

ART OF OLIDE LACTONES TO CONTROL OVER MALARIAL TONES

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ABSTRACT

ART OF OLIDE LACTONES TO CONTROL OVER MALARIAL TONES is a quotation which comes from ART (**Ar**temisinin, **Di**hydroartemisinin, **Ar**temether, **Ar**teether, **Ar**tesunate); OLIDE from **macrol**ides; TONES from **lact**ones because this article focuses on sesquiterpene lactones as antimalarials. Malaria is an illness caused by a variety of parasites transmitted by the anopheles mosquito. The parasites infect the human red blood cells and cause a variety of non-specific symptoms – most commonly high fevers, excessive sweats, back ache and joint pain. If the symptoms are neglected the person may become severely ill and eventually die. There are many remedies available but one of the most effective is the traditional remedy of Artemisia Afra which has been used for centuries by Africans and as such has proven itself to be effective and safe. Artemisia is effective both as prophylaxis and treatment of malaria. Prophylaxis is nothing more than treatment in anticipation of yet hidden symptoms. Artemisia given correctly will abort the infection before it develops into malaria. A person who has not taken preventative treatment or prophylaxis can still be treated for malaria by tripling the dose should symptoms appear. Symptoms of malaria mimic a flu-like illness. This dosage should be maintained for between 10 to 30 days, depending on the kind of parasite. Medical attention should always be sought when symptoms appear. A parasite count is vital for assessing the effectiveness of the treatment. The most widely researched ingredient of Artemisia is artemisinin. Artemisinin is a compound which consists of many constituents. The South African researcher Kraft (2003) confirmed that the South African variety Artemisia Afra has similar activity attributable to similar constituents as the Chinese relative. The anti-malarial activity of the plant is determined by the complex structure of all compounds contained in the plant which work synergistically and as such are more effective than a single constituent. This was confirmed by the researcher Wernsdorfer (1999) who found that parasites would find it easier to develop resistance to a single agent than to a battery of anti-malarial compounds such as contained in a whole plant. It is hydrolyzed in the cell and then eliminated rapidly. Unfortunately confusion has been created in the minds of the public as researchers have given what they believe the most active ingredient of the plant which they have synthesised chemically in the laboratory the same name as the natural compound namely artemisinin. All the artemisinin compounds induce a more rapid reduction of parasites than any other known anti-malarial drug. Because of the rapid action of ingredients in the Artemisia plant it does not have to be taken over extended periods before entering or after leaving a malaria area.

KEYWORDS: Lactone, Isoprene, Sesquiterpene, Germacranolides, Artemisinin, Dihydroartemisinin, Artemether, Arteether, Artesunate.

INTRODUCTION

Lactones are cyclic esters of hydroxy carboxylic acids, containing a 1-oxacycloalkan-2-one structure, or analogues having unsaturation or hetero atoms replacing one or more carbon atoms of the ring. Lactones are formed by intramolecular esterification of the corresponding hydroxycarboxylic acids, which takes place spontaneously when the ring that is formed is five- or six-membered. Lactones with three- or four-membered rings (α -lactones and β -lactones) are very reactive, making their isolation difficult. Special methods are normally required for the laboratory synthesis of

small-ring lactones as well as those that contain rings larger than six-membered.^[1-3]

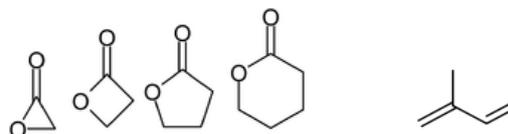


Figure-1: Lactones and Isoprene

Lactone nomenclature: α -acetolactone, β -propiolactone, γ -butyrolactone and δ -valerolactone

Lactones are usually named according to the precursor acid molecule (*aceto* = 2 carbon atoms, *propio* = 3, *butyro* = 4, *valero* = 5, *capro* = 6, etc.), with a *-lactone* suffix and a Greek letter prefix that specifies the number of carbon atoms in the heterocycle — that is, the distance between the relevant -OH and the -COOH groups along said backbone. The first carbon atom after the carbon in

the -COOH group on the parent compound is labeled α , the second will be labeled β and so forth. Therefore, the prefixes also indicate the size of the lactone ring: α -lactone = 3-membered ring, β -lactone = 4-membered, γ -lactone = 5-membered, etc. The other suffix used to denote a lactone is *-olide*, used in substance class names like butenolide, macrolide, cardenolide or bufadienolide.

