Artemisinin, a Potential Antimalarial Drug: Current Status

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ABSTRACT

Artemisinin, known as Qinghaosu in China, is one of the constituents of quinhao, a Traditional Chinese Medicine (TCM) and is known to possess antimalarial activity since centuries in China. Artemisinin constitutes the frontline treatment to aid rapid clearance of parasitaemia and quick resolution of malarial symptoms. Combination regimens that include artemisinin derivatives are recommended as first line antimalarials in most countries where malaria is endemic. Artemisinin possessed an unique chemical structure with an inter-peroxyl ketal-acetal-lactone consisting of –OO-C-O-C-O-C=O segment. In the present review article artemisinin as a potential antimalarial drug and a lead molecule is discussed by including its chemistry, mechanism of action, artemisinin derivatives and structure-activity relationship (SAR) study, and commercial production of artemisinin.

Key words: Artemisinin, antimalarial activity, structure activity relationship (SAR) study

INTRODUCTION

Malaria, caused by the protozoan parasite *Plasmodium falciparum,* remains a major global health problem that kills almost one million people each year. According to the latest estimates from WHO, there were 214 million new cases of malaria worldwide in 2015 (range 149–303 million). The African region accounted for most global cases of malaria (88%), followed by the South-East Asia Region (10%) and the Eastern Mediterranean Region (2%). In 2015, there were an estimated 438 000 malaria deaths (range 236 000–635 000) worldwide. Most of these deaths occurred in the African Region (90%) [1]. Artemisinin, known as Qinghaosu in China and is one of the constituents of quinhao, a Traditional Chinese Medicine (TCM) and is known to possess antimalarial activity since centuries in China. Artemisinin was discovered in 1972 from the leaves of *Artemisia annua* by Zhenxsin Wei and it was one of the many candidates tested by Chinese scientists from a list of around 200 TCM for treating malaria [2, 3]. The discovery of artemisinin gave fresh impetus to natural product-based drug discovery and also helped in modernisation, popularization of TCM in China. Further it was significant that artemisinin is a non-nitrogenous compound (different than quinolines) that showed potent antimalarial activity.

Chemistry of artemisinin
The structure of isolated artemisinin (**1**) from *A. annua* was elucidated using spectroscopic methods. The molecular formula, $C_{15}H_{22}O_5$ was determined by elemental analysis and high resolution mass spectrometer (HRMS) and NMR (^{1}H- and ^{13}C-NMR) data, indicated that it may be sesquiterpenoid compound. Major difficulty in assigning its structure was the arrangement of 5 oxygen atoms in the C_{15} sesquiterpene skeleton. The peroxide structure of yingzhaosu (**2**) isolated from *Atrabotryis hexapetalu* in 1975 inspired researchers that artemisinin might also be containing peroxide moiety. The fragment of 250 amu observed in mass spectrum of artemisinin was due to loss of molecular oxygen from artemisinin. Based on the reported structure of arteannuin B (**3**) isolated earlier from *A. annua* and physical data and existence of peroxy lactones in literature at that time, the structure of artemisinin was proposed (Figure 1). The complete structure and relative configuration were confirmed by single crystal X-ray crystallography [4]. Thus, artemisinin possessed an unique chemical structure with an inter-peroxyl ketal-acetal-lactone consisting of –OO-C-O-C-O-C=O segment.
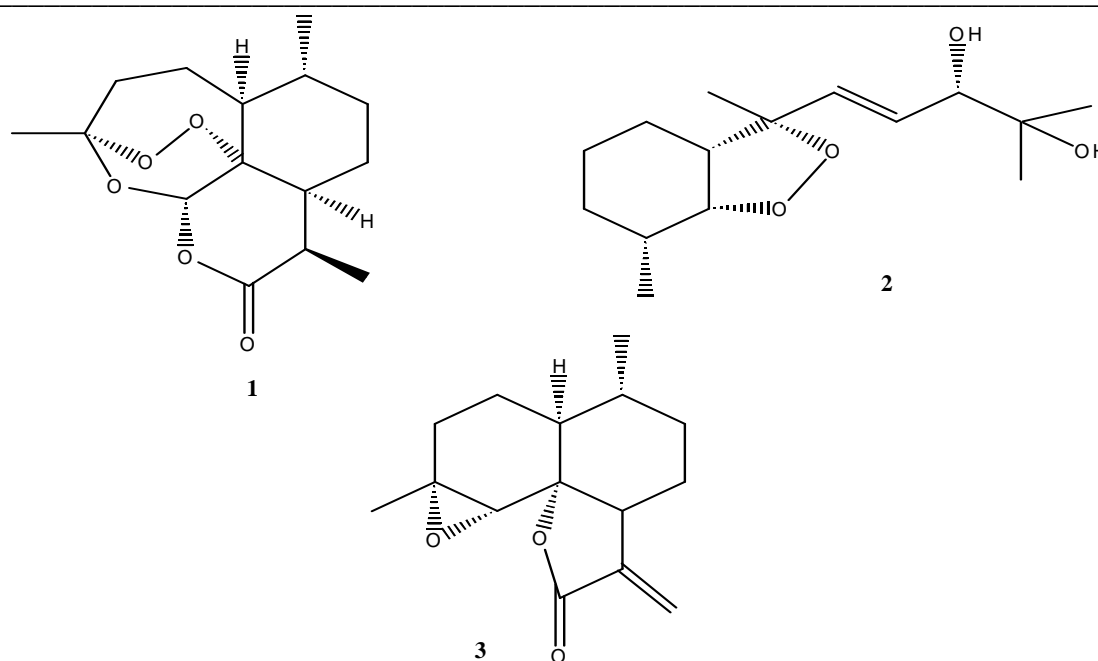
Figure 1 Structure of artemisinin and related peroxide compounds

Also the fact that non-quinoline structure of artemisinin possessing potent antimalarial activity was reported for the first time in literature, making it a potential antimalarial lead molecule for further development.

