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Aim : To Review On Pharmacological Action On Artemisinin

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ABSTRACT: Artemisinin's are widely known for treating malaria, even in extremely drug-resistant forms, and are extracted from extracts of sweet wormwood (Artemisia annua). Their effectiveness also covers parasitic illnesses with different evolutionary relationships, like schistosomiasis. In cell lines and animal models more recently, they have also demonstrated strong and extensive anticancer activities. We explore recent developments in identifying the function of artemisinins in medicine in this review. with a focus on their debatable methods of action in particular. This affordable medication class that prevents malaria and saves lives also has significant potential in on cology. One of the most often prescribed antimalarial medications, artemisinin has recently drawn more attention due to other potential biological effects. This review's objective is to describe recent advancements in basic science on artemisinin's pharmacological effects, as well as its molecular action and exciting clinical study findings, with an emphasis on its anticancer activity. According to scientific data, the biological activity of artemisinin is mediated through the production of reactive oxygen species (ROS), which cause DNA damage, mitochondrial depolarization, and cell death. The scientific evidence presented in this article review points to artemisinin as a potential treatment agent for a number of disorders. Therefore, this analysis is anticipated to inspire interested researchers to carry out more preclinical and clinical investigations to assess these biological activities.

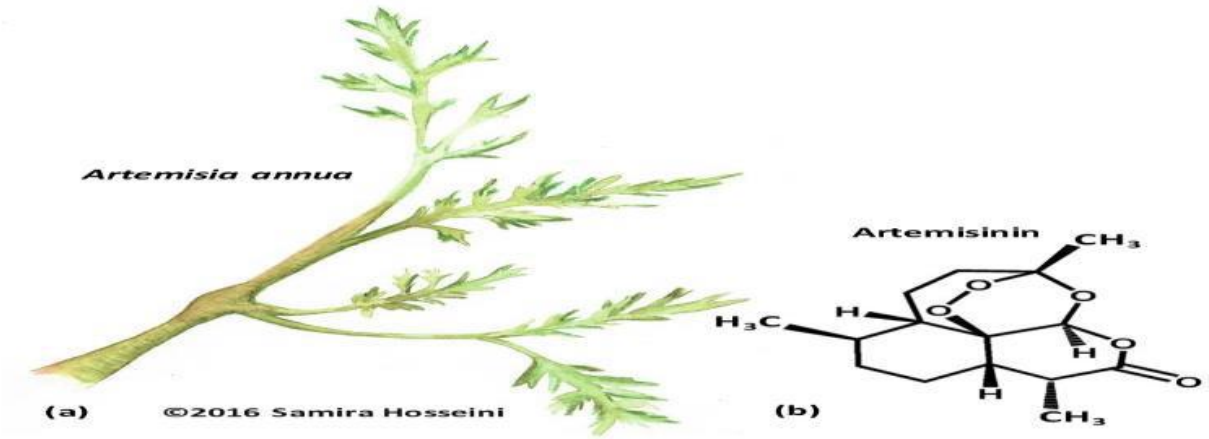
KEYWORD: Chemishtry And Synthesis,Metabolism And Pharmacokinetics,Antimalarial Properties.

INTRODUCTION: Artemisinins are derived from a plant called sweet wormwood (or sweet Annie :Artemisiaannua). In China, where they were first discovered, ‘‘qinghao’’ extracts werereported to have antipyretic properties more than1500years ago. In 1967 an outstanding coordinated programme was started by the Chinese government to discover antimalarial principles in various medicinal herbs including qinghao. In1971, a highly active chemical from qinghao ,known as qinghaosu was obtained and is now called artemisinin. Since this initial discovery, an array of semi-synthetic oil and water soluble derivatives of artemisinin have been developed, with a variety of formulations entering clinical studies. These compounds have impressive