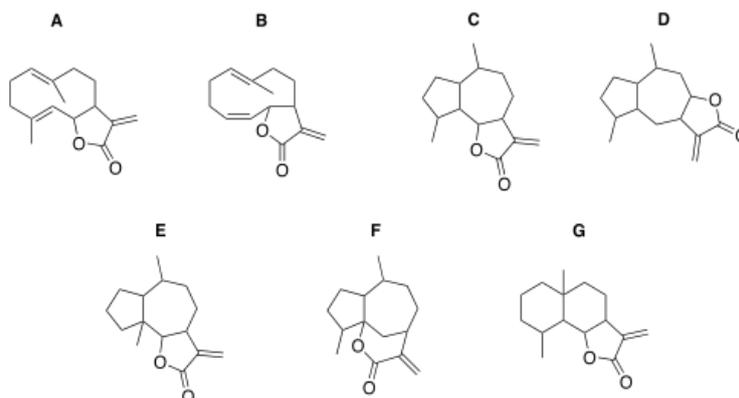


Figure-2: Sesquiterpene lactones from Chinese herb

Isoprene, or 2-methyl-1,3-butadiene, is a common organic compound with the formula $\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$. In its pure form, it is a colorless volatile liquid. Isoprene is produced by many plants. The isoprene skeleton can be found in naturally occurring compounds called terpenes (also known as isoprenoids), but these compounds do not arise from isoprene itself. Terpenes can be viewed as multiples of isoprene subunits, and this perspective is the cornerstone of the "isoprene rule". Terpenes are derived biosynthetically from units of isoprene, which has the molecular formula C_5H_8 . The basic molecular formulae of terpenes are multiples of that, $(\text{C}_5\text{H}_8)_n$ where n is the number of linked isoprene units. This is called the **isoprene rule** or the **C5 rule**. The isoprene units may be linked together "head to tail" to form linear chains or they may be arranged to form rings.

One can consider the isoprene unit as one of nature's common building blocks.^[4-6]

SESQUITERPENE CHEMISTRY

Sesquiterpene lactones are a class of chemical compounds; they are sesquiterpenoids (built from three isoprene units) and contain a lactone ring, hence the name. They are found in many plants and can cause allergic reactions and toxicity if overdosed, particularly in grazing livestock. Some are also found in corals such as *Maasella edwardsi*. Sesquiterpene lactones can be divided into several main classes including germacranolides, heliangolides, guaianolides, pseudoguaianolides, hypocretenolides and eudesmanolides.^[7-9]

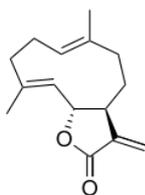


Figure-3: Germacranolide

Germacranolides are a group of natural chemical compounds classified as sesquiterpene lactones. They are found in a variety of plant sources.

Structures of some sesquiterpene lactones

A: Germacranolides, **B:** Heliangolides, **C+D:** Guaianolides, **E:** Pseudoguaianolides, **F:** Hypocretenolides, **G:** Eudesmanolides.