Mechanism of antimalarial activity of artemisinin
It was proposed that heme-mediated decomposition of endoperoxide bridge of artemisinin takes place to produce carbon-centred free radicals. These carbon-centred free radicals alkylate heme and proteins of the parasite resulting in its death. The detailed insights in to mechanism of action of artemisinin provides the information that detoxification of hematin to produce non-toxic hemozoin is caused by malarial parasite. Further studies revealed that bioactivation of 1,2,4-trioxane is triggered by iron (II) to generate toxic activated oxygen. The selectivity of artemisinin towards parasite-infected erythrocytes over normal erythrocytes was rationalized by the iron-dependent activation of endoperoxide bridge. It was proposed that oxygen centred radicals rearrange to form carbon centred radicals (Figure 2).
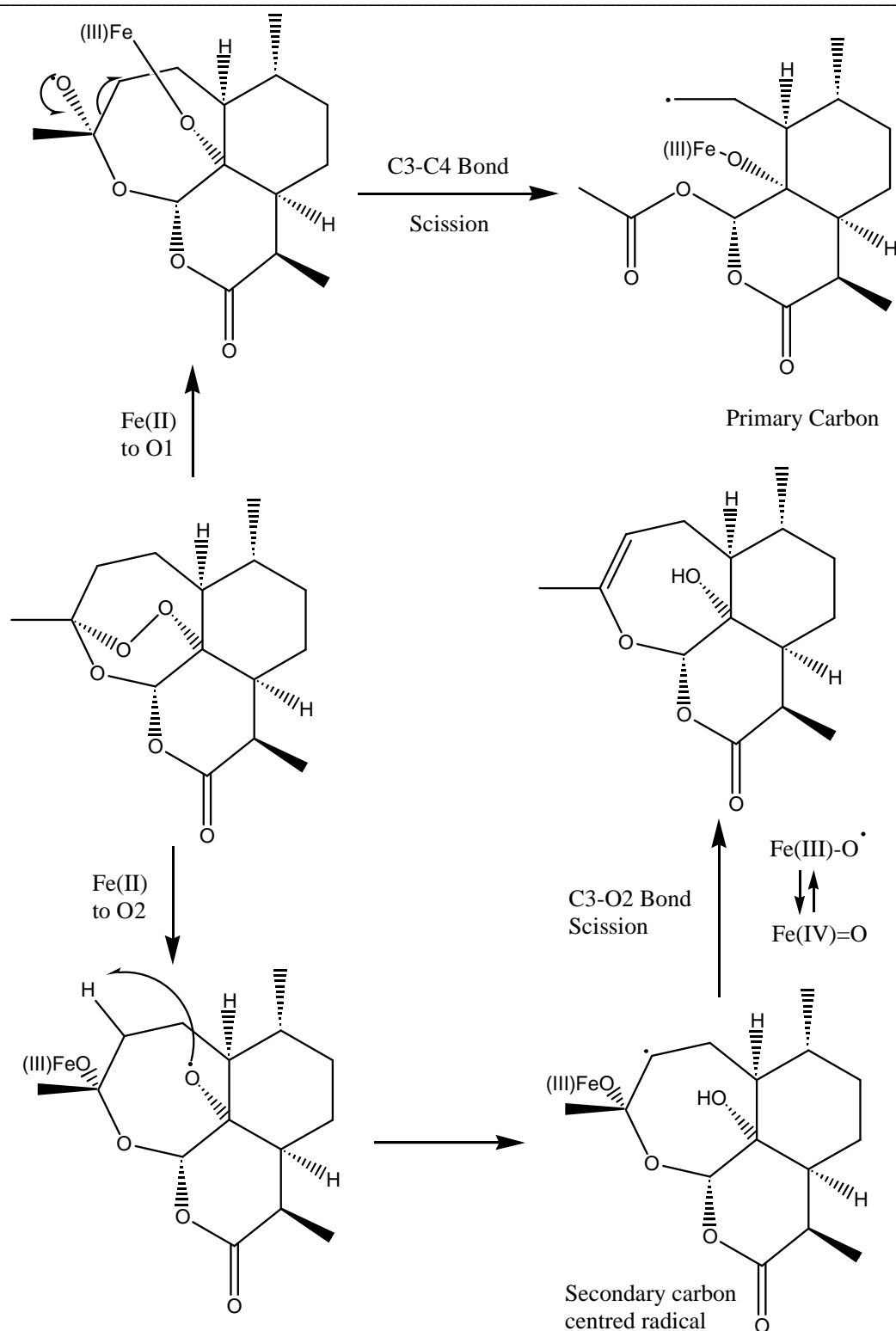
Figure 2 Activation of artemisinin to generate carbon centred radical

Due to unsymmetrical nature of endoperoxide bridge, iron was found to interact with the peroxide in two different ways to produce either primary carbon centred radical or secondary carbon centred radical [5-7]. Recently yet another computational study proposed mechanism of action for artemisinin. The study showed that iron-artemisinin adduct upon binding to an open jaw like structure of PfATP6, a calcium pump, comprising phosphorylation, nucleotide binding and actuator domains, is seen to cause large conformational changes in PfATP6 leading to a closure of these three domains causing inaccessibility of Ca^{2+} pump of the parasite and hence loss of function of Ca^{2+} pump of the parasite resulting in its death. Thus, it leads to inference that iron-artemisinin adduct inhibits PfATP6 through an allosteric mechanism [8].

