**Artemisinin: An efficient antimalarial drug with potent anti-cancer property**

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**Abstract**

Malaria- a disease that world is familiar with from 19th century, still possessing a great threat to mankind. Many quinine-based drugs are available but their side effects and resistance developed by *Plasmodium falciparum* strains made this disease a horrendous one. Artemisinin and its derivatives containing 1,2,4-trioxane endoperoxide ring, which was originally extracted from Chinese medicinal plant, Sweet Wormwood (*Artemisia annua* L)­­, a medicinal plant shows excellent antimalarial activity without adverse effects in patients. Despite having great antimalarial activity, the use of artemisinin for treatment of malaria is obstructed by high IC50 value resulted from poor solubility in oil and water, low blood plasma half-life. As a result, scientists are looking for its semisynthetic derivatives which are found to be more efficient against *Plasmodium falciparum* malaria. Along with antimalarial activities, later research reveals that artemisinin possesses anticancer properties also, which allows scientists to do extensive research in this field. In this chapter, we are mainly focussing on the brief discovery and invention course of artemisinin, mechanism of action of artemisinin and its derivatives against *Plasmodium falciparum*, recent advances in this field, and its potential application in cancer therapy.

**Keywords**: *Plasmodium falciparum*, artemisinin, *Artemisia annua* L, antimalarial, 1,2,4-trioxane, cancer therapy.

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9. **Introduction**

**Malaria has been a great threat to mankind since decades and was familiar from 19th century.** **According to the recently published World Malaria Report by World Health Organization (WHO), there were around 241 million malaria cases with 627000 deaths occurred worldwide in 2020. Compared to 2019, 14 million more cases and 69000 more deaths took place in 2020 [1]. Malaria in human arises by any of the four species of protozoa which are included under the genus *Plasmodium-vivax*, *falciparum*, *ovale*, and *malariae* among which *Plasmodium-vivax* causes majority of the disease and *Plasmodium falciparum* is the most fatal one [2].** **Malaria infection includes various signs and symptoms which are high fever, muscle pain, chills, sweating, bloody stools, abdominal pain, convulsions, headache, vomiting and even coma [3]. Female Anopheles mosquitoes which are already infected by malaria parasite can act as a vector to transmit the disease to human. Approximately 400 species of Anopheles mosquitoes were identified till now, among which 60 species can act as malaria vector under normal condition [4]. Bite of the infected Anopheles mosquito introduces sporozoites into the blood stream and it reaches the liver, grows up there and finally infects the red blood cells.** **The easy way of transmission makes malaria a hideous disease all over the world.**

**I(a). Discovery of quinine**

**Quinine, the first successful drug to treat malaria was extracted from the bark of the cinchona (quina-quina) tree in 1820 [5]. Pelletier and Caventou, two experts in alkaloids, isolated it from the yellow bark of the tree [6]. Along with quinine, other cinchona alkaloids such as quinidine, cinchonidine, and cinchonine are also effective in malaria treatment. Extensive clinical trials were carried out on these four alkaloids; however, quinine became the predominantly used drug against malaria until 1920 [5]. Quinine is the longest period effective drug used for the malaria treatment. However, its clinical application was decreased because of the adverse side effects such as headache, vomiting, nausea, tinnitus, deafness, low blood platelet count, irregular heartbeat, disseminated intravascular coagulation, leukopenia, kidney failure etc [7-9].Quinine can also cause some other side effects including urticarial, bronchospasm, granulomatous hepatitis, Stevens-Johnson syndrome and so on [7-11]. So, beginning of the 1940s, its clinical uses was replaced by some other more effective synthetic drugs among which chloroquine was the most important one with mild side effects [12]. With extensive use of chloroquine, *plasmodium parasites* became resistant to the drug in late 1950s and was widespread throughout all the countries by the 1980s [13-16]. Since, the resistance of malaria parasites to quinine is slow, it played again important role in treating malaria until 2006 [5]. As of 2006, quinine is not suggested to use by WHO as the first-line drug; but, for severe malaria treatment it is still recommended as a second-line drug [17].**



