AVERMECTIN AND ARTEMISININ: WEAPONS TO ANTIPARASITIC DISEASE-FREE TROPICAL WORLD

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Nobel Prize winning discovery of Avermectin by Campbell and Ômura have drastically reduced the occurrence of river blindness and lymphatic filariasis, as well as showing effectiveness against an increasing number of various parasitic diseases. Tu's discovery of artemisinin extensively lowered the mortality rates for malaria patients. These two discoveries have lowered down millions of death annually in the tropical world. Global initiatives sponsored by WHO, non-governmental organizations (NGOs) and Governments set target of elimination of lymphatic filariasis and river blindness by 2025.

Introduction

The aura of Nobel Prize is not because of the prize itself, but this is the ultimate recognition of the scientific discoveries that have changed the way of living of the mankind. Nobel Prize was established in 1895 by Swedish chemist Alfred Nobel, the inventor of dynamite, in his will. The Nobel Prize is given to the recipients once in a year on 10th December, the anniversary of Nobel's death in the Nobel Assembly at Karolinska Institute, Stockholm. The first Nobel Prize in Physiology or Medicine was presented to Emil Adolf von Behring in 1901 for his work on serum therapy and its application against diphtheria, and by this he has opened a breakthrough in medical science, thereby placing a strong biological weapon against diphtherial deaths. The Nobel Prize in Physiology or Medicine has till date been awarded 106 times to 210 Nobel Laureates during 1901-2015.

In 2015, the Nobel Prize in Physiology or Medicine was awarded equally to William C. Campbell and Satoshi Ômura for their discoveries of avermectin, a novel treatment against infections of roundworm parasites and the other half to Youyou Tu for her discovery of artemisinin, a novel therapy against malaria. Avermectin has drastically reduced frequency of river blindness and lymphatic filariasis, along with showing efficiency against various other parasitic diseases. Artemisinin has extensively reduced the mortality rates of malaria patients. Parasitic diseases are affecting mankind from centuries and thus cause the most important global health problem. It is a huge barrier to human health improvement as it specifically affects the world's poorest populations. Nobel Laureates' discoveries of last year have revolutionized the treatment of some of the most devastating parasitic diseases of tropical world. These two drugs together have saved millions of death every year. Parasitic worms influence almost one third of world's population, predominantly in sub-Saharan Africa, South Asia and Central and South America.[1]

Scientific Journey of the Nobel Laureates

William Cecil Campbell, 85, is currently a Research Fellow Emeritus at *Drew University,* Madison, New Jersey, USA. He had received his PhD from the University of Wisconsin, Madison, USA in 1957. From 1957-1990, he was with the Merck Institute for Therapeutic Research, from 1984-1990 as a Senior Scientist and Director for Assay Research and Development. In 1979 Campbell recognized avermectin B_{1a} produced by *Streptomyces*

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avermitilis which had a broad effectiveness against roundworm infections in a varied range of domestic animals like cattle, sheep, dogs and chickens. Following this, he also developed a modified form of avermectin B_{1a}, known as ivermectin, which shows a positive clinical efficacy in animal models of parasitic infection. After its introduction in 1982, ivermectin has become a key treatment against parasitic infections, particularly to river blindness (onchocerciasis) and lymphatic filariasis (in severe condition elephantitis or lymphedema) with scrotal hyrdrocele. Ivermectin is thereafter on the World Health Organization's list of Essential Medicines.

Satoshi Ômura, 80, is Professor Emeritus at Kitasato University from 2007. He received his PhD in Pharmaceutical Sciences in 1968 from the University of Tokyo, Japan and a PhD in Chemistry in 1970 from Tokyo University of Science. He was a researcher at Kitasato Institute, Japan during 1965-1971 and Professor at Kitasato University during 1975-2007. Ômura isolated novel strains of *Streptomyces* sp. from soil samples that had antibacterial components with potential to combat other harmful microorganisms. From thousands of different cultures, he selected about 50 of the most capable ones and further analyzed them for their activity against pathogenic microorganisms. One of these was *Streptomyces avermitilis producing avermectin.* Ivermectin (Fig 1), modified form of avermectin, was later tested in parasite-affected humans and resulted in successful killing of microfilaria larvae. Together, Ômura and Campbell's contributions led to the discovery of a novel class of drugs that had astonishing usefulness against parasitic diseases.