Artemsinin derivatives and SAR

Early pharmacological and clinical studies showed that qinghaosu possessed fast action, low toxicity, and high activity on both drug-resistant and drug-sensitive malaria, even if the severe patients suffering from cerebral malaria could rapidly recover after nasal feeding of qinghaosu. However, the high rate of parasite recrudescence was observed. There was great need for improvement on the inconvenient administration and the high recrudescence rate. It has been noted that qinghaosu has a special structure bearing peroxy group and rare –O–C–O–C–O–C–O segment, which is different from that of all known antimalarial drugs. In the primary chemical structure-activity study the function of the peroxy group for antimalarial activity was first examined. The negative result of deoxyartemisinin for the antimalarial activity against *Plasmodium berghei* in mice showed that the peroxy group was essential. Soon afterwards, it was found that some other simple peroxides including monoterpene ascaridol had no activity. These facts demonstrated that the peroxy group was an essential, but not a sufficient factor. When dihydroartemisinin was found to be more active than artemisinin and the introduction of the hydroxy group into the molecular nucleus could not improve its solubility in water, three types of dihydroartemisinin derivatives i.e. ethers, esters and carbonates were synthesized and evaluated in China (Figure 3).
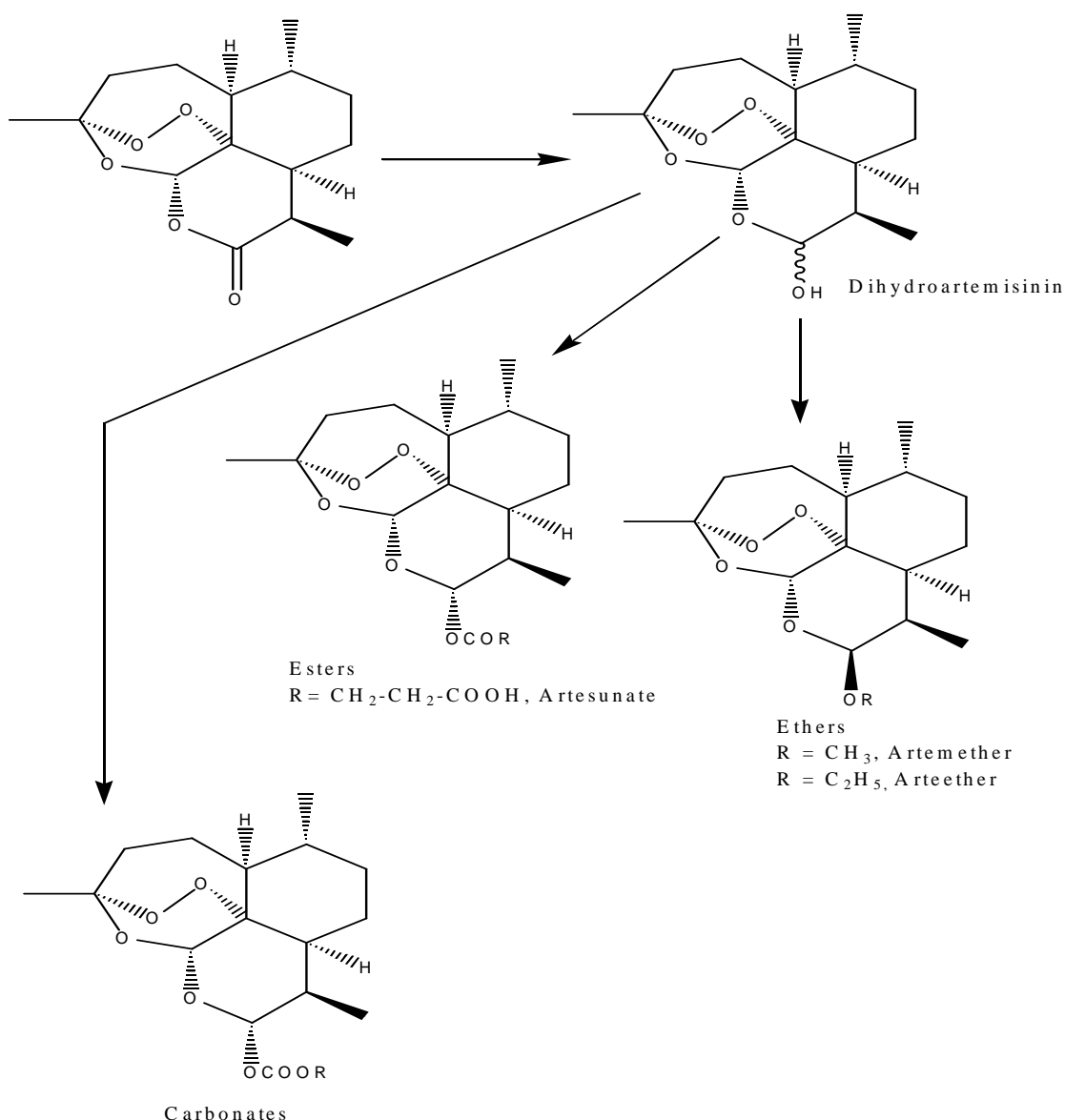

Figure 3. Artemisinin derivatives

The first 25 compounds (in oil solution) were tested in the mice-infected chloroquine-resistant *P. berghei* by administration of intramuscular injection. Most of these derivatives showed more activity than qinghaosu and dihydroartemisinin. Oil-soluble artemether and water-soluble sodium artesunate were developed and approved as new antimalarial drugs by the Chinese authorities in 1987. After 1992, dihydroartemisinin, Coartem (a combination of artemether and benflumetol), and Artekin (a combination of dihydroartemisinin and piperaquine) were also marketed as new antimalarial drugs. Since then, over 10 million malaria patients on a global scale have been cured

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after administration of these drugs. As a result, artemether, artesunate, and Coartem were added by the World Health Organization to the ninth, eleventh, and twelfth Essential Medicine List respectively. When artemether and sodium artesunate were successfully used by intramuscular or intravenous administration for treatment of severe malaria patients, their shortcomings, such as short half-life and instability of aqueous solution of sodium artesunate, were recognized. Hence, thousands of artemisinin derivatives and analogs were synthesized and evaluated by many research groups worldwide.

Modifications at C-12 of artemisinin

From the chemistry point of view, the C-12 position of dihydroartemisin is similar to the C-1 position of carbohydrates. So, these C-12 derivatives may be divided into three types: O-glycosides, N-glycosides, and C-glycosides using a similar term in carbohydrate chemistry.