**Figure 1: Structures of common antimalarial drugs.**

**I(b). Discovery of artemisinin**

Scientific research of common tribal medicinal plants are often worthwhile in drug discovery because of their time-tested applications for decades. Modern scientific researches on these plants lead to the uncovering of their active principles that allow researchers to identify the essential pharmacophore. Because of the fast transmission of malaria parasites and its resistance to the common quinoline based antimalarial drugs, scientists were trying to find some other effective drugs that can kill the parasites with minimum side effects in human beings. During the Chinese “Cultural Revolution” in 1970, Chinese government launched a secret mission called 523 Project on traditional tribal medicinal plant called *Sweet Wormwood* or *Qinghaosu* (*Artemisia annua-*L) [18]. Hong Ge was the first fellow to describe the cold juice of artemisinin as a remedy to treat fever and chills in his “*Handbook of* *Prescriptions for Emergency Treatment*” during 4th century. In the year 1596, Li Shizen listed artemisinin in the text “*Compedium of Materia Medica*”. Inspired by the detailed method written in Hong Ge’s book, Professor Youyou Tu, the lead scientist of Chinese 523 Project on artemisinin and her group did an ethereal extraction of cold solution of artemisinin for the first time in between 1969 and 1972 which showed 100% activity against mouse *Plasmodium falciparum* [19]. For artemisinin, Youyou Tu was honoured with numerous awards, including Nobel Prize for Medicine or physiology in 2015.

1. **Mechanism of action of artemisinin**

The antimalarial activity of artemisinin arises mainly from the reaction between central endoperoxide linkage with iron of haemoglobin. Various experiments were done with deoxy forms of artemisinin *in vitro* which gave negative results. Malaria parasites consume haemoglobin as its source of amino acid and in this process build-up of hematin takes place which is toxic to the parasite. So, to prevent the toxicity, the parasite converts this hematin to hemozoin by biomineralization which is insoluble, non-toxic to the parasite [20]. Studies revealed that artemisinin reacts with hematin (which is the oxidised form of heme) more efficiently than hemozoin. If the red blood cells are uninfected by the malaria parasite, in that case artemisinin would not react with haemoglobin at all. These observations reveal that artemisinin possesses a time table of its action between the period- “after catabolism of haemoglobin to hematin and before oxidation to hemozoin”. Mode of action of artemisinin proceeds through a free radical mechanism. Iron of heme decomposes the endoperoxide 1,2,4-trioxane ring of artemisinin to free radicals. Involvement of iron was confirmed by using various iron chelating compounds. When these compounds form chelates with iron, *in vitro* studies reveal the efficacy of artemisinin decreases significantly, which confirms direct involvement of iron with artemisinin in its mode of action. As shown in the figure, Fe2+ donates one electron to 1,2,4-trioxane tosylate (Fig. 2: entry **6)** and homolytic fission takes place on the endoperoxide ring that results the breaking of C3-C4 bond to form a carbon centered radical. This species undergoes cyclisation and loses the iron to produce ester (Fig. 2: entry **9**)**.** If iron binds with the other oxygen, then a 1,5 H-shift would be taking place to form a carbon centered radical (Fig. 2: entry **11**)[2]. Formation of reactive carbon centered free radicals and reactive oxygen species during the reaction as intermediates are responsible for antimalarial activity of artemisinin.



**Figure 2: Mechanism of action of action of 1,2,4-trioxane tosylate induced by iron of heme.**

Although antimalarial properties of artemisinin and its derivatives are well established, recent studies confirmed its efficiency against cancer cells also. It is found to be more toxic to cancer cells than normal healthy cells, as cancerous tumour cells contain more Fe2+ ions than normal cells. By the formation of reactive oxygen species, artemisinin helps inducing oxidative stress, damage of DNA, alkylation of targeted proteins and apoptosis [21]. Along with these major antimalarial and anticancer properties, antifungal, antiarrhythmic, antiproliferative, anti-inflammatory properties of artemisinin are also coming into the picture [22].

