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Artemisinin: A Promising Antimalarial Herbal Drug

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ABSTRACT

Quinghaosu (artemisinin) was discovered by the Chinese scientist from Artemisia annua L. in 1972. Artemisinin is widely used anti-malarial drug. It can be synthesized easily and more economically from the extract of the plant. It acts by combining with red blood cell in which it consumes haemoglobin and liberates free heme and iron porphyrin ring and this iron reduce the peroxide bond of artemisinin and generates the free oxygen species which damages the parasite.

Key words: Quinghaosu, Artemisia annua L., Artemisinin, Artesunate, Artemether, Dihydroartemisinin.

INTRODUCTION

Malaria is a parasitic disease caused by protozoa *Plasmodium Species* which is transmitted by female anopheles mosquito. It is a public health problem in more than 90 countries and about 40% of the global population is suffering from this deadly disease [1]. It is attributed to the emergence of drug resistant organism [2]. This is attributing mainly to the emergence of drug-resistant organism [3, 4, 5]. Malaria infection during pregnancy is the major problem in tropical and sub-tropical regions [6], it mainly causes low birth weight and increased mortality, maternal anemia etc [7, 8].

Traditionally, the medicines that have been used for the treatment of malaria are from the two main source groups i.e. artemisinin and quinine derivative [9]. Artemisinin came to the attention of the World Health Organization in the 1970s when Quinine lost efficacy against malaria. Artemisinin is the only drug effective against malaria and hundreds of millions of doses are prescribed for that purpose every year. With the emergence of drug resistant malaria parasite, artemisinin became the first choice medicine in the treatment of malaria in several countries [10, 11]. Artemisinin is an endoperoxide sesquiterpene lactones which is isolated by the aerial parts of the plant *Artemisia annua L*, not all plant of this species contain artemisinin [12, 13].

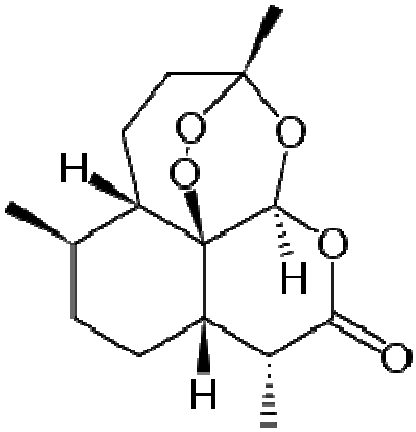


Figure 1: Structure of Artemisinin

Artemisinin and its derivatives are considered to be safe and effective however mainly the studies are based on the non-pregnant patients which renders concern about the safety for the use of medicine during pregnancy [14, 15].

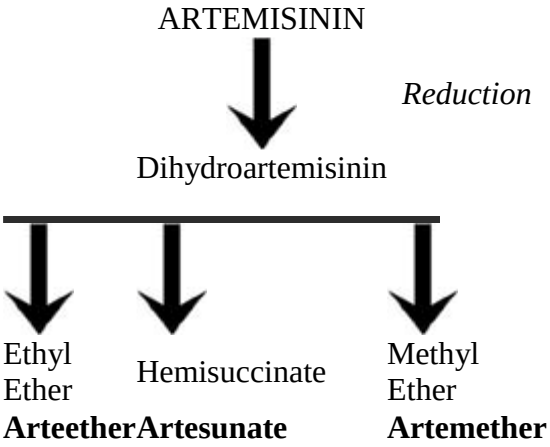
Source-

The only commercial source of artemisinin is plant. There are three species in the genus of the *Artemisia* that contain artemisinin i.e. *Artemisia annua*, *Artemisia apiacea* and *Artemisia lanceolata* [16]. The simplest method for isolation [17] of artemisinin from the *Artemisia annua* is its crystallization from the extracts of the dried plant material, yield of about 1.5% dry weight should be reported [18]. Studies for developing high artemisinin *Artemisia annua* using advanced molecular breeding techniques is in progress in UK. Considerable effort has been put into the development of transformed root cultures (hairy roots) for artemisinin production. As with other plant metabolite of commercial interest, several attempts have been made to produce 1 in cell and in tissue culture [19].