Artemisinin, also known as *qinghao su* and its semi-synthetic derivatives are a group of drugs that possess the most rapid action of all current drugs against *Plasmodium falciparum* malaria. It was discovered by Tu Youyou, a Chinese scientist, who was awarded half of the 2015 Nobel Prize in Medicine for her discovery. Treatments containing an artemisinin derivative (artemisinin-combination therapies, ACTs) are now standard treatment worldwide for *Plasmodium falciparum* malaria. Artemisinin is isolated from the plant *Artemisia annua*, sweet wormwood, an herb employed in Chinese traditional medicine. A precursor compound can be produced using genetically engineered yeast. Artemisinin, a new, highly-effective anti-malarial compound, is a sesquiterpene lactone found in Chinese wormwood. Lactucin, desoxylactucin, lactucopicrin, lactucin-15-oxalate, lactucopicrin-15-oxalate are some of the most prominent found in lettuce and spinach, giving

most of the bitter taste to these crops. One eudesmanolide, 3-oxo-5 α H,8 β H-eudesma-1,4(15),7(11)-trien-8,12-olide, can work with vernolic acid and other compounds in plants to reduce inflammation.

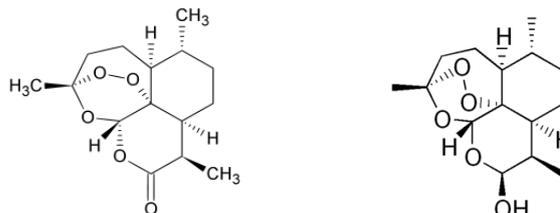


Figure-4: Artemisinin and Dihydroartemisinin

Chemically, artemisinin is a sesquiterpene lactone containing an unusual peroxide bridge. This peroxide is believed to be responsible for the drug's mechanism of action. Few other natural compounds with such a peroxide bridge are known. Artemisinin and its endoperoxides derivatives have been used for the treatment of *Plasmodium falciparum* related infections but low bioavailability, poor pharmacokinetic properties and high cost of the drugs are a major drawback of their use. Use of the drug by itself as a monotherapy is explicitly discouraged by the WHO, as there have been signs that malarial parasites are developing resistance to the drug. Therapies that combine artemisinin or its derivatives with some other antimalarial drug are the preferred treatment for malaria and are both effective and well tolerated in patients. The drug is also increasingly being used in *Plasmodium vivax* malaria, as well as being a topic of research in cancer treatment.