O-glycosides

The ethers and esters of dihydroartemisinin may be considered as its O-glycosides. A series of ethers and esters in which C-12 substituents contained halogen (especially, F), nitrogen, sulfur atoms, and others were prepared [9]. Pu et al. reported several mono- and polyfluorinated artemisinin derivatives [10]. French scientists reported synthesis of trifluoromethyl analogs of dihydroartemisinin, artemether, artesunate, and other analogs [11-13]. The presence of the CF3 group at C-12 of artemisinin clearly increased the chemical stability under simulated stomach acid conditions. Another type of O-glycosides, 12-β aryl ethers of dihydroartemisinin, was synthesized by a reaction of acetyl dihydroartemisinin or trifluoroacetyl dihydroartemisinin with various substituted phenols in presence of trifluoroacetic acid. Most of these compounds were proved to have better antimalarial activity against *P. berghei* in mice than artemisinin, but less activity than artemether. Some of these compounds showed much higher cytotoxicity (against KB, HCT-8, A2780 cell lines) than artemether [14] (Fig. 4).
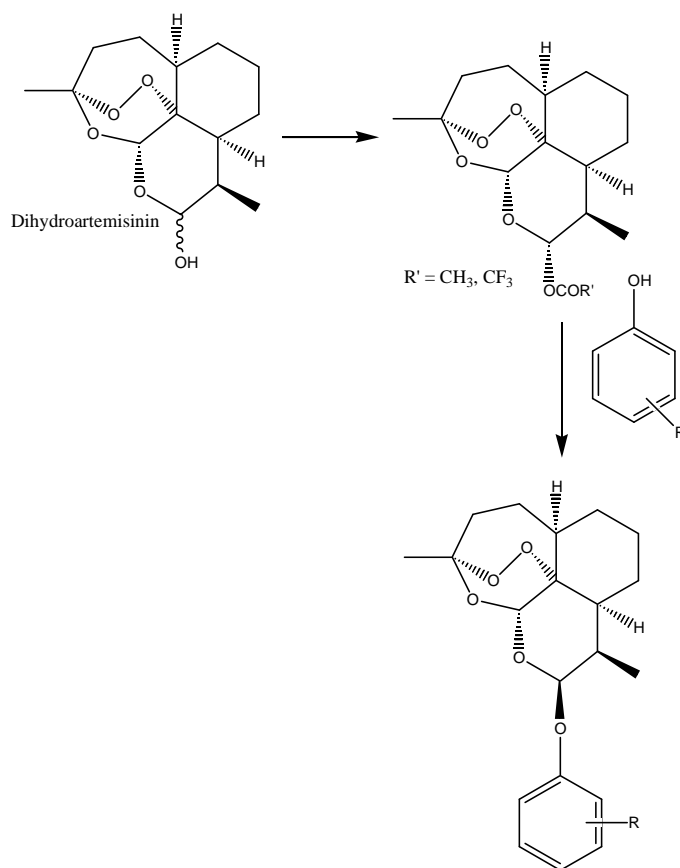

Figure 4 O-glycoside derivatives of artemisinin

N-glycosides

Dihydroartemisinin or trifluoroacetyl dihydroartemisinin reacted with aromatic amines or heterocycles, such as triazole and benzotriazole, in the presence of acidic catalyst to afford its N-glycosides, which were more active in vivo than artemisinin [15, 16] (Fig. 5).
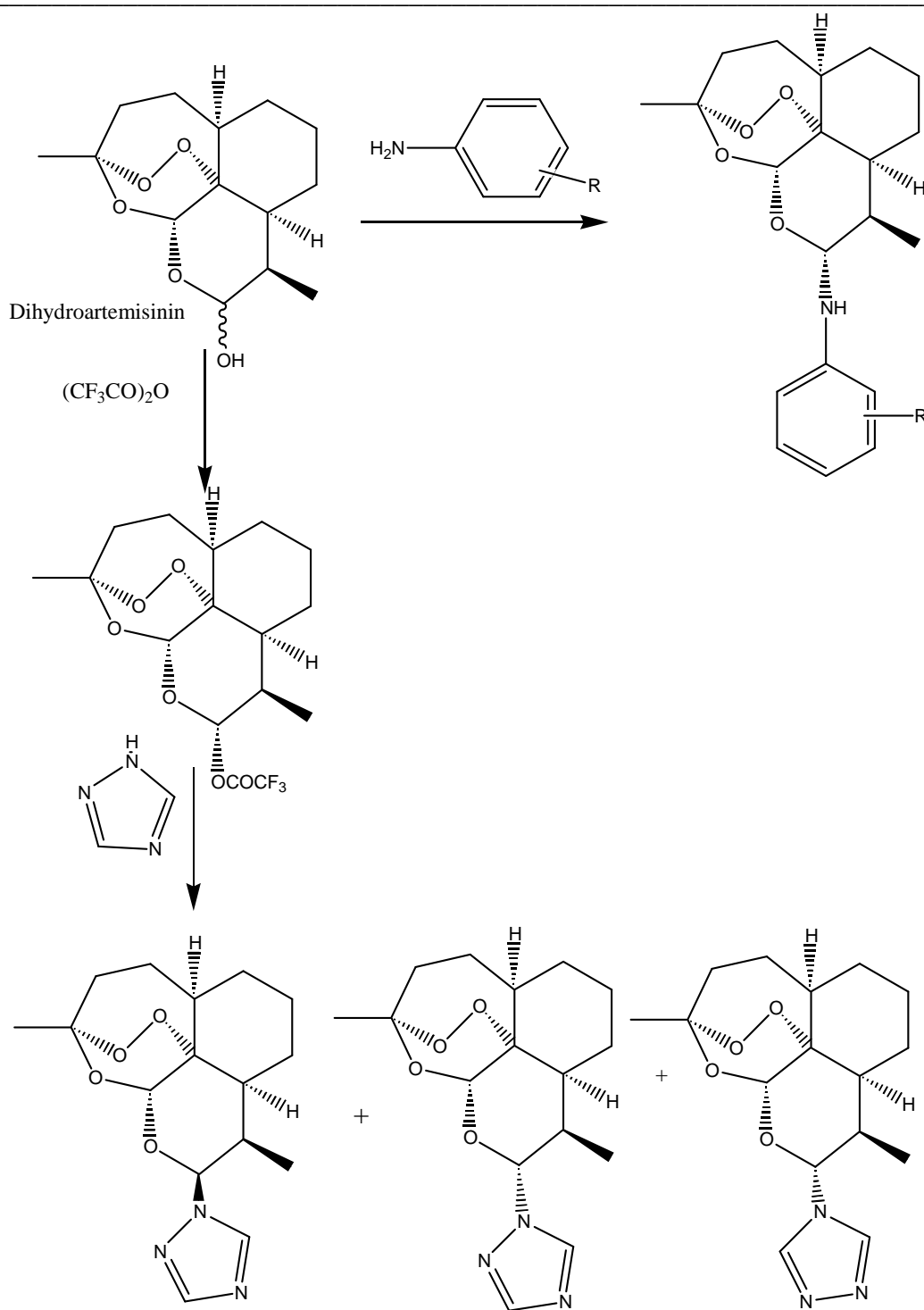
Figure 5 N-glycoside derivatives of artemisinin