Possibilities for production of artemisinin in decreasing order of chemical synthesis requirements.

Biological host	Starting material	References	Comments
None	Monoterpenes	Schmid and Hofheinz ,1983	Expensive:-low yield
E.coli	Amorphadiene	Martin et.al.,2003	High biosynthetic yield
Tobacco	Amorphadiene	Wu.et al.,2006	Low yield
E.coli	Artemisinic acid	Chang et al.,2007	Efficient cyt.P450 expression is a challenge
Yeast	Artemisinic acid	Ro et al.,2006	High yield
Yeast	Dihydroartemisinic acid	Zhang et al.,2008	Yield not optimized, simple chemistry
Chicory	Artemisinic acid/ dihydroartemisinic acid (3a)	www.dafra.com	In progress
A.annua hairy roots	None	Towler et al.,2007	Low yield
A.annua	None	Delabays et al.,2001	Expensive compared to other malaria drugs.

THE ARTEMISININ DERIVATIVE



Chemically Modified Analogues

There are number of derivatives and analogues in the artemisinin family;-

- Artesunate
- Artemether
- Dihydroartemisinin
- Artelinic acid
- Artenimol
- Artemotil

Mechanism of Action

Their site of action is within the parasite and also remains controversial. At chemical level, it states that when the parasite causes malaria it infects red blood cells, which consumes heamoglobin with liberating free heme and an iron porphyrin complex. This iron reduces the peroxide bond in artemisinin which generates the high valent iron-oxo species that produces reactive oxygen radicals which damage the parasite leading to its death [20].

