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### REVIEW ARTICLE

## Review on Alkaloidal and Non Alkaloidal Natural Products of Antimalarial Drugs

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### ABSTRACT

Malaria is most dangerous parasitic infectious disease in many countries. Plasmodium falciparum which infects red blood cells(RBC).This disease is getting worse, mainly due to the increase resistance of Plasmodium falciparum against the widely available antimalarial drugs. Natural products have played a important role in the discovery of leads for the development of drugs to treat human diseases .The new antimalarial drugs may certainly emerge from plant sources. This review contains most of the recently published alkaloidal and non alkaloidal natural compounds from plants with antiplasmodial and antimalarial properties; non alkaloidal compounds belong under the classes of terpenes, limonoids, flavonoids, chromones, xanthenes, anthraquinones and related compounds. Alkaloidal compounds belong to the classes of aminoquinolines, quimolinomethanol derivatives, diaminopyrimidines, sulphonamides, biguanides. Consider many antimalarial activities observe for all crude extracts and natural compounds are described here, by continuing investigation of plants used in traditional medicines for the treatment of malaria and they will lead the scientific discovery of more new efficient drug molecules and phytomedicines for this disease.

**Keywords:** malaria; alkaloidal products, non-alkaloidal products, Plasmodium falciparum, anti-malarial activity

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### 1. Introduction

Malaria is most dangerous parasitic infectious disease in many countries. Plasmodium falciparum which infects red

blood cells(RBC). The name "mal aria" (meaning "bad air" in Italian) was first used in 1740 by H. Walpole. The term

was shortened to "malaria" in the 20th century. C. Laveran in 1880 was the first to identify the parasites in human blood. Malaria is a life-threatening disease. It's typically transmitted through the bite of an infected Anopheles mosquito. Infected mosquitoes carry the Plasmodium parasite. When this mosquito bites you, the parasite is released into your bloodstream. Malaria is typically diagnosed by the microscopic examination of blood using blood films, or with antigen-based rapid diagnostic tests. Methods that use the polymerase chain reaction to detect the parasite's DNA have been developed, but are not widely used in areas where malaria is common due to their cost and complexity. The recommended treatment for malaria is a combination of antimalarial medications that includes an artemisinin. The second medication may be either mefloquine, lumefantrine, sulfadoxine/pyrimethamine. Quinine along with doxycycline may be used if an artemisinin is not available. It is recommended that in areas.

Where the disease is common, malaria is confirmed if possible before treatment is started due to concerns of increasing drug resistance. Resistance among the parasites has developed to several antimalarial medications; for example, chloroquine-resistant *P. falciparum* has spread to most malarial areas, and resistance to artemisinin has become a problem in some parts of Southeast Asia. Some non alkaloidal compounds belong under the classes of terpenes, limonoids, flavonoids, chromones, xanthenes, anthraquinones and related compounds are used to treat malaria. Four Plasmodium species are causing agents – *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.

#### ***P. falciparum*:**

This is the most common malaria parasites, and it causes the most malaria-related deaths in the world. *P. falciparum* multiplies very quickly, causing severe blood loss and clogged blood vessels.

***P. vivax*:** This is the malaria parasite most commonly found outside of sub-Saharan Africa, especially in Asia and Latin America. This species can lie dormant, then rise up to infect your blood months or years after the mosquito bite.

## 2. Symptoms

Initial manifestations of the disease—common to all malaria species—are similar to flu-like symptoms, and can resemble other conditions such as sepsis, gastroenteritis, and viral diseases. The presentation may include headache, fever, shivering, joint pain, vomiting, hemolytic anemia, jaundice hemoglobin in the urine, retinal damage, and convulsions. Severe malaria is usually caused by *P. falciparum* (often referred to as falciparum malaria). Symptoms of falciparum malaria arise 9–30 days after infection.

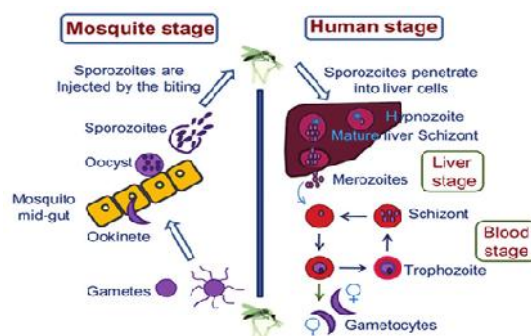
- Chills, Sweating
- Muscle aches (Fatigue, Pain)
- Central headache.
- Nausea
- Vomiting

- Dry Cough
- Diarrhoea
- Spleen enlargement
- abnormal posturing
- nystagmus
- Conjugate gaze palsy (failure of the eyes to turn together in the same direction)
- opisthotonus
- Seizures or coma.