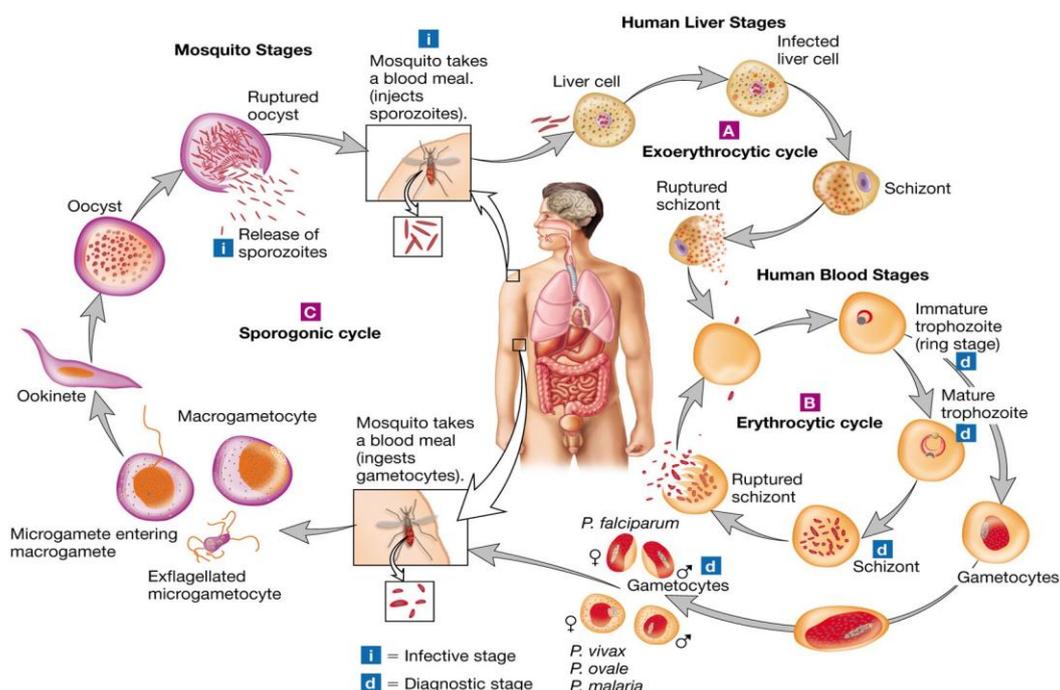


Figure-5: Malaria life cycle

As of 2015, the mechanism of action of artemisinins was not known, but the most widely accepted theory was that they are first activated through cleavage after reacting with h em and iron (II) oxide, which results in the generation of free radicals that in turn damage susceptible proteins, resulting in the death of the parasite. In 2016 artemisinin was shown to bind to a large number of targets suggesting that it acts in a promiscuous manner. Artemisinin is a Chinese herb (qinghaosu) that has been used in the treatment of fevers for over 1,000 years, thus predating the use of Quinine in the western world. It is derived from the plant *Artemisia annua*, with the first documentation as a successful therapeutic agent in the treatment of malaria is in 340 AD by Ge Hong in his book *Zhou Hou Bei Ji Fang* (A

Handbook of Prescriptions for Emergencies). Ge Hong extracted the artemisinin using a simple macerate and this method is still in use today. The active compound was isolated first in 1971 and named artemisinin. It is a sesquiterpene lactone with a chemically rare peroxide bridge linkage. It is this that is thought to be responsible for the majority of its anti-malarial action, although the target within the parasite remains controversial. At present it is strictly controlled under WHO guidelines as it has proven to be effective against all forms of multi-drug resistant *Plasmodium falciparum*, thus every care is taken to ensure compliance and adherence together with other behaviors associated with the development of resistance. It is also only given in combination with other anti-malarials.^[10-12]



Figure-6: Artemisinin formulation

Artemisinin Side Effects

In general Artemisinin has low toxicity. In malaria treatment, only 3.4% showed any occurrence of side effects including nausea, vomiting, abdominal pain and diarrhea. If taken by injection it has caused allergic reactions at the injection site and abscesses. There have been cases of mild intramuscular pain when taking the Artemisinin aqueous suspension. Other Artemisinin side effects include abdominal pain, bouts of low fever, darkening of urine, dizziness, drowsiness and hypertension. Itching, nausea, skin rashes, sweating, tinnitus and vomiting may also occur. It can also cause a reduction of immature blood cells. An over dosage of Artemisinin has caused cardiovascular disturbances. In prolonged use, a single case of liver inflammation that was not related to Malaria has been reported.

Dihydroartemisinin (also known as **dihydroqinghaosu**, **artemimol** or **DHA**) is a drug used to treat malaria. Dihydroartemisinin is the active metabolite of all artemisinin compounds (artemisinin, artesunate, artemether, etc.) and is also available as a drug in itself. It is a semi-synthetic derivative of artemisinin and is widely used as an intermediate in the preparation of other artemisinin-derived antimalarial drugs. It is sold commercially in combination with piperazine and has been shown to be equivalent to artemether/lumefantrine. Dihydroartemisinin is used to treat malaria, generally as a combination drug with piperazine.

In a systematic review of randomized controlled trials, both dihydroartemisinin-piperazine and artemether-lumefantrine are very effective at treating malaria (high quality evidence). However, dihydroartemisinin-piperazine cures slightly more patients than artemether-lumefantrine and it also prevents further malaria infections for longer after treatment (high quality evidence). Dihydroartemisinin-piperazine and artemether-lumefantrine probably have similar side effects (moderate quality evidence). The studies were all conducted in Africa. In studies of people living in Asia, dihydroartemisinin-piperazine is as effective as artesunate plus mefloquine at treating malaria (moderate quality evidence). Artesunate plus mefloquine probably causes more nausea, vomiting, dizziness, sleeplessness and palpitations than dihydroartemisinin-piperazine (moderate quality evidence).

