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News and Perspectives

Honoring antiparasitics: The 2015 Nobel Prize in Physiology or Medicine

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ABSTRACT

Protozoa and helminths are the two main groups that cause parasitic diseases with a broad spectrum of clinical symptoms. Protozoa are unicellular organisms like the malaria parasite *Plasmodium*, which is responsible for the majority of deaths associated with parasitic infections. Helminths are alternative parasites that can produce debilitating diseases in hosts, some of which result in chronic infections. The discovery of effective therapeutic drugs is the key to improving health in regions of poverty and poor sanitation where these parasites usually occur. It is very encouraging that the 2015 Nobel Prize in Physiology or Medicine was awarded to Youyou Tu as well as William C. Campbell and Satoshi Ōmura for their considerable contributions in discovering artemisinin and avermectin, respectively. Both drugs revolutionized therapies for filariasis and malaria, significantly reducing by large percentages their morbidity and mortality.

Malaria is one of most important parasitic diseases, remaining a major health problem in most tropical developing countries in Africa, Asia, and Latin America. The *Plasmodium* protozoans *P. vivax, P. ovale, P. malariae, P. falciparum, and/or P. knowlesi* are the etiological agents of malaria in humans, and all are transmitted by *Anopheles* mosquitoes in nature [1]. Approximately 3.4 billion people worldwide are exposed annually and 1.2 billion of them are at high risk. Of these, 198 million malaria cases with clinical symptoms were reported in 2013, causing at least 650,000 deaths every year [2]. In addition to being a health threat, endemic malaria is an economic and social burden, particularly in low income countries [3].

Nematodes or roundworms like whipworm, pinworm, hookworms, and filariae are also important human parasites that currently or formerly occurred widely in tropical regions of the world. A number of nematodes are intestine-dwelling; however, filariae mostly live in other tissues, such as lymphatics and skin. *Onchocerca volvulus*, which causes onchocerciasis, is one important species naturally transmitted by black flies (*Simulium* spp.). Adults of *O. volvulus* usually develop a nodular form under the skin, frequently resulting in disfiguring skin conditions, visual impairment, and even permanent blindness (river blindness). Onchocerciasis is geographically distributed in sub-Saharan Africa and parts of Latin America. Meanwhile, *Wuchereria bancrofti* and *Brugia malayi/Brugia timori* are the species transmitted by mosquitoes and cause clinical symptoms similar to those of elephantiasis (lymphatic filariasis); *i.e.*, impaired lymphatic drainage,

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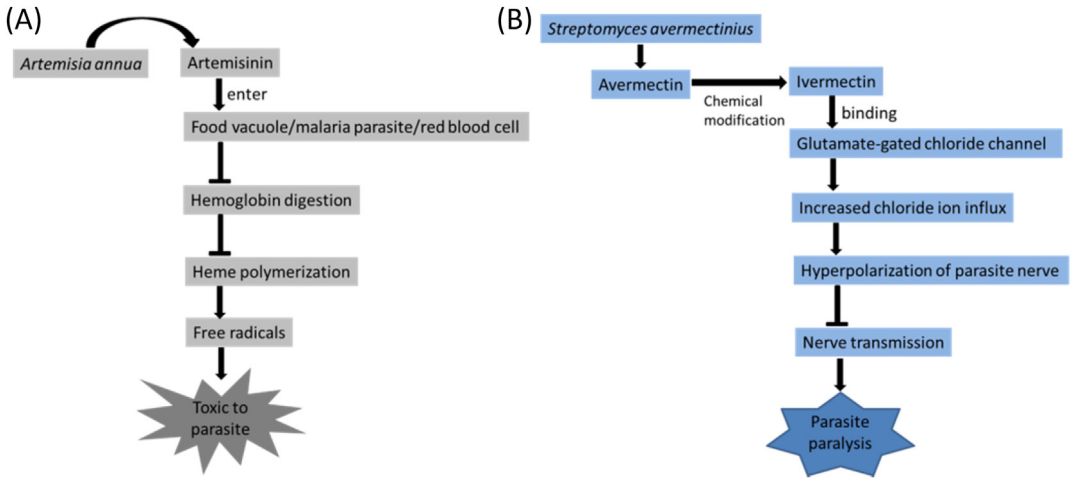