C-Glycosides
Dihydroartemisinin or its acetate was treated with allyl trimethylsilane in the presence of an acid catalyst (boron trifluoride etherate or titanium tetrachloride) to prepare 12β-allyldeoxoartemisinin (R-CH$_2$CH=CH$_2$) and related compounds in high stereoselectivity (Fig. 6). The most active compound 12β-*n*-propyldeoxo-artemisinin, (R-CH$_2$CH$_2$CH$_3$), proved to be as active and toxic as arteether [17, 18].
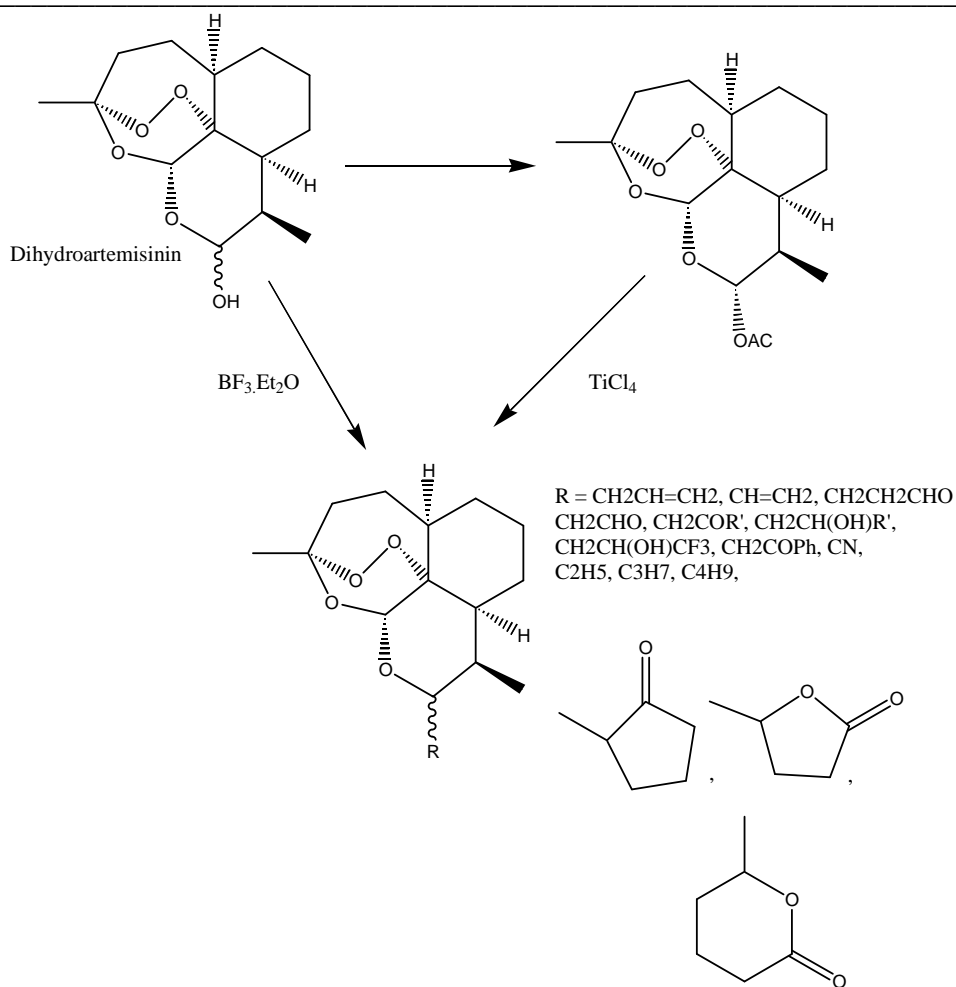
Figure 6 C-glycoside derivatives of artemisinin

Some C-glycosides of artemisinin were synthesized by using 12-F-deoxoartemisinin as an intermediate (Fig. 7). These compounds had high antimalarial potencies in vitro against *Plasmodium falciparum*. Some were active in vivo, but less than arteether [19, 20].