Sometimes symptoms may occur later in those individuals who have taken antimalarial medications. Initial propagation are similar to flu-like symptoms, septicemia, gastroenteritis and viral diseases. They also may include headache, fever, shivering, joint pain, vomiting.

## 3. Life cycle

In the life cycle of Plasmodium, a female Anopheles mosquito (the definitive host) transmits a motile infective form (called the sporozoite) to a vertebrate host such as a human (the secondary host), thus acting as a transmission vector. A sporozoite travels through the blood vessels to liver cells (hepatocytes), where it reproduces asexually (tissue schizogony), producing thousands of merozoites. These infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 24 new infective merozoites, at which point the cells burst and the infective cycle begins a new. Other merozoites develop into immature gametocytes, which are the precursors of male and female gametes. When a fertilized mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut. The male and female gametocytes fuse and form an ookinete a fertilized, motile zygote. Ookinetes develop into new sporozoites that migrate to the insect's salivary glands, ready to infect a new vertebrate host. The sporozoites are injected into the skin, in the saliva, when the mosquito takes a subsequent blood meal. Only female mosquitoes feed on blood; male mosquitoes feed on plant nectar and do not transmit the disease. Females of the mosquito genus Anopheles prefer to feed at night. They usually start searching for a meal at dusk and will continue throughout the night until taking a meal. Malaria parasites can also be transmitted by blood transfusions, although this is rare.



**Fig 1:** *P. Vivax* life cycle

#### 4. Antimalarial activity

The effectiveness of early diagnosis and prompt treatment as the principal technical components of the global strategy to control malaria is highly dependent on the efficacy, safety, availability, affordability and acceptability of antimalarial drugs. The effective antimalarial therapy not only reduces the mortality and morbidity of malaria, but also reduces the risk of resistance to antimalarial drugs. Therefore, antimalaria chemotherapy is the KEYSTONE of malaria control efforts. On the other hand, not many new drugs have been developed to tackle malaria; 1223 new drugs registered between 1975 and 1996, only 3 were antimalarials; Hence the need for a rational antimalaria treatment policy.

##### Classification;

Anti-malarial drugs can be classified according to anti-malarial activity and according to structure.

##### 1. According to anti-malarial activity:

**Tissue schizonticides for causal prophylaxis:** These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented. Pyrimethamine and Primaquine have this activity. However since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.

**Tissue schizonticides for preventing relapse:** These drugs act on the hypnozoites of *P. vivax* and *P. ovale* in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

**Blood schizonticides:** These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in anti-malarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines etc.

**Gametocytocides:** These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against *P. vivax* and *P. malariae*, but not against *P. falciparum*. Primaquine has gametocytocidal activity against all plasmodia, including *P. falciparum*.

**Sporontocides:** These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action. Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide and a tissue schizonticide (in case of *P. vivax* and *P. ovale*). A combination of chloroquine and primaquine is thus needed in all cases of malaria.

##### 2. According to the structure:

**Aryl amino alcohols:** Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine.

**4-aminoquinolines:** Chloroquine, amodiaquine.

**Folate synthesis inhibitors:** Type 1 – competitive inhibitors of dihydropteroate synthase – sulphones,

**Sulphonamides;** Type 2 – inhibit dihydrofolate reductase

– biguanides like proguanil and chloroguanil; diaminopyrimidine like pyrimethamine

**8-aminoquinolines:** Primaquine

**Antimicrobials:** Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones

**Peroxides:** Artemisinin (Qinghaosu) derivatives and analogues artemether, arteether, artesunate, artelinic acid

**Naphthoquinones:** Atovaquone

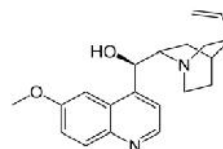
**Ironchelatingagents:** Desferrioxamine

##### Alkaloidal Antimalarial Drugs:

##### Quinine and related agents:

Quinine is an alkaloid obtained from cinchona acts as a blood schizonticidal and weak gametocide against *Plasmodium vivax* and *Plasmodium malariae*. Quinine is accumulated in the food vacuoles of *Plasmodium* species, especially *Plasmodium falciparum* and inhibit the hemozoin biocrystallization, thus facilitating an aggregation of cytotoxic heme. Quinine is very effective and widely used in the treatment of acute cases of severe *P. falciparum* but it is less effective and more toxic than chloroquine. Mostly useful in areas where high level of resistance to chloroquine, mefloquine, and sulfa drug combinations with pyrimethamine.