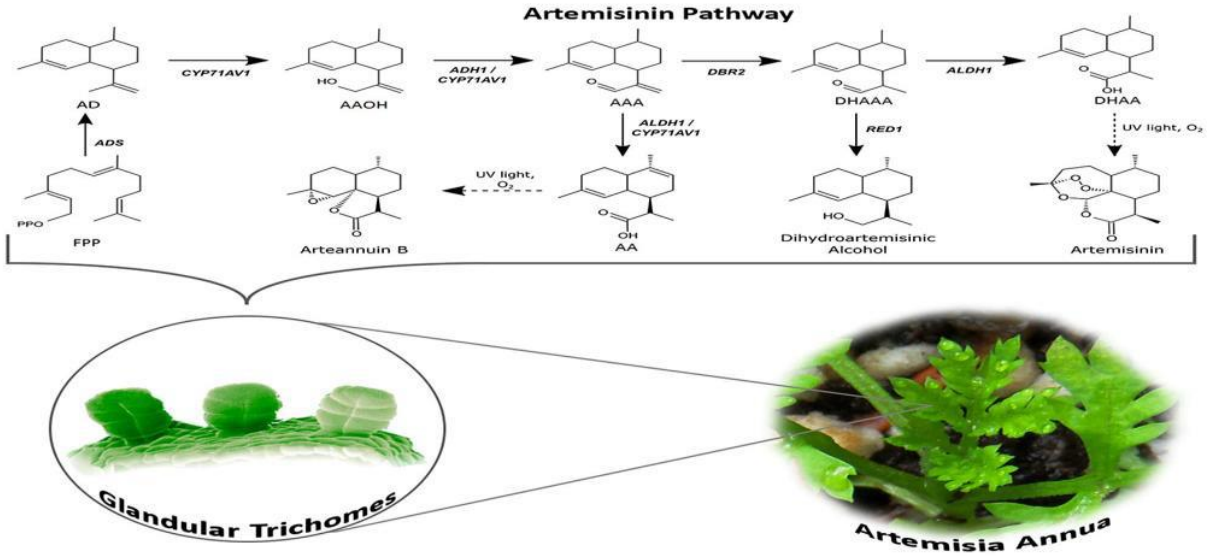
parasiticidal properties in vitro, rapidly arresting parasite metabolism in concentrations within the lower nano molar range, and killing parasites more quickly than other antimalarial drugs.

These and other properties described below make artemisinins our most important class of antimalarial agent, and a main stay against otherwise multidrug resistant Plasmodium falciparum. Their use in many countries has been severely restricted by cost, because artemisinins in combination are several-fold more expensive than the now almost useless chloroquine, or sulfadoxine pyrimethamine, whose efficacy is also waning. However, providing mechanisms and the political will to subsidise and control the use of artemisinins can be implemented, it is probable that some regimens combining artemisinins with other antimalarials will supersede cheaper and now ineffective alternatives. Registration of artemisinins for use in developed countries is being actively pursued but only one fixed dose oral combination (artemether-lumefantrine) is so far available to treat uncomplicated malaria.

If available, parenteral artemisinins can be used to treat severe malaria in the UK on a namedpatient.



CHEMISTRY AND SYNTHESIS: After being extracted from Artemisia annua plants, artemisinin is very easily refined by crystallisation, but it is very challenging to synthesise from scratch. The unique endoperoxide trioxane moiety in fig. is intrinsically related to the antimalarial activity of artemisinin, a sesquiter-pene lactone structure. Because artemisinin is a highly crystalline substance that does not dissolve in either water or oil, it can only be administered intravenously. The semi-synthetic derivatives of artemisinin, such as artesunate, artemether, arteether, dihydroartemisinin, and artelinic acid, are derived from the parent component artemisinin (fig). These substances have undergone numerous formulations for parenteral, rectal, and oral administration. In order to provide these derivatives via parenteral routes, sodium salts of artesunate and artelinate are utilised. Arteether was developed under the aegis of the World Health Organisation despite lacking clear advantages over artemether, for which a much larger clinical experience already exists; arteetheris no longer being investigated as an antimalarial agent. However, locally formulated products are used in India (alfa beta arteether, E-mal) and the Netherlands (beta-arteether, Artemotil (Artecef)). Artelinic acid (a water soluble derivative) was developed by Walter Read Army Institute for Research. Although artelinate will not be further developed, various formulations and combinations of artesunate with other antimalarials are under active development.



METABOLISM AND PHARMACOKINETICS

Once absorbed, the artemisinin derivatives are largely metabolised to dihydroartemisinin (DHA), and subsequently via hepatic cytochrome P-450 and other enzyme systems, to inactive metabolites. DHA has a half-life of around 45 minutes and is a strong antimalarial by itself. Different derivatives undergo different amounts