1. **Various artemisinin derivatives and their efficacy in antimalarial activity**

Artemisinin, a sesquiterpenoid lactone with an unusual endoperoxide linkage (Fig. 3: entry **13**) is white crystalline solid in nature with mp 151-153 oC [19]. The endoperoxide bridge of artemisinin is the most active moiety responsible for its effectiveness against *plasmodium* infections. Despite having great antimalarial activity, the therapeutic use of artemisinin for treatment of malaria was limited to great extent by high IC50 value resulted from poor solubility in oil and water, low blood plasma half-life [23]. Again, the *Plasmodium falciparum* malaria has already developed resistance to artemisinin treatment. To overcome these factors, researchers developed its semisynthetic derivatives such as dihydroartemisinin (DHA), artesunate, artemether, arteether (Fig. 3: entries **14-17**) which showed higher efficacy against multi-drug resistant *plasmodium falciparum* strains [24-26].





**Figure 3: Chemical structures of artemisinin, its derivatives and other antimalarial agents.**

To make artemisinin a water or oil soluble drug, its carbonyl group can be reduced to DHA by using NaBH4 which further can be converted to other semisynthetic first-line antimalarial drugs like oil-soluble artemether and arteether, and water-soluble artesunate derivatives (Scheme 1) [27].

**Scheme 1: Conversion of artemisinin to its other derivatives**

Although these derivatives have promising antimalarial activities, because of metabolic instability they have poor bioavailability (Scheme 2). Various approaches have been made for synthesizing other artemisinin-based derivatives to increase the metabolic stability [28,29].



**Scheme 2: Oxidative dealkylation of artemether.**

Since, artemisinin has a very short half-life period with high rate of malaria recrudescence after treatment, it requires another drugs in cooperation to obtain maximum efficacy. For effective management of *P. falciparum* malaria hazard, practicing of artemisinin-based combination therapy (ACT) with other antimalarial agents (Fig. 3: entries **18-24**) is taken up globally [30-32].The clinical trials of ACTs are found to be effective in children as well as pregnant women with no adverse reactions or mild side-effects [33,38]. ACTs are now the highly effective treatment for malaria and the common ACTs include [3,34]:

1. Artesunate/Amodiaquine.
2. Artemether/Lumefantrine.
3. Dihydroartemisin/Piperaquine.
4. Artesunate/Mefloquine.
5. Artesunate/Pyronaridine.
6. Artesunate/Sulfadoxine/Pyrimethamine.
7. **Anticancer properties of artemisinin-recent developments**

Jana and group recently synthesized some aza-artemisinin derivatives and studied their anticancer activities. They synthesized aza-artemisinin **26** from artemisinin by reacting it with ammonia, after that compound **26** was reacted with propargyl bromide to give aza-artemisinin **27** (scheme 3) which undergoes click reaction with different azides to give 1,4-disubstituted triazole derivatives **28**. They also synthesized other two series of compounds following triazolization strategy (scheme 4 and 5). All the compounds were tested for anticancer activities against one endothelial cell line and two cancer cell lines. Among all the synthesized derivatives, compound **28a** showed highest activity with IC50 values of 1.2 mM and 0.92 mM in HeLa cells and CEM respectively. Compound **28a** was found to be 30-fold more active in tumour cells than endothelial cells [35].



**Scheme 3. Synthesis of 1,4-disubstituted triazole derivatives.**



**Scheme 4. Triazolization reaction with different ketones.**



**Scheme 5. Triazolization reaction with different amines.**

Ding and group synthesized novel dihydroisoxazoline-alkyl carbon chain hybrid artemisinin analogues through 1,3-dipolar cycloaddition (Scheme 6 and 7). Most of these compounds displayed significantly improved antiproliferation effects against three human tumour cell lines compared with artemisinin and dihydroartemisinin. Among these derivatives, compound **39a** and **44a** exhibited potent activity with sub-micromolar IC50 values. Further investigation showed direct cytotoxic effects on multidrug-resistant cancer cell lines [36].





**Scheme 6. Artemisinin-dihydroisooxazoline derivatives.**





**Scheme 7. Artemisinin-dihydroisooxazoline derivatives.**

Tsogoera and group synthesized novel hybrids of thymoquinone and artemisinin which showed special activity against colon cancer. Among the derivatives, **46a** was most active against the colorectal cancer cell lines with IC50 of 2.4 μM in HCT116 cells and 2.8 μM in HT29 cells. It was found to have 20-fold higher activity than the parental compounds artemisinin and thymoquinone (Scheme 8) [37].