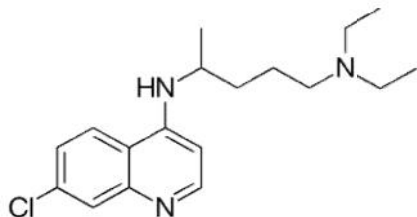
The World Health Organization recommendation for quinine by oral, intravenous or intramuscular routes, is 20 mg/kg first times and 10 mg/kg 8 hr for 5 days whereas in quinine sensitivity quinine may combined with doxycycline, tetracycline or clindamycin. Use of quinine is characterised by a frequently experienced syndrome called cinchonism. Tinnitus, rashes, vertigo, nausea, vomiting and abdominal pain are the most common symptoms. Quinine can cause hypoglycemia through its action of stimulating insulin secretion. This effect can be exaggerated in pregnancy and therefore additional care in administering and monitoring the dosage is essential. Repeated or over-dosage can result in renal failure and death through depression of the respiratory system.



##### Chloroquine :

Chloroquine was least expensive, best tested, safest and the most widely used anti-malarial. It was the original prototype from which most methods of treatment are derived. The emergence of drug-resistant parasitic strains is rapidly decreasing its effectiveness. Now Chloroquine is suggested to use in combination with other antimalarial drugs to extend its effective usage. Popular drugs based on chloroquine phosphate (also called nivaquine) are Chloroquine FNA, Resochin and Dawaquin. Chloroquine is a 4-aminoquinolone compound which is believed to reach high concentrations in the vacuoles of the parasite and raises the internal pH. It controls the conversion of toxic heme to hemozoin by inhibiting the biocrystallization of hemozoin, thus poisoning the parasite through excess levels

of toxicity. Children and adults should receive 25 mg of chloroquine per kg given over 3 days, recommended by the WHO, involves giving an initial dose of 10 mg/kg followed 6–8 hours later by 5 mg/kg, then 5 mg/kg on the following 2 days.



#### Amodiaquine:

Amodiaquine is a 4-aminoquinolone anti-malarial drug similar in structure and mechanism of action to chloroquine. Amodiaquine has tended to be administered in areas of chloroquine resistance while some patients prefer its tendency to cause less itching than chloroquine. Amodiaquine is now available in a combined formulation with artesunate (ASAQ) and is among the artemisinin-combination therapies recommended by the World Health Organisation. The drug should be given in doses between 25 mg/kg and 35 mg/kg over 3 days in a similar method to that used in chloroquine administration. Adverse reactions are generally similar in severity and type to that seen in chloroquine treatment. In addition, bradycardia, itching, nausea, vomiting and some abdominal pain have been recorded. Some blood and hepatic disorders have also been seen in a small number of patients.

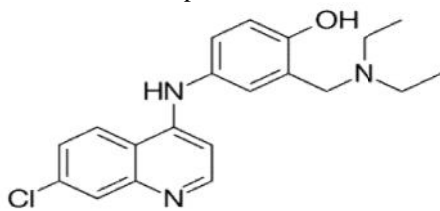
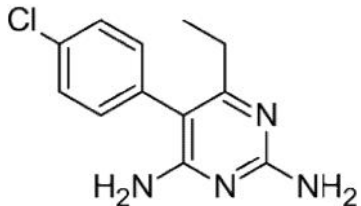


Fig 4: Structure of Amodiaquine

#### Pyrimethamine:

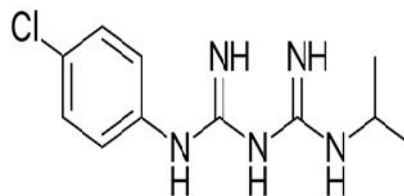
Pyrimethamine is used in the treatment of uncomplicated malaria, particularly in cases of chloroquineresistant *P. falciparum* strains when combined with sulfadoxine. It acts by inhibiting dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, thereby halting the processes of DNA replication, cell division and reproduction. It acts primarily on the schizonts during the erythrocytic phase, and nowadays is only used in concert with a sulfonamide.



#### Proguanil:

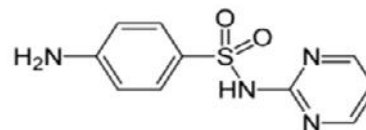
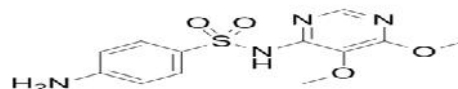
Proguanil (chloroguanide) is a biguanide, a synthetic pyrimidine derivative. It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil. This inhibits the malarial International Journal of Current Trends in Pharmaceutical Research

dihydrofolate reductase enzyme. It has a weak blood schizonticidal activity and is not recommended for therapy of acute infection. However it is useful in prophylaxis when combined with atovaquone or chloroquine (in areas where there is no chloroquine resistance). 3 mg/kg is the advised dosage per day, (hence approximate adult dosage is 200 mg). There are very few side effects to proguanil, with slight hair loss and mouth ulcers being occasionally reported following prophylactic use.