Dihydroartemisinin side effects: nausea, vomiting, dizziness, sleeplessness, and palpitations.^[13-15]

Artemether is an antimalarial for the treatment of multiple drug-resistant strains of *Plasmodium falciparum* malaria. Chemically, it is a semi-synthetic derivative of artemisinin. It is on the WHO list of essential medicines, the most important medications needed in a basic health system. It is available in

combination with lumefantrine. This combination is available as generic medication.

It is a methyl ether derivative of artemisinin, which is a peroxide lactone isolated from the antimalarial plant *Artemisia annua*. It is also known as dihydroartemisinin methyl ether, but its IUPAC name is (+)-(3- α ,5 α - β ,6- β ,8 α - β , 9- α ,12- β ,12aR)-decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano(4,3-*j*)-1,2-benzodioxepin. It is a relatively lipophilic and unstable drug. Artemether is a methyl ether derivative of dihydroartemisinin. It is similar to artemisinin in mode

of action but demonstrates a reduced ability as a hypnozoiticidal compound, instead acting more significantly to decrease gametocyte carriage. Similar restrictions are in place, as with artemisinin, to prevent the development of resistance, therefore it is only used in combination therapy for severe acute cases of drug-resistant *Plasmodium falciparum*. It should be administered in a 7 day course with 4 mg/kg given per day for 3 days, followed by 1.6 mg/kg for 3 days. Side effects of the drug are few but include potential neurotoxicity developing if high doses are given.^[16-18]

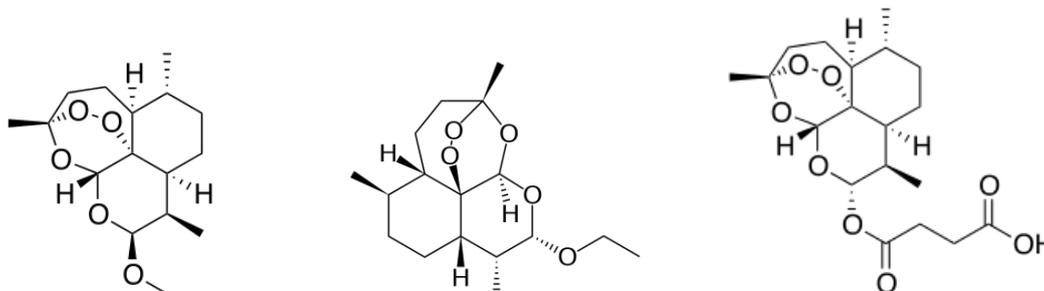


Figure-7: Artemether, Arteether and Artesunate

Artemether side effects: Common side effects of Coartem include headache, dizziness, loss of appetite, weakness, fever, chills, tiredness, muscle or joint pain, nausea, vomiting, abdominal pain, cough and trouble sleeping.

Artemotil (β -arteether), is a fast acting blood schizonticide specifically indicated for the treatment of chloroquine-resistant *Plasmodium falciparum* malaria and cerebral malaria cases. It is a semi-synthetic derivative of artemisinin, a natural product of the Chinese plant *Artemisia annua*. It is currently only used as a second line drug in severe cases of malaria.^[19]



Figure-8: Artemether, Arteether and Artesunate formulations

Arteether side effects

Less common adverse events were body ache, general weakness, vomiting, pain at injection site, abdominal pain, leg pain, chills and rigors, and watery diarrhea. Most of the adverse events appear to be due to malaria rather than the drug because the adverse events appeared on days 1–4.