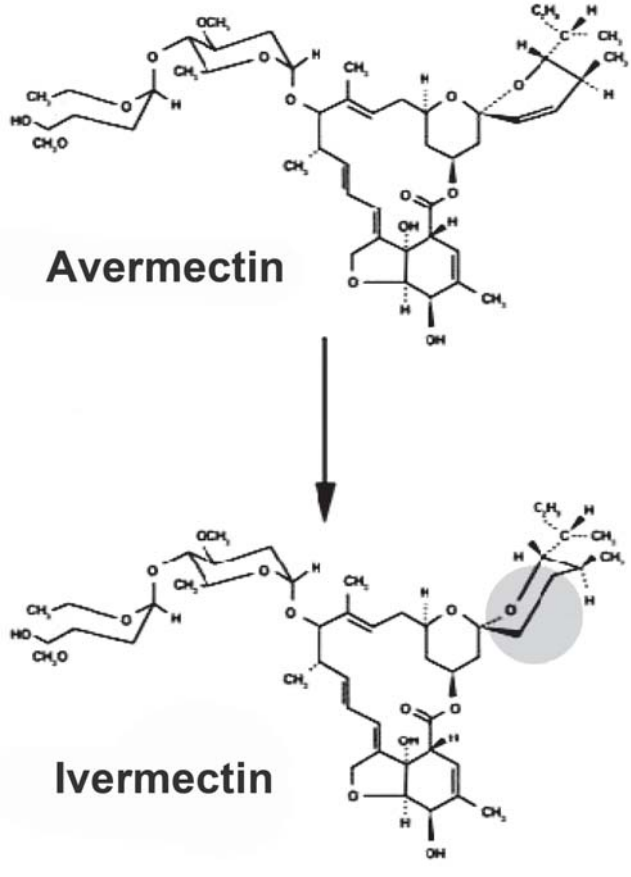

Fig. 1-Structure of ivermectin- a broad spectrum anti-parasitic drug modified from macrocyclic lactone avermectin produced by *Streptomyces avermitilis* (Source: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2015/press.html)

Youyou Tu, 85, is currently the Chief Professor at the China Academy of Traditional Chinese Medicine. She graduated from the Pharmacy Department at Beijing Medical University in 1955. During 1965-1978 she was Assistant Professor at the China Academy of Traditional Chinese Medicine, from 1979 to 1984 Associate Professor and from 1985 Professor at the same Institute. At that time, malaria was usually treated by quinine or chloroquine with increasing failure rates. By late 1960s, efforts to eradicate malaria had abrupt fall and the disease was on its mount. At that point, Youyou Tu turned to Chinese traditional herbal medicines to handle the challenge of discovering novel malaria therapies. From a large-scale screening of herbal remedies in malaria-infected animals, an extract of *Artemisia annua* plant showed maximum potential. But as these results were contradictory, Tu went through the ancient Chinese literature too and discovered some written facts that resulted in successful extraction of artemisinin from *Artemisia annua*. Artemisinin (Fig 2) was extremely effective in both infected humans and animals against early developmental stage of malaria parasite, with also having surprising effectiveness in severe malaria treatment.[1]

The Path-breaking Research Leading to Nobel Prize

Efficacy of avermectin against pre-adult stage filarial parasite in mammalian host : Avermectin is a macrocyclic lactone produced by *Streptomyces avermitilis*. Ivermectin is a modified form avermectin. Campbell showed that avermectin was effective against various stages of filarial parasites with respect to pre-adult stages in mammalian host. Efficacy against filarial parasites was observed in oral or parenteral administration of drug at exceptionally low dosage against third larval stage (L3) , fourth larval stage (L 4) and immature adult (L5). [2]