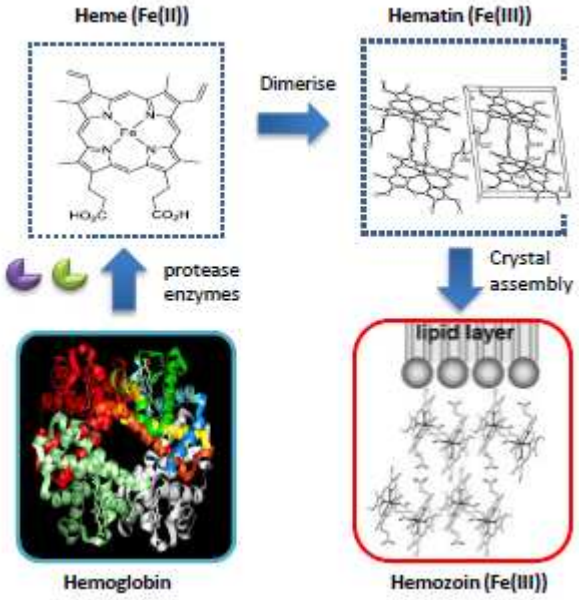


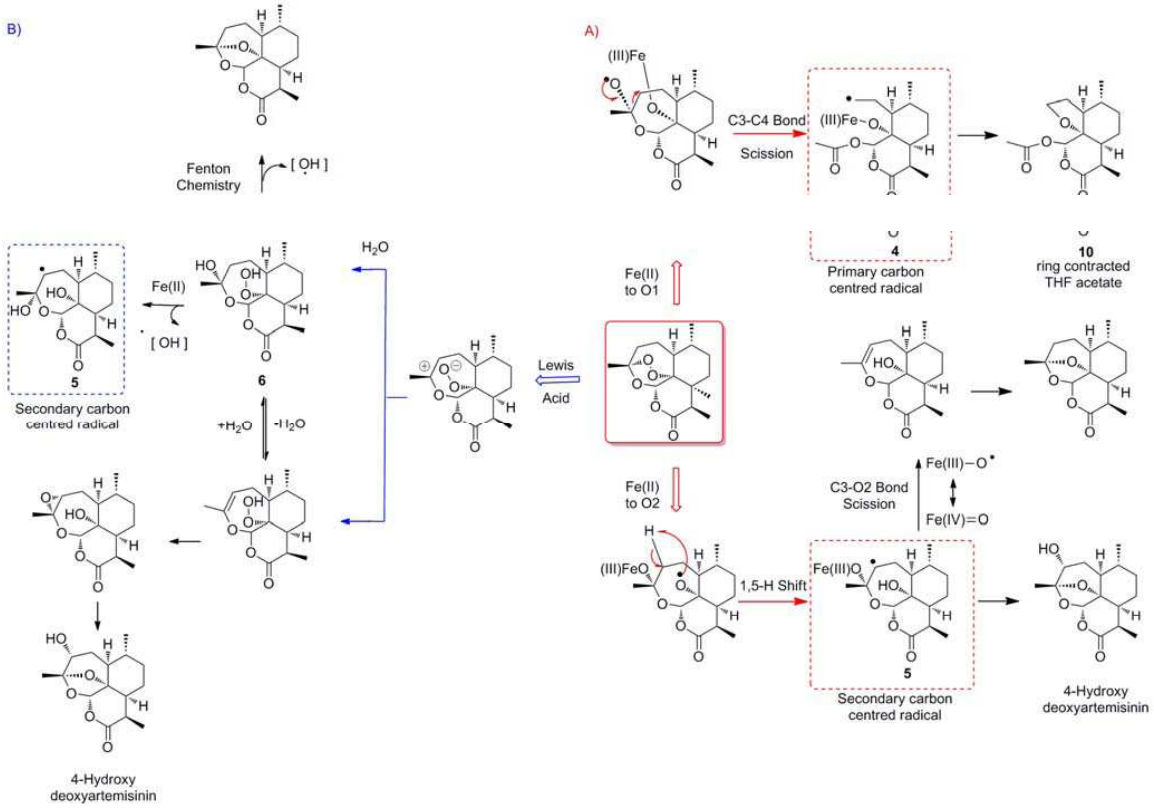
Figure 2. Detoxification of hemoglobin: toxic hematin (formed by hydrogen bonding of heme monomers) [21] is converted by the parasite to an insoluble non-toxic compound called hemozoin (it has recently been suggested that the propionate group of each Fe (III) PPIX molecule coordinates to the Fe(III) centre of its partner) [22].

Activation of artemisinin

Bioactivation in Parasites

Hemoglobin is degraded by a series of protease enzymes to release peptides and amino acids which are required for the development and to create space within its digestive vacuole when the malarial parasite is within the body of the host. During this process, hematin occurs which is toxic to the parasite (Fig. 2) to this toxicity, the parasite developed a mechanism in which hematin undergoes biomineralisation to form insoluble non-toxic hemozoin (malaria pigment).

Figure 3. Bioactivation of artemisinin; A) Reductive scission model; B) Open peroxide model.



Meshnick group [23] was one of the first who completed the studies and suggested that the bioactivation of 1, 2, 4-trioxanes is triggered by iron (II) to generate toxic activated oxygen. By the iron dependent bioactivation of the end peroxide bridge we can rationalize the selection of artemisinin towards parasite infected erythrocytes over normal erythrocytes. Since, by these findings two models of ring opening suggested the dependency on iron and involvement of carbon centered radicals.

Reductive Scission Model

These oxygen centered radicals subsequently rearrange to form carbon centered radicals which is proposed by Posner [24, 25] and Jefford [26, 27] although the nature of proposed radical and the mechanistic pathways give rise to their formation which is different in each case. Artemisinin were found to bind with low valent transition ions and subsequent transfer of ions which induce reductive scission of the peroxide bridge to produce oxygen centered radicals which rearrange to give carbon centered radicals (Figure 3).

Iron was found to interact with the peroxide in different ways to produce either a primary carbon centered radical or a secondary carbon centered radical, due to unsymmetrical nature of the end peroxide bridge. By electro paramagnetic resonance spin trapping techniques after being

activated by iron [28], spins are trapped of both the primary and secondary radicals 4 and 5 [29, 30].