**Scheme 8. Artemisinin and thymoquinone hybrids.**



Along with monomer derivatives, synthesis of artemisinin-derived dimers and trimers are also came into the picture from the last few years as increasing of the peroxide centre may increase its activity. Woerdenbag *et al*. in 1993, reported artemether, arteether, artesunic acid, and ether dimer of artemisinin in which ether dimer (**32**) exhibited cytotoxicity towards Ehrlich ascites tumor (EAT) cells with IC50 value 1.4 μM. The artemisinin ether dimer was 22 times more cytotoxic than artemisinin because of the presence of two reactive peroxide centers. Moreover, this dimer was found to be good radical generator because of homolytic cleavage of ether bridges linking to two monomeric units (Scheme 9) [35].



**Scheme 9. Synthesis of artemisinin-based ether dimer.**

Inclusion of the detailed findings regarding artemisinin is out of the boundary of this chapter. From the above reaction schemes, we can assume how extensively research is going on in this field. Researchers constantly trying to make artemisinin and its derivatives a better anticancer drug with minimum side effects.

1. **Toxicity of artemisinin and its analogues**

No drugs can be perfect without any side effects. Artemisinin is also of no difference. In several studies carried out on animals showed neurotoxicity when artemisinin is administered in high doses. Toxicity to neuronal cells *in vitro* follows a mechanism similar to antimalarial mechanism [38]. Artemether-lumefantrine, an antimalarial drug used for treating uncomplicated malaria causes abdominal pain, nausea, vomiting, diarrhoea, headache in many patients [10]. Brewer and his group in 1994 conducted some experiments on rats and dogs by direct administering arteether (a derivative of artemisinin) over 3-4 weeks. Results showed neurotoxicity and cardiorespiratory collapses and finally death of the animals. It is unclear whether these neuronal defects is from interaction of the drug with neurotransmitter receptors, intracellular enzymes or intracellular organelles [39]. Although artemisinin shows several side effects to animals, adverse effects on humans are quite less than that of its quinine competitors. Researches are going on to minimise its side effects so that artemisinin will arise as a better and fast acting drug in the field of malaria and cancer along with other diseases with minimal toxicity to humans. Resistance developed by malaria parasites to chloroquine and other early drugs increased the importance of artemisinin. Recent studies confirmed that artemisinin is also slowly started to go in that path. Due to its widespread uses, *Plasmodium falciparum* is now developing resistance against it in various parts of the world. However, proper developments and research can minimise this as artemisinin, in its mode of action produces short-lived free radicals. Due to a very short time existence of these radicals, it gets an advantage of not developing resistance so easily.

1. **Summary**

In the treatment of malaria and cancer, the great challenge is the resistance development which ultimately decrease the efficacy of the drug [40]. For this reason, continuous searching and developments of alternating drugs are must essential. Lots of progresses have been achieved during the past years to develop various artemisinin derivatives against malaria and understanding the mode of action of it against tumour cells. While most of the anticancer studies were done *in vitro*, there are few *in vivo* studies also that showed positive results [41]. Due to the short-lived radical species, artemisinin has advantage over other drugs in resistance development. Also, less toxicity to normal cells makes it a very potential user-friendly drug. To develop the effectiveness and better quality two or more natural product fragments are now attempted to link, so that the new compound possess improved properties than its parent compound [40]. Using ferrocene as a linker to artemisinin and its derivatives also emerging out as a very effective antimalarial and anticancer agents [42,43]. Low solubility of artemisinin can also be easily overcome by derivatisation. So, from all the directions, artemisinin proves itself as a very effective yet less toxic drug in treatment of malaria as well as cancer.

1. **Conclusion**

In this chapter, we briefly discussed on artemisinin and its other derivatives as potential antimalarial and anticancer drugs. A comprehensive overview on the efficiency of artemisinin and its derivatives over the other common antimalarial agents was also given in brief. However, this field deserves further attention and contribution. New synthetic approaches and strategies will surely make artemisinin derivatives less resistant with minimal adverse effect, which can serve the society in the treatment of life threatening diseases.

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