of conversion to DHA. While artesunate is quickly (within minutes) hydrolyzed to DHA and its antimalarial activity is mostly mediated by DHA, artemisinin itself is not metabolised to DHA but operates as the principal antimalarial. Because they are metabolised to DHA more slowly than DHA, artemether and arteether both contribute to antimalarial activity, possibly to a similar level. 90% of DHA is incorporated into plasma proteins. Pharmacokinetic studies on artemisinins have been limited by difficulties of as say; several techniques with differing accuracies have been used by various groups. Furthermore, studies must necessarily take into account active metabolites (mostly DHA). Bioassay techniques measuring total antimalarial activity account for this and, along with advances in assay methods, have allowed clearer pharmacokinetic profiling to emerge for drug formulations that have often been used empirically for many years. These studies are improving our understanding pharmaco dynamic and toxicological aspects of this group of compounds. In uncomplicated malaria, when artemisinins are used orally, most pharmacokinetic information is now available for artesunate followed by artemether. The absolute bio availabilityof antimalarial activity after a single dose of oral artesunate in uncomplicated adult malaria is about 60% although there is greater interpatient variation than in healthy volunteers. Time to maximum DHA concentrationis typically one to two hours. Studies suggest that clearance after artesunate is reduced during acute infection compared with recovery, either via disease effects on pharmacokinetics or enzyme autoinduction.Although absolute bioavailability studies for artemether, artemisinin, and DHA are not possible given lack of intravenous formulations, pharmacodynamic activity (parasite clearance) after oral dosing of these derivatives is satisfactory. When studied, oral formulations show appropriately reliable and rapid absorption in the treatment of uncomplicated malaria As for artesunate, studies of oral artemether and artemisinin show increasing clearance with multiple dosing and during recovery from acute infection. In severe malaria, the delayed and variable absorption of the oil soluble derivatives artemether and arteether when given by the intramuscular route is of great potential clinical relevance.

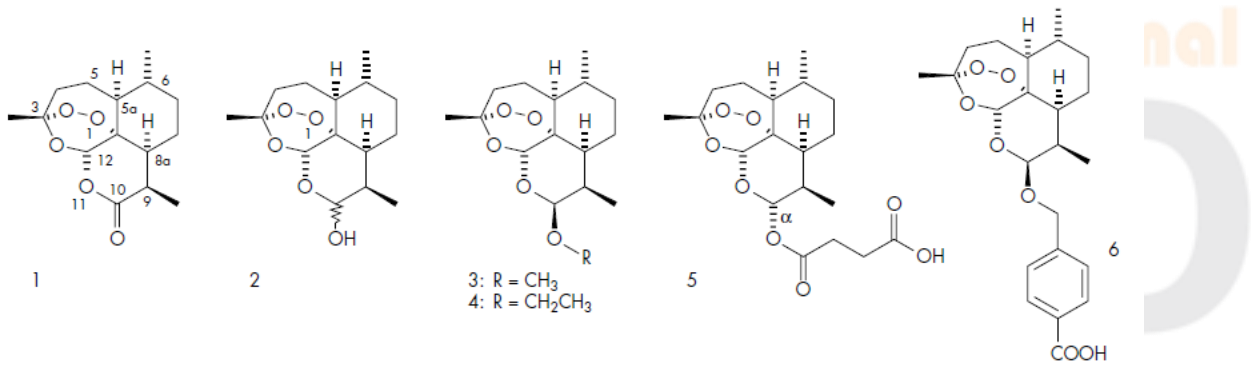


Figure 1 : artemisinin 1 and derivatives dihydroartemisinin 2, artemether 3, arteether 4, artesunic acid (artesunate) 5, and artelinate 6.

ANTIMALARIAL PROPERTIES: Artemisinins kill all species of plasmodium that infect humans. The asexual stages of infection are the most susceptible, with artemisinins inducing up to a 10000-fold reduction in parasite biomass per asexual cycle. In common with other antimalarials, artemisinins are particularly active against the large ring stage of infection when parasites are beginning to become most metabolically active. However, in contrast with other currently useful antimalarials, artemisinins also target tiny ring stages of infection (present only a few hours after red cells are invaded by merozoite stages). This killing results in

removal of parasites from within infected cells, probably by the reticuloendothelial system, which returns these ‘‘pitted’’ erythrocytes to the circulation carrying an immunological marker of the presence of the parasite on its surface (an early stage antigen called RESA). Artemisinins also inhibit metabolism of parasites more quickly than other antimalarials used to treat severe malaria, a pharmacodynamic property that is of potential benefit given that most deaths in African children occur in the first 12 to 24 hours after admission. They also reduce cytoadherence of infected red cells, a recognised virulence determinant. Artemisinins do not interfere with hepatic stages of parasite development and therefore have no causal prophylactic value. They do kill early gametocyte stages of development and have the potential to interfere with mosquito transmission. This property may be useful in areas where transmission rates for malaria are comparatively low, but has not provided benefit in areas of high transmission despite reported reduction of gametocyte rates.