Water soluble artemisinin derivatives
Sodium artesunate is the first water-soluble artemisinin derivative and used for treatment of the severe malaria patients by intravenous or intramuscular administration. However, the aqueous solution is unstable, and its hydrolysis product dihydroartemisinin, quickly subsides. Hence, the synthesis of stable, water-soluble artemisinin derivatives is an important research program. Because artemether has greater stability than artesunate, it was supposed that the replacement of the ester linkage by the ether linkage in the artesunate molecule would enable the derivative to be more stable. To search for stable, water-soluble dihydroartemisinin derivatives with higher efficacy and longer plasma half-life than artesunate and artelinic acid, deoxoartelinic acid was prepared and tested in vitro and in vivo. It was reported that this compound showed superior antimalarial activity and was more stable in simulated stomach acid than arteether [21, 22].
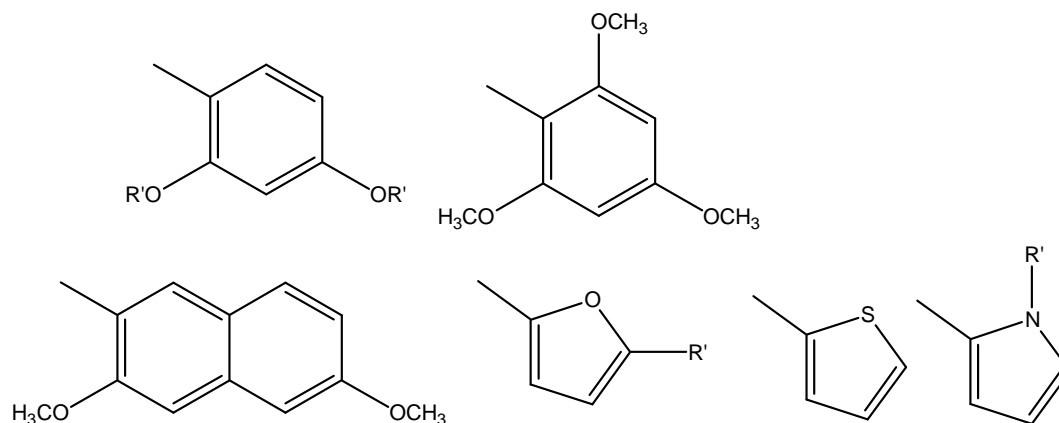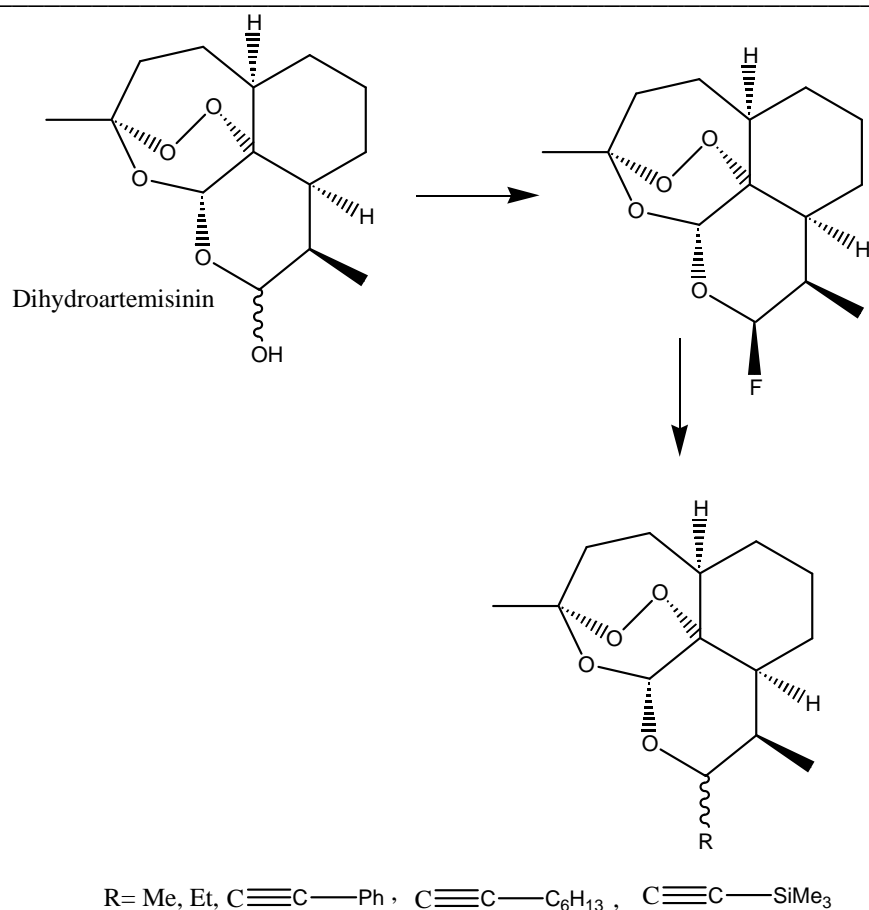
Dihydroartemisinin

R= Me, Et, C≡C—Ph, C≡C—C$_6$H$_{13}$, C≡C—SiMe$_3$

Figure 7 C-glycosides: Alkyne and aryl derivatives of artemisinin

Artemisinin derivatives containing basic substituents

In view of the known basic antimalarial drugs (such as chloroquine, quinine) that are being used as salts for injection, it was proposed that introducing an amino group into artemisinin molecule may lead to water-soluble derivatives. Thus, five types of basic artemisinin derivatives were synthesized (Fig. 8). These basic compounds were combined with organic acid (such as oxalic acid and malic acid) to yield the corresponding salts. Generally, they had good water solubility and stability. Some compounds showed much more activity against *P. berghei* in mice than artesunate. However, their efficacies were less than that of artesunate against *P. knowlesi* in rhesus monkeys [23-25].
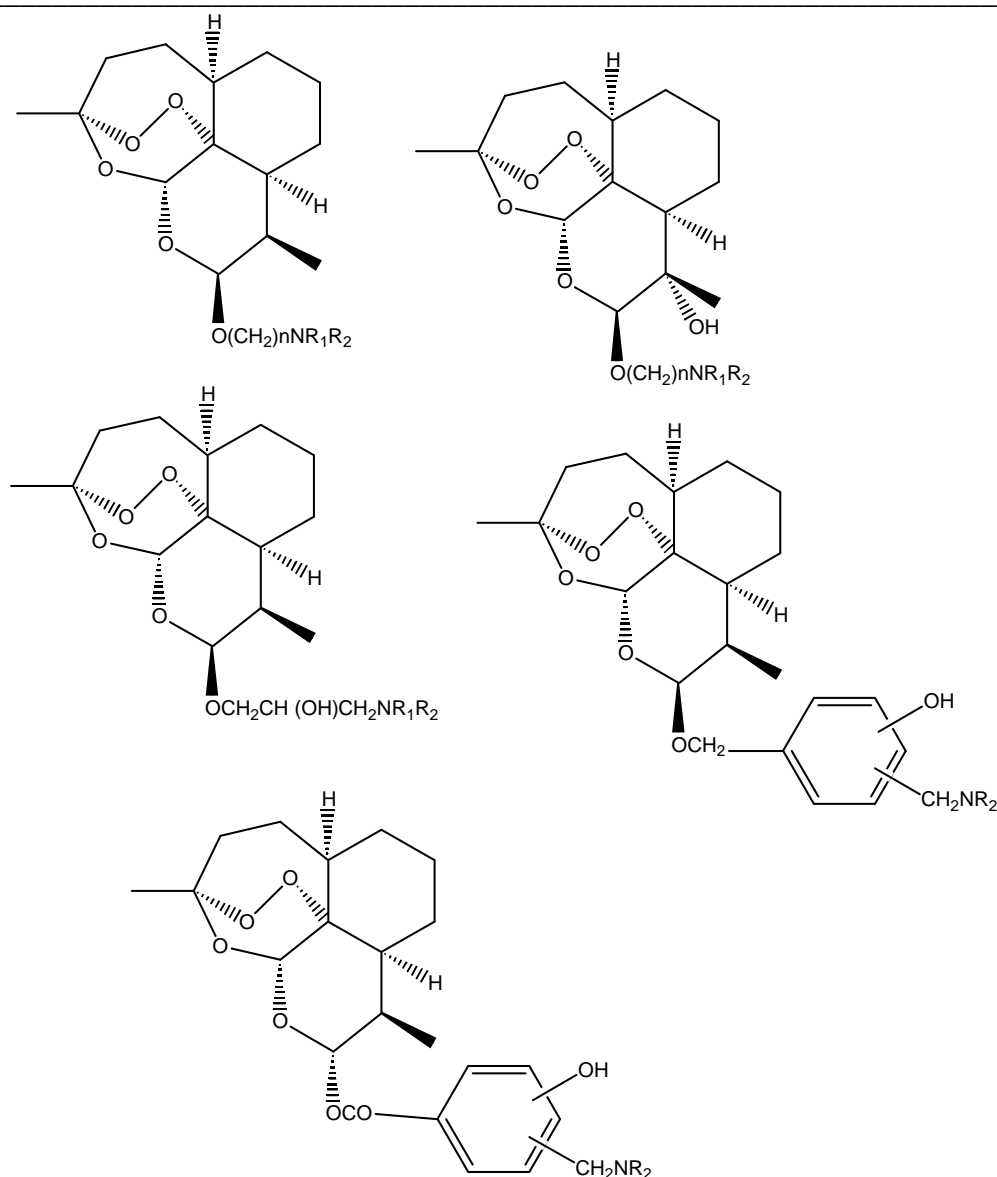
Figure 8 Basic derivatives of artemisinin