#### Sulfonamides:

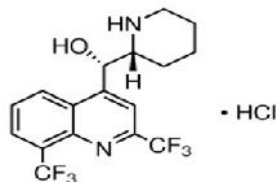
Sulfadoxine & sulfamethoxy pyridazine are specific inhibitors of the enzyme dihydropteroate synthetase in the tetrahydrofolate synthesis pathway of malaria parasites. Sulfonamides act on the schizont stages of the erythrocytic cycle. When sulfonamides are co-administration with the antifolate pyrimethamine, most commonly as fixed-dose sulfadoxine-pyrimethamine (Fansidar), produces synergistic effects sufficient to cure sensitive strains of malaria.



#### Mefloquine:

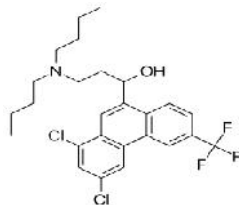
Mefloquine is a very potent blood schizonticide act by forming toxic heme complexes that damage parasitic food vacuoles. It is now used solely for the prevention of resistant strains of *P. falciparum* despite being effective against *P. vivax*, *P. ovale* and *P. malariae*. Mefloquine is effective in prophylaxis and for acute therapy. It is now strictly used for resistant strains and is usually combined with Artesunate. Mefloquine is recommended as a dose of 15–25 mg/kg, depending on the prevalence of mefloquine resistance. The increased dosage is associated with a much greater level of intolerance, most noticeably in young children; with the drug inducing vomiting and oesophagitis. It was not recommended for use during the first trimester, although considered safe during the second and third trimesters; nevertheless, in October 2011, the Centers for Disease Control and Prevention (CDC) changed its recommendation and approved use of Mefloquine for both prophylaxis and treatment of malaria in all trimesters, after the Food and Drug Administration (FDA) changed its categorization from C to B. Mefloquine can only be taken for a period up to 6 months due to side effects. After this,

other drugs (such as those based on paludrine/nivaquine) again need to be taken. Mefloquine frequently produces side effects, including nausea, vomiting, diarrhea, abdominal pain and dizziness. Several associations with neurological events have been made, namely affective and anxiety disorders, hallucinations, sleep disturbances, psychosis, toxic encephalopathy, convulsions and delirium. Cardiovascular effects have been recorded with bradycardia and sinus arrhythmia being consistently recorded in 68% of patients treated with mefloquine.



#### Halofantrine:

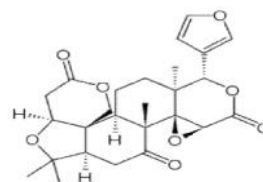
Halofantrine is a phenanthrene methanol, chemically related to Quinine and acts acting as a blood schizonticide effective against all plasmodium parasites. Its mechanism of action is similar to other anti-malarials. Cytotoxic complexes are formed with ferritoporphyrin XI that cause plasmodial membrane damage. A popular drug based on halofantrine is Halfan. A dose of 8 mg/kg of halofantrine is advised to be given in three doses at six hour intervals for the duration of the clinical episode. It is not recommended for children under 10 kg despite data supporting the use and demonstrating that it is well tolerated. The most frequently experienced side-effects include nausea, abdominal pain, diarrhea, and itch. Severe ventricular dysrhythmias, occasionally causing death are seen when high doses are administered. Halofantrine is not recommended for use in pregnancy and lactation, in small children, or in patients that have taken mefloquine previously. Lumefantrine is a relative of halofantrine that is used in some combination antimalarial regimens.



#### Non - Alkaloidal Antimalarial DRUGS:

##### Limonoids:

Limonoids are phytochemicals of the triterpenoid class which abundant in sweet or sour-scented citrus fruit and other plants of the families Cucurbitaceae, Rutaceae and Meliaceae. Certain limonoids are antifeedants such as azadirachtin from the neem tree. Chemically, the limonoids consist of variations of the furanolactone core structure. The prototypical structure consists of four six-membered rings and a furan ring. Limonoids are classed as tetranortriterpenes. Citrus fruits contain the limonoids limonin, nomilin and nomilinic acid, while both neem seeds and leaves contain the limonoid azadirachtin, although higher concentrations are present in the former.