MECHANISM OF ACTION : Artemisinins' antimalarial effects have long been related to their capacity to produce free radicals chemically. This method of action has been proposed in part because to the fact that well-known free radical sources, such as tert-butyl peroxide, have been shown to be capable of killing malaria parasites, albeit at rather high (mM) concentrations. . The peroxide structure (essential for antimalarial activity) has been studied in detailed chemical experiments aiming to decipher exactly how it may act as an antimalarial. It is held by many workers that artemisinins upon reaction with Fe2+ are converted first into oxygen centred free radicals derived by reductive cleavage of the peroxide bridge, which are then converted into carbon centred free radicals by intramolecular hydrogen abstraction from CH2 groups on the periphery of the artemisinin by the O centred radicals. Fe2+ is a catalyst that can generate free radicals from peroxidic structures in other peroxides, but in the case of the antimalarial action or artemisinins, this is further maintained to take place in the food vacuole by either free Fe2+ or by ferroprotoporphyrin IX (reduced haem). Carbon centred free radicals have been put forward as principal intermediates in the parasiticidal process, but this theory of action sees artemisinins killing parasites via an indiscriminate process, a view that is hard to integrate with the exceptionally high in vitro activities of artemisinins and stands in pronounced contrast with the mechanism of action of most bioactive molecules where activity is mediated by high affinity binding to an active site. More recently, an alternative mechanism of action for artemisinins based on inhibition of the malarial parasite’s calcium ATP ase (sarcoplasmic endoplasmic reticulum calcium ATPase, SERCA) has been suggested

CLINICAL APPLICATIONS : Derivatives of artemisinin are used to treat both mild and severe malaria in both adults and children. In a study of more than 500 women treated with artemisinins in Thailand, there was no increase in the rate of abortion, congenital abnormality, or stillbirth compared to background incidences in this population, which has historically raised some initial concerns about the safety of artemisinins in pregnant women (a population that is particularly at risk from malaria). When artesunate was added to an intermittent pyrimethaminesulfadoxine regimen in pregnant women in the Gambia, there was again no significant adverse effect after gestational exposure. However, data on artemisinin use in the first trimester of pregnancy remain scanty, and more experience is needed before recommendations can be made on a firm basis.

Artemisinins are unique among antimalarials in that there is still no evidence of significant resistance in clinical isolates. Their short half life renders them inappropriate for prophylaxis.

Severe malaria

Despite receiving appropriate antimalarial and supportive care, severe malaria in hospitalised patients is associated with a death rate of 15% to 20%. The cinchona alkaloids (quinine and quinidine) and artemisinins are the only two groups of compounds that are effective in treating severe malaria in light of the widespread development of chloroquine resistance. Despite having several downsides, quinine is still the medicine of choice across Europe and Africa. When administered parenterally, quinine has a narrow therapeutic range, prolonging the QTc interval and inducing hyperinsulinaemic hypoglycemia (more common and severe in pregnancy). . Intramuscular quinine is effective, but can cause local toxicity as well as hypoglycaemia in patients who may not have intravenous access. Furthermore, in south east Asia there is evidence of increasing quinine resistance so that artemisinins are now used as first line treatment for severe malaria in most units. Several trials have compared quinine and intramuscular artemether for severe infection in both south east and Africa. Despite improved parasite clearance parameters in most trials, definitive evidence for improved mortality with artemether in individual trials and meta analysis is lacking. Many important observations have emerged from these studies. Firstly, the incidence of postadmission hypoglycaemia is significantly higher with quinine compared with artemether. Secondly, the frequency of dosing (more with quinine) also adds extra demands on scarce nursing resources. Most significantly, artemether may not have been the best choice of artemisinin to study in the first place, as suggested more than a decade ago (Dr Hien, Cho Quan Hospital, Vietnam, personal communication to SK). Compared with artesunate, artemether is less completely bio transformed to the more potent dihydroartemisinin and has slow, erratic absorption after intramuscular administration in fact the ability of artemether to provide equivalent benefit to quinine is probably testament to the antimalarial potency of the artemisinin derivatives as a group. Attention has therefore switched to artesunate. Parenteral artesunate has been used in adults and children with severe malaria in south east Asia where intramuscular administration was comparable in efficacy and safety to the intravenous route. In an analogous manner to parenteral artemether, artesunate (intravenously) shows reduced incidence of hypoglycaemia compared with quinine.