Modifications on C-11 and/or C-12
Some C-11 substituted artemisinin derivatives were prepared and tested against *P. berghei* in mice [26]. Their observed lower antimalarial activity may be attributed to the introduction of 11-α- substituent [27].

Modifications on C-4 and/or C-12
The 4-methyl is located near the peroxy group, so the modification on C-4 may offer the important information about the SAR. Some derivatives with substituents at C-4 were therefore synthesized. These compounds showed more activity than artemisinin. It was noteworthy that deoxoartemisinin was also more active than artemisinin in vitro and in vivo [28, 29].

Modifications on C-13
Under non- or base-catalyzed conditions, artemisitene reacted with triazole, benzotriazole, or benzimidazole to yield a series of Michael addition products. All of these compounds had antimalarial activity in vivo [30].

Azaartemisinin
It was reported that the reaction of artemisinin and methanolic ammonia or primary alkyl-and heteroaromatic amines yielded azaartemisinin or N-substituted azaartemisinin and N-substituted azadesoxyartemisinin as byproducts (Fig. 9). Some N-substituted azaartemisinin had good antimalarial activity, such as compound with R = CH_2CHO, which was 26 times more active in vitro and 4 times more active in vivo than artemisinin [31].

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Carbaartemisinin
To inspect the effect of the segment of O–O–C–O–C–O–C=O in the artemisinin molecule, carbaartemisinin and its analogs were synthesized and evaluated. These compounds displayed much lower antimalarial activity in vitro than artemisinin [32].

1,2,4-Trioxanes and 1,2,4,5-Tetraoxanes
Since the 1990s, many research studies have demonstrated that 1,2,4-trioxanes and 1,2,4,5-tetraoxanes are important artemisinin analogs. Some compounds are promising because of their high antimalarial activity and easy preparation [33, 34].
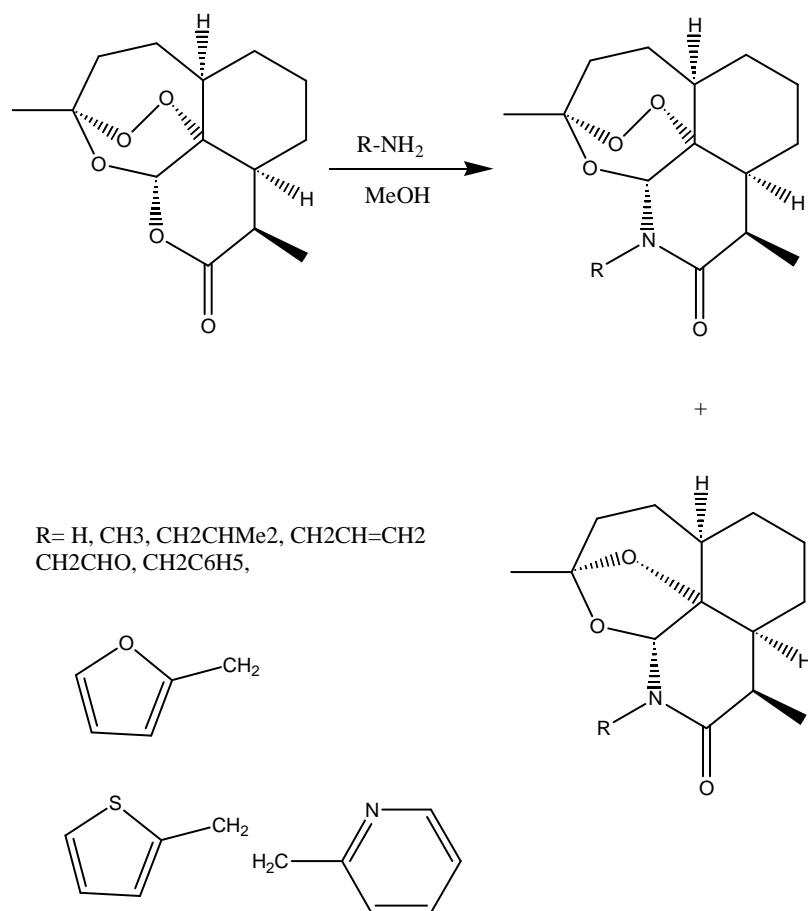
R= H, CH3, CH2CHMe2, CH2CH=CH2
CH2CHO, CH2C6H5,

