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An Innovative Cornerstone For Anti-Malarial Therapy: Case Study Of Artemisinin.

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ABSTRACT

Science-based innovation emerged from novel and discontinuous innovations which provoked irreversible yet significant changes in science and technology. This research investigated the commercialization process of artemisinin, a typical science-based innovation in China. Due to her research in-volvement with artemisinin (qinghaosu), Tu Youyou received the 2011 Lasker Award in clinical medicine and the 2015 Nobel Prize in Physiology or Medicine jointly with William C. Campbell and Satoshi Ōmura. In this paper, the authors reviewed the process of artemisinin's innovation from labs in a research institute to its entrance into the market. Process analytical technology (PAT) is used in each step to understand the nature of material systems and separation characteristics of each separation method. In the present work, this methodology is applied to generate a process flow sheet for recovery of artemisinin from the plant Artemisia annua (A. annua). Based on the research, we reached the following conclusions. First, during the process of science-based innovation, a new technology platform might be established and a series of applications might be invented. Second, the extensive cooperation among research institutions and companies played a vital role in science-based innovation. Third, the science-based innovation emerged through multidisciplinary research teams as well as contacts among scientists with cross-fields expertise.

Keywords: Artemisinin, anti-malarial drug, malaria, case study.

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INTRODUCTION

Innovative Cornerstone

Artemisinin is a new class of antimalarial compounds explained by Chinese scientists **Prof.** Tu You-You from the sweet wormwood *Artemisia annua* in the 1970s.who shared the 2015 Nobel Prize in Physiology or Medicine for her innovation. Artemisinin is collected generally from the dried leaves of the plant A annua. Artemisinin and its derivatives are front anti-malarial drugs known for their potency and low toxicity [1].

Case study

Science-based innovation refers to those developments of new-to-market technologies highly dependent on frontier scientific discoveries. In our cases, artemisinin was a new chemical entity which was discovered and developed completely in China. After the discovery of artemisinin, new technology platforms of artemisinin and a series of anti-malarials had been developed. In each drug development process, there was necessary science-based research, application development as well as commercialization phases [2].

Artemisinin is a most natural product permitted by the World Health Organization (WHO) for use in merge with other drugs opposition drug resistant plasmodium falciparum induced malaria. Artemisinin is obtained mainly from dried leaves of the plant A. annua. Artemisinin and its derivatives are frontline anti-malarial drugs known for their efficacy and low toxicity. After decades of wide use, artemisinins remain our bulwark against malaria. Artemisinin-based combination therapies (ACTs) are now standard treatment worldwide for P. falciparum malaria as well as malaria due to other species of Plasmodium. The use of artemisinin-based combination therapies (ACTs), which combine an artemisinin derivative with a partner drug. The unique characteristic of artemisinins is that they clear parasitemia more rapidly than all other anti-malarial, including quinine. Their efficacy can be ascribed to the fact that these compounds target not only the late erythrocytic parasite stages, like most anti-malarial drugs, but also the early stages. Artemisinins, by killing the ring stage forms, allow the parasite to be pitted out of the host red blood cells, hence removing them from circulation and preventing these parasite stages from maturing and sequestering in the vessels. Malaria remains the most prevalent and deadly vector-borne disease in the world. With an estimated two hundred million cases and over four hundred thousand deaths recorded in 2015. Maleria disease is caused by five species of Plasmodium parasites: P. falciparum, P. vivax P. malariae P. ovale, and P. knowlesi. Among these P. falciparum is the major cause of malaria infection and P. vivax is the most widely distributed malaria-causing parasite globally [3, 4].

Figure 1: Plant of Artemisia Annua

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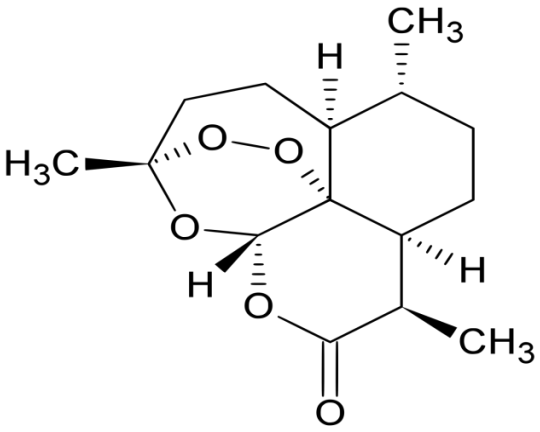

Figure 2: Chemical structure of Artemisinin

Molecular formula	**$C_{15}H_{22}O_5$**
Molecular mass	**282•33g/mol**
Melting point	**152°c - 157°c**
Phase	**Crystalline solid**
Performance	**Antimalarial drug (Pharmacy)**
Boilling point	**Decomposes**
Density	**1.24+0.1g/cm^3**
Solubility	**Insoluble at room temperature**
Other name	**Qinghaosu**

Table 1: Properties of Artimisinin

Information about Artemisia Annua

- annua belongs to the Asteraceae family native to china.
- Artemisinin is mainly found on the surface of dried leaves in glandular trichomes in plant.

