of them leprosy, lymphatic filariasis, visceral leishmaniasis (kala-azar) and yaws are identified as major problem in Southeast Asian region. Besides mortality and burden of morbidity, many a time the victims often face discrimination in the society due to the disease.**[4-6]**WHO is planning to eliminate leprosy, sleeping sickness, blinding trachoma, guinea worm disease, lymphatic filariasis; and control schistosomiasis, helminthiases, visceral leishmaniasis, onchocerciasis and Chagas disease by 2020. However, it appears that we are far behind the target.

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Multiplicity of challenges

a. **Administration & health Policy:** Since NTDs are mostly associated with economically poorer section of society, concerted and long-term strategies have to be adopted to address social and economic issues. Such strategies should focus to meet the multifaceted challenges of poverty, strengthening social intervention, ensure availability of drugs and easy access to health care.

b. **Drug manufacturers** have largely ignored NTDs for decades. The newer drugs developed for treating NTDs, fail to return sufficient benefits for the drug manufacturers. Consequently, drugs for NTD control is still inadequate and difficult. Though of late, there are some efforts at drug discovery and development, yet inadequate supply of effective and affordable medicines pause hurdle.

c. **Research:** Adequate fund, innovative research, active effort and use of advanced technology is needed for drug discovery. Further, intracellular parasites like leishmania need more elaborate basic research. But, new drug for NTD is not expected to generate enough profit in comparison to others. Therefore, pharma companies show little enthusiasm for supporting research and development (R&D) in this area.

d. **Complex biology involved in NTDs:** Many vector borne parasitic diseases of NTDs have complex biology, and vector control remains an integral part of disease control. Drug discovery programs should also include appropriate screening tools for vector control. In absence of which, high attrition rate will prevail in target-based drug discovery.

The way out

To mitigate the challenges of drugs for NTDs, people of under-developed or developing countries have to start thinking about the low-cost solution for themselves. NTDs for its complex nature of disease, need low-cost generic drugs, sustainable funding, and harmonization of stakeholder/donor activities, efficient healthcare and drug delivery systems.

a. Traditional medicine

Traditional medicine, play a great role in treatment of neglected tropical diseases (NTDs) among rural and poor people. In recent times, even the rich or urban people are inclined towards using herbal products.

Medicinal plants are the repository of remedies with diverse chemical and bio-active agents against several health disorders. Limited information on their constituents and pharmacokinetics is a big hindrance to make useful compounds out of them. Presently, majority of herbal formulation are empirical and based on unwritten belief passed on from generation to generation with limited documentation. Lack of accessibility to traditional practice has prevented documentation of its potential.

Rainforests in Africa, South America or Southeast Asia, are the store house of medicinal plants. Many plants used in traditional medicine, with claims of benefit, have never been investigated either phytochemically or for their bioactivity. Use of plants have been limited mostly to crude extracts and/or their essential oils.

Potent herbal cures for malaria (extracts of quinine bark (Cinchona) and *Artemisia annua)* are the glaring example of success story. Today the molecules isolated from these two plants (quinine and artemisinin) remain the 1st line therapies for malaria. Acetylvismione D, isolated from the stem bark of *Psorospermumglaberrimum*, showed both strong anti-plasmodial and anti-leshmanial activities. Malaria or fever of unknown origin are being treated using >1200 plant species belonging to 160 families **[7]** and some of these natural products are quite effective**.[8]** Therefore, it can be assumed that molecule originating from rich flora of rainforests can offer a solution for the challenge.

b. Infrastructure and manpower

Since various pathogens of NTDs have a complex life cycle, drug sensitivity for various life stages are useful. Cellular assays instead of in-vivo assay can be suitable for preliminary pharmacokinetic and/or pharmacodynamics assay. Development oflaboratories to dophytochemical analysis, isolation of bioactive molecule, studying pharmacokinetic and pharmacodynamics activity, toxicology and bio-availability are needed.

c. Clinical trial infrastructure

Most of the clinically effective herbal formulation or molecules developed from plants are not universally accepted due to lack of proper documentation and clinical trials. Large scale clinical trial can be conducted within the region to establish it as drug. For these trials, adequate manpower should be trained. Even, it can provide business opportunities and employment to the local people. Many academic/career oriented researcher, can address to social/health needs of the population.

d. Resource and benefit sharing

Wide ranging automated rapid screening of natural products and extracts might be a way to build repository for therapeutically useful molecules. Government, Philanthropist, private investors may come forward to invest for such futuristic initiative. However, Public private partnership (PPP) is another way to share the resource and benefit. China has established the Chinese National Compound Library (Shanghai) in 2008 through PPP mode. This consists of the National Center for Drug Screening (China), Shanghai Institute of MateriaMedica, Chinese Academy of Sciences, WHO and Novo Nordisk A/S (Denmark). This arrangement helped in resource-sharing, and provided opportunities to access large quantities of compounds.

e. Silver lining

Funding for development of drug for NTD was negligible in 2010. Though there is some increase in funding, yet it is still very low in comparison to other diseases. During 2000 to 2013 there were three approval and five are in phase III trial for Dengue fever, onchocerciasis/ schistosomiasis, leishmaniasis, chagas disease and African sleeping sickness. **[9]** On January 2012, top executives of nine pharmaceutical company, the chief of WHO, Bill Gates foundation and several political leaders from different countries signed a declaration at London, **[10]** to emphasize on elimination of 10 out of the 17 targeted NTDs by 2020. In the Global Partners Meeting of April 19, 2017, governments, philanthropists, industry and some other partners proposed to spend good amount of fund over 5 to 7 years for NTDs.

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