Open Peroxide Model

The ring opening model is driven by the protonation of the peroxide or by the complexation by Fe (Fig. 3). Iron acts as a Lewis acid to facilitate ionic, rather than radical bioactivation of the artemisinin and it is proposed by the Haynes and co-workers [31]. It has also been suggested that non-peroxide oxygen plays an important role in facilitating ring opening of the peroxide to generate the open hydro-peroxide [32, 33]. In this the positive charge stabilization is provide by the oxygen atom and according to transition state theory, for ring opening model low was required. Formation of unsaturated hydro-peroxide 6 was lead capable of the heterolytic cleavage of endo- peroxide bridge and subsequent capture of water; by direct oxidation we are capable of irreversibly modifying protein residues. Fenton degradation of the hydro peroxide 6 produces a hydroxyl radical, a species that contain oxidized target amino acid residues [34].

Artemisinin as antimalarial agent

Artemisinin is a herbal drug which is used in the treatment of infections and malaria. For over two million people artemisinin proves itself as a safe and effective for the treatment in malaria. It has along history of use as an anti-malarial remedy [35]. Artemisinin and its two derivatives are artemether and sodium artesunate, were evaluated in the 1970. In China 1979, 2099 patients were infected by *Plasmodium viva* and *Plasmodium falciparum*. In which artemisinin had good therapeutics effects and cured all peoples. Artemisinin are also effective in cerebral malaria. The temperature in malaria should be normalized within 72 hours and asexual parasites are also eliminated within 72 hours. However, relapse rate is 21% [36]. Children of ages 1 to 15 years were randomly selected to receive artemisinin suppositories or oral quinine, in clinical trial in Vietnam. The result shows that the suppositories rapidly cleared asexual *Plasmodium falciparum* parasitemia in children and confirmed the problem of reoccurence rates [37]. For malaria extensively researched has been made on Artemisinin, and has been used for million of patients, mostly in China and Vietnam. It is helpful in drug resistant malaria [38, 40].

Artemisinin and its derivatives have been studied for their efficacy as anti-malarial agents. Artemisinin *in-vitro* trials was conducted in China, artemisinin and all its three compound viz. artesunate, artemether and artether have been effective against erythrocytic stages of two chloroquine-resistant. Alternative treatments are based on new compounds such as artemisinin and their derivatives are actively being sought. Malaria and cerebral malaria are treated by artemisinin and its derivatives in human subjects with no apparent adverse effect nor side effect.

Adverse effects of artemisinin

Artemisinin are generally well tolerated dose to treat malaria [41]. The side effects of artemisinin are: nausea, vomiting, anorexia and dizziness. Mild blood abnormalities have also been notice. One serious adverse effect of artemisinin is an allergic reaction and liver inflammation has also reported [42, 43]. Drugs that are used in combination therapies can also contribute to adverse effect that is experienced by those undergoing patients. Patients with acute falciparum are treated with artemisinin and its derivatives [44].

Future Research

Traditionally medicine is widely used to treat malaria, which is often more available and affordable than Western medicine. Firstly, few clinical data is available on safety and efficacy. Secondly, in plant species the concentrations of active-ingredients varies considerably. None the less, these limitations are all remediable, through research [45].

The IVmal system is the way which is more important than plant species for future research. Plants that are used to treat malaria in different areas are more likely to be effective. Though there are some drawbacks. Plants may be prepared in many ways; which might be more useful to discuss the IVmal system rather than of a plant species. The IVmal is also limited by the geographical distribution of plants and by the extent of ethnobotanical studies. Some herbal drugs may be safe and effective for the treatment of malaria. Clinical trials are needed before the herbal remedies can be recommended on large scale. In remote areas with poor resources modern anti-malarial are not steadily available. The evidences summarized in this article is this, the person should not assist the researchers working in this specialty but inspire the others to finding the bodies who give this serious consideration [46].

CONCLUSION

Malaria is the leading disease in many parts of the world. Thus, increase in multi-drug resistant parasites has become malarial control parasite impractical, risky and cost effective. An effective, inexpensive *Artemisia annua L.* drug should be accessible in these regions. The constituent of *Artemisia annua L.*, especially the Artemisinin is affected by growth condition, seasonal and geographical variations. In plant's anti-malarial activity except artemisinin, flavanoids are also involved; thus it is important technique used for the analysis of the various plant extract and samples to detect the both types of constituents i.e. quality and stability.

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