Parameter of Artemisinin

- ACCESS
- PHARMACOLOGY
- ADVERSE EFFECT
- ACTs IN CHILDREN
- ACTs IN PREGNANCY
- ACTs ON PLASMODIUM VIVAX
- EFFECT ON TRANSMISSION

ACCESS

Artemisinin-based combination treatments are highly effective and really could make a major contribution to global malaria control, but despite the recent changes in policy in most malaria endemic countries only a minority of people who need these drugs actually receive them. Cost and access remain formidable obstacles. only a minority of people who need these drugs actually receive them. Cost and access

remain formidable obstacles. Few public health structures reach out far enough or efficiently enough to provide good coverage of effective and affordable drugs to rural communities [5-7].

PHARMACOLOGY

Artemisinin, the parent drug has now largely given way to the more potent dihydroartemisinin and its derivatives, artemether, artemotil, and artesunate. The 3 derivatives are all converted back in vivo to dihydroartemisinin. Oral absorption is good (bioavailability > 60%) with peak concentrations usually achieved within 4 hours. All are eliminated rapidly by metabolic biotransformation with half-lives of 1 hour or less. Artesunate is readily hydrolyzed at neutral and acidic PH. These drugs are highly active against all Plasmodium species. The artemisinin derivatives are the most rapidly acting of all antimalarial drugs and produce the fastest clinical responses to treatment. They are noticeably better than other antimalarial drugs. They have a broad spectrum of antimalarial activity acting against the young ring form parasites and preventing their development to the more mature pathogenic stages [8-10].

ADVERSE EFFECT

Artemisinin and its derivatives are safe and remarkably well tolerated. There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, and bradycardia, although none of these associations are convincing. The only potentially serious adverse effect that has been reported with this class of drugs in clinical trials is type 1 hypersensitivity reactions in approximately 1 in 3,000 patients. Transient reticulocytopenia, neutropenia, and elevated liver enzyme values have been reported but none have been clinically significant. Electrocardiographic abnormalities, including prolongation of the QT interval, have also been reported although most studies have not found any significant electrocardiographic abnormalities. Indeed the weight of evidence suggests these drugs have no adverse cardiovascular effects at all [11].

ACTs IN CHILDREN

The ACTs seem to be tolerated as well or better in children than in adults. There is no specific age-related toxicity. In younger children vomiting or regurgitation of the administered dose are always a concern but are no more common with ACTs than mono therapies. Recent pharmacokinetic studies indicate that the dose regimen advocated for SP in children for many years is probably too low. Dose regimens for artesunate–mefloquine and artemether–lumefantrine in children are justified by pharmacokinetic studies. Further work is needed to optimize dosing in children based on weight or surface area and, where necessary, to introduce specific pediatric formulations [12].

ACTs IN PREGNANCY

Pregnant women are a high-risk group. They are more susceptible to malaria, more likely to develop anemia, and if non-immune are more likely to develop complications. Birth-weight is consistently reduced by malaria. Therefore, pregnant women desperately need effective and safe antimalarial treatments. The main concern surrounding the general deployment of ACTs is their safety in the first trimester of pregnancy. Work by Chinese scientists in rodents and rabbits conducted in the 1970s indicated that early pregnancy exposure could induce fetal resorption. Recent reproductive toxicity studies have confirmed that this is a class effect of the compounds and is seen in all experimental animal species studied [13].

ACTs ON PLASMODIUM VIVAX

The artemisinin derivatives and the ACTs work as well or better against Plasmodium vivax compared with Plasmodium falciparum infections. The exception to this is artesunate–SP, which is ineffective in those areas with high-level antifoul resistance in P. vivax. These drugs do not affect the hypnozoites, so relapses are not prevented [14].

EFFECT ON TRANSMISSION

All effective antimalarials prevent the development of gametocytes in P. vivax, P. malaria, and P. ovale infections and the early-stage gametocytes (stages 1 to 3) of P. falciparum. The artemisinin derivatives inhibit development of more mature P. falciparum gametocytes. Gametocytemia is greater in

recruits than primary infections. In low-transmission settings this gametocytocidal effect and the high cure rates obtained with ACTs both contribute to reducing transmission, and thus the incidence of malaria [15-17].

Methodology

According to the task target of isolating compound from its source and purification from a crude complex extract classified in two sub- types. The difficulty breakdown is aimed at dealing with the complexity of the difficulty in a stepwise and the mainly economical method. Primary collection of individual unit operations and operating conditions can be obtained with the help of available heuristics and bench scale tests to generate a procedure flow sheet followed by experimental estimation on the basis of yield and clarity of target compound. PAT (Process Analytical Technology) apparatus such a special investigative techniques and chemo metrics are emphasized in the development for improvement of natural products. PAT is broadly accepted as a most important process system engineering instrument used for improved understanding and control of the manufacturing processes. It has previously been a well-established performs in petrochemical and biotechnology production [18-20].

High performance liquid chromatography
Gas chromatography
UV spectroscopy
Particle size analyzer
Differential scanning colorimetry
Densitometry

Table 2: PAT TOOL (Process Analytical Technology).

CONCLUSION

Chinese scientists proved the final products to be both labs effective and clinically validated. Artimisinin was one of the most successful and unique science-based innovations in Chinese history and was a great example of the Nobel Prize's scientific products that were internationally distributed. We draw on the following conclusions: In science-based innovation scientists not only invented and improved the scientific products to ready-to-market applications.

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