During his 40-year career, Professor Ômura has discovered many novel methods for isolation, culture and screening of microbes. Dominant among the microbe-derived compounds was avermectins/ivermectin, and he developed it through a joint research program with Merck & Co. Inc. (USA). Ivermectin is one of the world's most

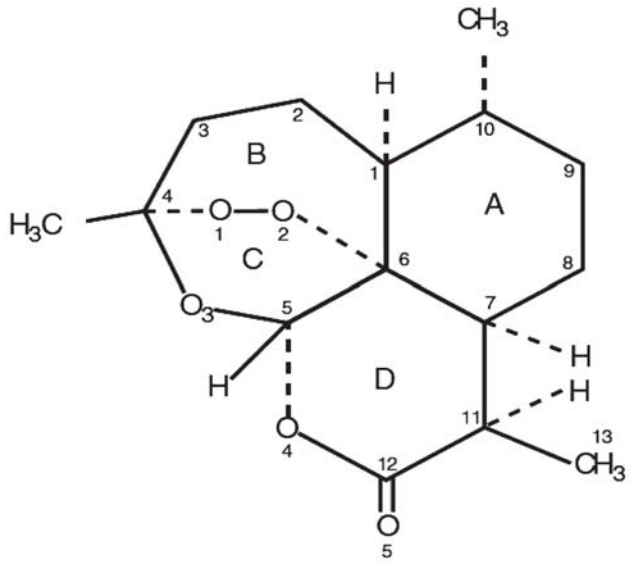

Fig. 2-Chemical structure of artemisinin, an anti-malarial drug obtained from the plant *Artemisia annua* (Source: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2015/press.html)

important animal and human medicines ever created with one of the foremost public health discovery ever in developing world and compete penicillin for its extreme beneficial impact on global health - with over 300 million people's use annually. [3]

Ivermectin kills the parasite by interference with its nervous system and muscle function mainly by enhancing inhibitory neurotransmission. The drug binds and activates glutamate-gated chloride channels. These channels in neurones and myocytes are not invertebrate-specific, but vertebrates are protected from ivermectin by blood–brain barrier. [4] Ivermectin irreversibly triggers up channel receptors in worm and finally result in an inhibitory postsynaptic potential. So the possibility of further action potentials in synapses decreases, and the nematodes get paralyzed, followed by death. Ivermectin is directly effective against larval stage *Onchocerca volvulus* microfilariae by paralyzing and killing it by action of eosinophils and macrophages. It is not capable of killing the adult female macrofilariae, but it stops their microfilariae production probably by paralyzing their reproductive tract. [5]

Artemisinin: Discovery of Antimalarial Effect from Ancient Chinese Medicine

Malaria, caused by *Plasmodium falciparum*, has been a life-threatening disease for past thousands of years. After the letdown of various international attempts to eradicate malaria in 1950s, the disease reappered due to emergence of resistant parasites against existing antimalarial drugs like chloroquine. During the initial stage of Youyou Tu's research, she had worked through more than 2,000 Chinese herb preparations and identified 640 possible antimalarial compounds among them. More than 380 extracts were prepared from around 200 Chinese herbs that she had examined against malarial mouse model. After the positive clinical outcome of *Artemisia annua* L., a colorless, crystalline active compound (mol. wt. 282 Da), $C_{15}H_{22}O_5$, and melting point of 156–157°C was identified from the extract and was named qinghaosu or artemisinin. Addition of a hydroxyl group to the molecule introduced more opportunities for development of other artemisinin derivatives by esterification. Later on, a new derivative named dihydroartemisinin was also developed. In 2005, WHO announced artemisinin combination therapy (ACT), and ACT is now days widely used in Africa saving many lives, mostly of children. It evidently reduces malarial symptoms with its antigametocyte activity. [6]