Fig. 1 – (A) Artemisinin identified from *Artemisia annua* contains an endoperoxide bridge reacts with the iron atoms, leading to disruption on the hemoglobin catabolism and heme detoxification systems in the food vacuole of *Plasmodium* species by forming free radicals. Malaria parasites developing inside the erythrocyte are consequently damaged which treated with artemisinin. (B) *Streptomyces avermectinius* – originated avermectin possesses activity against nematodes including those cause river blindness and lymphatic filariasis by binding to glutamate-gated chloride channels in treated parasites, causing increased chloride ion influx and hyperpolarization of the parasite nerves. It, in turn, interferes with the transmission of nerve signals, leading to paralysis and death of the parasite in consequence.

fibrotic skin tissue, and scrotal hydrocele [4,5]. Most cases occur in the tropics and it has been identified by the World Health Organization as the second leading cause of permanent or long-term disability [6].

Treatment for patients is essential in order to prevent morbidity and mortality, and conventional drugs have been developed against both important parasites. Quinine/chloroquine was identified as effective against malaria decades or even centuries ago. In contrast, diethylcarbamazine (N, N-diethyl-4-methyl-1-piperazine carboxamide; DEC or Hetrazan) was developed and has been used to treat filariasis since the last mid-century. Unfortunately, their efficacies have largely decreased due to induced resistance caused by the prevalent use of these drugs over time. Discoveries of artemisinin and avermectin have recently opened a new era of chemotherapy for these two important parasitic diseases, not only relieving a number of diseases but also saving many lives from infections.

Discovery of artemisinin

The malaria parasite was not identified until the military doctor Alphonse Laveran described his finding in "New parasite found in the blood of several patients suffering from marsh fever" in 1802. Its natural cycle via transmission by *Anopheles* mosquitoes between humans was subsequently demonstrated by Ronald Ross a few years later [7]. Humans and female mosquitoes both provide adequate environments for the development of malaria parasites in their complex life cycle [8]. In humans, the parasite forms male (micro-) and female (macro-) gametocytes as the final developmental stage, which are ingested by mosquitoes along with a blood meal. The opposite gametocyte sexes subsequently mate in the lumen of the midgut where infective sporozoites form within the resultant oocysts. They then migrate to the salivary glands, from which they can be passed along with saliva to another human when infected female mosquitoes bite again [9]. After injection into humans via mosquito bites, sporozoites rapidly multiply in the liver to form merozoites, which then invade red blood cells in the bloodstream. Infected red blood cells usually burst and release merozoites, which cyclically enter and infect other red blood cells. This feature results in typical clinical symptoms such as chills and fever, as well as anemia in most cases. Complications like cerebral malaria, acute renal failure, black water fever, hypotension, shock, and even death also occur in many cases of *P. falciparum* infection [10].

Quinine was identified from the bark of *Cinchona* (Family: Rubiaceae) as early as 1820, while its first derivate compound, chloroquine, was first synthesized in 1934 and has since been used as a therapeutic for malaria [11]. Unfortunately, resistance to chloroquine appeared in most of the areas harboring malaria by the late 1960s while the incidence of the disease continued to rise [12]. This makes it urgent to develop new approaches to replace chloroquine in malaria treatment and control. Artemisinin was first identified in 1972 by Youyou Tu and her team in the Academy of Traditional Chinese Medicine, China (ScienceNet.cn; http://tinyurl.com/gkw7mjh). After graduating from Peking University Medical School/Beijing Medical College with a major in Pharmaceutical Sciences, Youyou Tu started working on traditional herbal medicine in 1955. During the Cultural Revolution period in China, Youyou Tu was appointed the director of Project 523 in 1969, which strove to develop novel therapeutic drugs to heal chloroquine-resistant malaria. In a large-scale screening of herbal medicines, *Artemisia* spp. (Family: Asteraceae), or sweet wormwood, was selected from more than 640 traditional herb