LIMITATIONS OF ARTEMISININS :

Poor cure rate of monotherapy

Artemisinins reliably reduce initial malaria parasitaemia by a factor of 104 per 48 hour asexual cycle and modelling studies therefore suggest that six days of treatment should cure parasite burdens of up to 1012 parasites. This model is difficult to reconcile with the high recrudescence rates (10%– 15%) seen with artemisinin monotherapy. This poor efficacy of cure (which is not due to resistance) is usually attributed to the intrinsically short half life of artemisinins, which is further shortened by the increased drug clearance that develops during repeat dosing and/or convalescence with various oral artemisinin derivatives Blaming pharmacokinetic factors alone for the poor efficacy ofartemisininmonotherapy may not be justified because constant drug levels are not necessary for potent pharmacodynamic effects (at least in the initial, visible phase of parasitaemia). Furthermore, if pharmacokinetic behaviour were a problem, prolongation of treatment course may be predicted to compensate, but this is not generally observed in; seven days of monotherapy with artemisinin still only cures 80%–90% of uncomplicated falciparum infections. Parasite reduction ratio models for artesunate derived on data obtained at the start of treatment may not be applicable to the process of eradication of small numbers of residual parasites, which determines eventual cure rates. Other phenomena may exist that permit escape from artemisinin therapy,

necessitating a second (albeit less visibly effective) antimalarial. Although it has been strongly argued that, in any case, combination therapy has long term benefit in preventing resistance, the poor efficacy of monotherapy with the current generation of artemisinins remains a troubling and poorly explained phenomenon.

Neurotoxicity: Millions of doses in various formulations have been administered to people without substantial evidence of severe toxicity, even when special care is paid to monitoring for brainstem toxicity, which has been shown to be hazardous to animals in pre-clinical studies.

Pharmacokinetics of artemisinin derivatives : Artemisinin derivative oral formulations are often quickly absorbed. Many research on severe malaria have employed intramuscular artemether, although it has slow and unpredictable results. absorption. With its quick and dependable absorption, intramuscular artesunate is pharmacokinetically superior to artemether for the treatment of severe malaria. Since oral administration of intrarectalartesunate is not feasible and until hospital care is available, intrarectalartesunate exhibits fast absorption and is a promising treatment for patients with mild malaria.

Other toxicity and interactions: Delivery of artemisinins may be accompanied with brief gastrointestinal distress, which is a symptom of acute malaria in any event, and, less frequently, by severe allergic responses or hemolysis. Despite the fact that there is limited human data, artemisinins have not been demonstrated to be teratogenic, fetatoxicity is a significant risk based on animal studies. Although it is not recommended to use them during the first trimester of pregnancy, they have occasionally been utilised after all other options for life-saving care have been tried. Little drug metabolism and interaction studies for artemisinins and their combination partners have been conducted, which is surprising given the intention to introduce artemisinin combination therapy. Also, there aren't many stability studies for the majority of the current formulations of artemisinins (mostly artesunate).

ARTEMISININS—THE NEXT GENERATION : By using the therapeutic formulations that are already accessible, well-designed research could overcome some of the limitations of the present artemisinins. The best way to address such problems, though, may be to create the next generation of artemisinins, aiming for greater efficacy, lower toxicity, and better stability. Fully synthesised trioxalones now being developed as medications may assist quickly broaden the selection of new antimalarials in this regard. They benefit from not relying on artemisinin as a synthesis' starting point.

USES OUTSIDE MALARIA : Oral artemether has been known for some time to possess activity against immature worms of Schistosoma japonicumand Schistosoma mansoni, and has proved an efficacious chemoprophylactic agent against both infections. It should be noted that the long term consequences of artemether use in this context potentially include selection for resistant plasmodia. Artesunate shows antitumour cell activity.

CONCLUSION: For many years, artemisinins were used irrationally because it was unknown how they worked or what their pharmacokinetic characteristics were. Their unquestionably outstanding parasite clearance kinetics, which are better than those of other widely used antimalarials, have a tendency to impact empirical assessments of efficacy and the best method of administration. The current artemisinins have some way to go before they can be said to provide a clear cut advantage over other antimalarial combinations in some geographical areas, though, if the only fundamental and reliable measures of efficacy are cure and mortality rates for uncomplicated and severe malaria, respectively. As a monotherapy, artemisinins are ineffective at treating malaria, a phenomena that

is poorly understood. There are still some issues with neurotoxicity and its mechanism. Although artemisinins undoubtedly lower the frequency of hypoglycemia, no treatment has yet been shown to be more effective than quinine at reducing death from severe malaria. Despite these problems, artemisinins should be used as part of combination therapy for multidrug resistant malaria as soon as it is deemed necessary, with rectal delivery allowing for community-based treatment of mild malaria. Parenteral artesunate may ultimately replace quinine as the best treatment for the persistent issue of severe malaria if trial evidence demonstrating improved outcomes relative to quinine can be acquired.

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