Avermectin and Artemisinin Therapy: Benefit to Mankind

Roundworm infection outbreaks during childhood and causes lifelong suffering and disability. Among the various diseases caused by roundworms, river blindness and lymphatic filariasis stand out with 25 million and 120 million infected individuals, respectively. The global impact of avermectin and artemisinin treatment goes far beyond reducing the disease burden of individuals, and now the treatment is effective by one or two doses of ivermectin annually. These parasitic diseases place a massive disease burden by specifically affecting the poor and vulnerable. But today, river blindness and lymphatic filariasis are on the edge of eradication. Global initiatives by WHO, NGOs and Governments set the aim of eliminating lymphatic filariasis by 2020 and river blindness by 2025[1]. Several countries previously weighed down by malaria are now free from this indigenous transmission. The overall global death rate from malaria during the last 15 years has exclusively declined by 50% (WHO, 2015).

Conclusion

In India, CSIR-CIMAP, Lucknow introduced *Artemisia annua* crop under contractual cultivation and buy-back arrangement with pharma industries to avoid marketing problems for the farmers' benefit. In the different study areas of Uttar Pradesh, contractual cultivation is going on by M/s Ipca Laboratories, Ratlam from 2009 onwards. Farmers are cultivating this crop contractually guided by CSIR-CIMAP. Cultivation of *A. annua* gives high return to farmers in a short time span of about four months. The

total return is Rs 87,603/ha and the net benefit over variable cost is seen to be Rs 65,759/ha, resulting the benefit–cost ratio as 4.01. The contractual cultivation under Public-Private Partnership model strengthens the farmers to accept new technologies and crops, and also boost the marketplace of medicinal plant.[7] Clinical resistance to artemisinin recently emerged in southeast Asia, which is an alarming issue. These resistant parasites used to exhibit altered pattern of development in infected erythrocytes. Thus different artemisinin derivatives are now days used in combination with other antimalarial drugs to treat multidrug -resistant malaria worldwide.[8]

The discoveries of 2015 Nobel Laureates thus represents an archetype shift in medicinal field, which has not only provided a revolutionary therapy for patients suffering from these devastating tropical parasitic diseases, but has also promoted comfort and growth of both individuals and society. So, the global impact of their discoveries and the benefits to mankind isimmeasurable.

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References

1. Scientific Background Avermectin and Artemisinin - Revolutionary Therapies against Parasitic Diseases (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2015/advanced medicineprize2015.pdf)
2. W. C. Campbell, History of avermectin and ivermectin, with notes on the history of other macrocyclic lactone antiparasitic agents, *Current Pharmaceutical Biotechnology,* **13**, 853-865 (2012).
3. S. Omura, Microbial metabolites: 45 years of wandering, wondering and discovering, Tetrahedron, **67**, 6420-6459 (2011).
4. P. A. Rea, V. Zhang, Y. S. Baras, Ivermectin and River Blindness. *American Scientist,* **98**, 294–303 (2011).
5. D. M. Yates, A. J. Wolstenholme, An ivermectin-sensitive glutamate-gated chloride channel subunit from Dirofilaria immitis. *International Journal for Parasitology,* **34**, 1075–1081 (2004).
6. Y. Tu, The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine, *Nature Medicine,* **17**, 1217-1220 (2011).
7. S. Kumar, R. Suresh, K. D. Verma, A. Dangesh , V. K. S. Tomar, Public–private partnership towards rural development: a study of *Artemisia annua* in Uttar Pradesh, *Current Science*, **109**, 1237-1239 (2015).
8. A. Hott, D. Casandra, K. N. Sparks, L. C. Morton, G. Castanares, A. Rutter, D. E. Kyle, Artemisinin-Resistant Plasmodium falciparumParasites Exhibit Altered Patterns of Development in Infected Erythrocytes, *Antimicrobial Agents and Chemotherapy,* 59, 3156-3167 (2015).