Figure 9 Azaartemisinin derivatives

Production of artemisinin
Although total chemical synthesis of artemisinin has been achieved, it is not cost effective [35]. Current technology for artemisinin production is based on cultivated *A. annua* with best cultivars giving yields of artemisinin of *ca*. 1.5% of dry plant material [36]. Artemisinin is solvent-extracted from plant material, crystallized and typically used for semi-synthesis of artemisinin derivatives. For enhancing the production of artemisinin, conversion of artemisinic acid (AA) into artemisinin has been successfully carried out by several workers at laboratory scale. A viable Industrial process has been developed by Sanofi (supported by Bill and Melinda Gates Foundation) leading to a consistent source of artemisinin. The new generation process developed by Sanofi involved photooxidation as one of the key steps in the conversion [37]. European Patent (EP 2826779 A1) by Max-Planck-Gesellschaeft described the method and apparatus for the synthesis of dihydroartemisinin and artemisinin from dihydroartemisinc acid (DHAA) that is present in the mother liquor during commercial artemisinin extractions and it is discarded as a waste. The invention discusses a method for the production of artemisinin from DHAA using continuous flow reactor. This method involves the conversion of DHAA into artemisinin using photooxidative reaction in a continuous flow reactor and the method is claimed to be very efficient [38].

Market size analysis of artemisinin
Artemisinin market is expected to witness substantial growth over the forecast period owing to its increasing application scope in pharmaceutical industry. Demand for artemisinin has grown considerably over the past decade following the recognition of artemisinin based combination therapy by WHO as a first line treatment for malaria.

Increase in R&D activities and growing medical infrastructure particularly in emerging economies including China and India has triggered demand for artemisinin and its derivatives. Rising demand from malaria endemic countries such as Congo, Nigeria, Tanzania, Uganda and other South-East Asian countries including India is expected to drive market for artemisinin and its derivatives over the next six years. However, market for artemisinin is still in nascent stages owing to limited number of global manufacturers. In addition, lack of funding and programmatic uncertainties coupled with demand-supply gap are further expected to hamper market growth over the forecast period. Asia Pacific and Africa held the largest market share for artemisinin and its derivatives owing to the large production base of artemisinin herbs coupled with growing demand for artemisinin based therapy in malaria endemic countries. North America held the second largest market followed by Europe on account of well developed medical industry coupled with large number of pharmaceutical units.

Artemisinin herb is native to China and is found to be effective against malaria parasites. Ongoing research and development has also found artemisinin and its derivatives to be effective against the treatment of cancer. Market for artemisinin is segmented on the basis of its applications in treatment of malaria, cancer and helminth parasites. Largest application in 2013 was artemisinin based combination therapy in treatment for malaria. Market can also be segmented on the basis of its production mechanism as biosynthesis, chemical synthesis and synthesis in engineered organisms. Intensive research activities are underway to develop new and economical methods of artemisinin production. The main companies that manufacture artemisinin and its derivatives include Yeshua-Bio-Tech, Guilin Pharmaceutical Co. Ltd, Sanofi Aventis, Shanghai Desano Chemical Pharmaceutical Co. Ltd, Kunming Pharmaceutical Corporation, Calyx Pharmaceuticals and Chemicals and Mylan Laboratories Limited [39].

CONCLUSION

In the early 1980s, Wu and Ji performed the Hansch analysis of antimalarial activity and the distribution coefficient between oil and water of artemisinin derivatives and found that the more lipophilic, the more active the derivative. It is understandable that the lipophilic property of the artemisinin derivative is related to its permeating ability across the membrane of the cell, but it is just the first step for the mode of action. Recently, several laboratories have performed the cyclic voltammetry study of artemisinin and its derivatives. A correlation of the activities of artemisinin derivatives with their reduction potentials was reported. However, it was also indicated that the electrochemical reduction of artemisinin and its derivatives was a two-electron transfer reaction and it produced deoxyarteminin and its derivatives, but not free radical reduction products, which were confirmed by isolation and identification of the electrochemical reduction product. The major metabolites of artemisinin in vivo are the same as free radical reduction products, so it is confusing if there is a correlation between the electrochemical reduction and the cleavage of peroxy bridge of artemisinin in vivo.

Jefford has concluded that the killing of the parasite by alkylation with a carbon radical is a logical and convincing sequel, but the death of the parasite also may occur by oxygen atom transfer or by the action of an oxy-electrophilic species [40]. However, Haynes has argued totally against the C-centred radical proposal based on the consideration of redox chemistry and SARs [41]. Haynes et al. conclude that the antimalarial activity does not correlate with the chemical reactivity of artemisinin derivatives against Fe(II) based on an experimental observation of a special C-12 nitrogen-substituted derivative [42]. Another totally different viewpoint was presented in 2001 that the antimalarial activity of artemisinin may be caused by (1) the interaction of the intact compound without chemical reaction, (2) the chemical reaction of artemisinin and/or its degradation products with the parasite biomolecules, or (3) the oxygen free radical occurring during redox reaction [43]. Their consideration is based on an undefined experimental result that dihydroartemisinin is the product from the reaction of artemisinin and ferrous sulfate in an aqueous buffer. The formation of dihydroartemisinin determined only by TLC has no precedent, and the reduction of lactone to lactol with ferrous ion is also unbelievable in chemistry. O'Neill and Posner again mentioned that high-valent iron–oxo-intermediate is important for high antimalarial activity, but this opinion is not widely accepted [44].

In conclusion, the mode of antimalarial action of artemisinin has been a noticeable research object since its discovery. Several theories have been postulated until now; however, their further development has still been difficult as mentioned by Wu [45]. From several experimental results and proposed theories, the postulation that the carbon-centred free radical is the key active species killing the parasite would most likely be convincing. The additional key point is what might be the genuine target attacked by these catalytic amount of radicals and what might be destroying the whole biosystem of the parasite. Since the discovery of artemisinin four decades ago, artemisinin and its derivatives, as well as other corresponding peroxide compounds, have received great attention. A new generation of antimalarial drug was discovered from traditional Chinese medicine. It is expected that more medicinal applications will also be produced from this precious natural product. New ground in chemistry and biology has also been created during this exploration. With the continuing endeavour around the world, it is expected that more achievements will appear in the artemisinin research area.

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