Artesunate (AS) is a medication used to treat malaria. It is water-soluble and may therefore be given by injection. It is a semi-synthetic derivative of artemisinin. It is a hemisuccinate derivative of the active metabolite dihydroartemisinin. Currently it is the most frequently used of all the artemisinin-type drugs. Its only effect is

mediated through a reduction in the gametocyte transmission. It is used in combination therapy and is effective in cases of uncomplicated *Plasmodium falciparum*. The dosage recommended by the WHO is a 5 or 7 day course (depending on the predicted adherence level) of 4 mg/kg for 3 days (usually given in combination with mefloquine) followed by 2 mg/kg for the remaining 2 or 4 days. In large studies carried out on over 10,000 patients in Thailand no adverse effects have been shown. It is on the WHO list of essential medicines, the most important medications needed in a basic health system. In a hematin dependent manner, artesunate has been

shown to potently inhibit the essential *Plasmodium falciparum* exported protein 1 (EXP1), a membrane glutathione S-transferase. In 2016 artemisinin was shown to bind to a large number targets suggesting that it acts in a promiscuous manner.^[20,21]

Artesunate side effects: The symptomatic adverse reactions produced by Artesunate are more or less tolerable and if they become severe, they can be treated symptomatically, these include Flatulence, Dizziness, Headache, Vomiting, Diarrhea, Fever, Abdominal pain, Rashes, Itching, Hair loss, Convulsions.

CONCLUSION

According to WHO guidelines 2010, artemisinin-based combination therapies (ACTs) are the recommended first line antimalarial treatments for uncomplicated malaria caused by *Plasmodium falciparum*. The following ACTs are recommended by the WHO: artemether+lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + sulfadoxine - pyremethamine, dihydroartemisinin+piperquine. The choice of ACT is based on the level of resistance to the constituents in the combination. Artemisinin and its derivatives are not appropriate for monotherapy. As second-line antimalarial treatment, when initial treatment does not work, an alternative ACT known to be effective in the region is recommended, such as: artesunate+tetracycline or

doxycycline or clindamycin, quinine+tetracycline or doxycycline or clindamycin. Any of these combinations is to be given for 7 days.

In Africa, the overall treatment failure was less for dihydroartemisinin-piperquine when compared to artemether-lumefantrine and both drugs had polymerase chain reaction (PCR)-adjusted failure rates of less than 5%. However, in Asian countries, dihydroartemisinin-piperquine was found to be better tolerated, but as effective as artesunate plus mefloquine. For pregnant women, the recommended first-line treatment during the first trimester is quinine plus clindamycin for 7 days. Artesunate plus clindamycin for 7 days is indicated if this treatment fails. Still, an ACT is indicated only if this is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails or given uncertain compliance with a 7-day treatment. In second and third trimesters, the recommended treatment is an ACT known to be effective in the country/region or artesunate plus clindamycin for 7 days, or quinine plus clindamycin for 7 days. Lactating women receive standard antimalarial treatment (including ACTs) except for dapsone, primaquine and tetracyclines. In infants and young children, the recommended first-line treatment is ACTs, with attention to accurate dosing and ensuring the administered dose is retained.



For travellers returning to nonendemic countries, any of the following is recommended: atovaquone+proguanil, artemether-lumefantrine, quinine+doxycycline or clindamycin. Severe malaria: In severe falciparum malaria, rapid clinical assessment and confirmation of the diagnosis is recommended, followed by administration of full doses of parenteral antimalarial treatment without delay with whichever effective antimalarial is first available. For adults, intravenous (IV) or intramuscular (IM) artesunate is recommended. Quinine is an acceptable alternative if parenteral artesunate is not available. For children, especially in the malaria-endemic areas of Africa, any the following antimalarial medicines is recommended:

artesunate IV or IM, quinine (IV infusion or divided IM injection), artemether IM - should be used only if none of the alternatives is available, as its absorption may be erratic. Parenteral antimalarials should be administered for a minimum of 24 hours, irrespective of the patient's ability to tolerate oral medication earlier. Thereafter, complete treatment is recommended including complete course of any of the following: ACT, artesunate+clindamycin or doxycycline, quinine+clindamycin or doxycycline. If complete treatment is not possible, patients should be given prereferral treatment and referred immediately to an appropriate facility for further treatment. The following are options for prereferral treatment: rectal artesunate, quinine IM, artesunate IM, artemether IM.

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