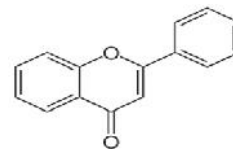


##### Flavonoids:

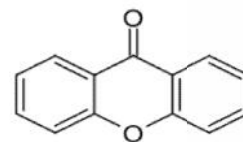
Flavonoids (or bioflavonoids) are a class of plant and fungus secondary metabolites. Chemically, flavonoids have the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and a heterocyclic ring (C). This carbon structure can be abbreviated C6-C3-C6. According to the IUPAC nomenclature, they can be classified into:

- ✓ Flavonoids or bioflavonoids
- ✓ Isoflavonoids, derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structure
- ✓ Neoflavonoids, derived from 4-phenylcoumarin (4-phenyl-1,2-benzopyrone) structure

The three flavonoid classes above are all ketone-containing compounds, and as such, are anthoxanthins (flavones and flavonols). This class was the first to be termed bioflavonoids. The terms flavonoid and bioflavonoid have also been more loosely used to describe non-ketone polyhydroxy polyphenol compounds which are more specifically termed flavanoids. The three cycle or heterocycles in the flavonoid backbone are generally called ring A, B and C.



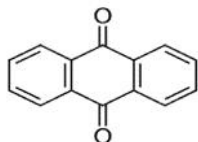
**Xanthenes:** Xanthenes, from the pericarp, whole fruit, heartwood, and leaf of mangosteen (*Garcinia mangostana* Linn., GML), are known to possess a wide spectrum of pharmacologic properties, including anti-malarial, antioxidant, anti-tumor, anti-allergic, anti-inflammatory, anti-bacterial, anti-fungal, and anti-viral activities. Five xanthenes from the bark of *Garcinia cowa*, namely 7-O-methylgarcinone, cowanin, cowanol, cowaxanthone, and beta-mangostin were found to possess in vitro antimalarial activity against *Plasmodium falciparum*.



##### Anthracenedione or dioxanthracene:

It is an aromatic organic compound. Several isomers are possible, each of which can be viewed as a quinone derivative. The term anthraquinone, however, almost invariably refers to one specific isomer, 9,10-anthraquinone (IUPAC: 9,10-dioxanthracene) where in the keto groups are located on the central ring. It is a building block of many dyes and is used in bleaching pulp for papermaking. It is a yellow highly crystalline solid, poorly soluble in water but soluble in hot organic solvents. For instance, it is almost completely insoluble in ethanol near

room temperature but 2.25 g will dissolve in 100 g of boiling ethanol.



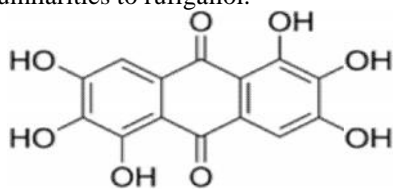
Synthetic dyes are often derived from 9,10-anthraquinone, such as alizarin. Important derivatives are 1-nitroanthraquinone, anthraquinone-1-sulfonic acid, and the dinitroanthraquinone. Natural pigments that are derivatives of anthraquinone are found, inter alia, in aloe latex, senna, rhubarb and cascara buckthorn, fungi, lichens, and some insects. Derivatives of 9,10-anthraquinone include many important drugs (collectively called anthracenediones). They include

**Laxatives:** Dantron, Emodin, and Aloe emodin, and some of the Senna glycosides

**Antimalarials:** Rufigallol.

**Antineoplastics** used in the treatment of cancer, such as Mitoxantrone, Pixantrone, and the Anthracyclines.

**Rufigallol** is particularly toxic to the malarial parasite *Plasmodium falciparum* and has a synergistic effect in combination with the antimalarial drug exifone, which has structural similarities to rufigallol.



Rufigallol forms a crimson colored complex with beryllium, aluminum, thorium, zirconium & hafnium, and this reaction has been used for the spot and spectrophotometric determination of beryllium in low concentrations.

## 5. Prevention

There are two general approaches to preventing the spread of resistance: preventing malaria infections and, preventing the transmission of resistant parasites. Preventing malaria infections developing has a substantial effect on the potential rate of development of resistance, by directly reducing the number of cases of malaria thus decreasing the requirement for anti-malarial therapy. Preventing the transmission of resistant parasites limits the risk of resistant malarial infections becoming endemic and can be controlled by a variety of non-medical methods including insecticide-treated bed nets, indoor residual spraying, environmental controls (such as swamp draining) and personal protective methods such as using mosquito repellent.

## 6. Conclusion

This work reviewed most recently-published non-alkaloidal natural compounds from plants with antiplasmodial and antimalarial properties, besides the majority of antiplasmodial crude extracts (alkaloidal plants) published in the last five years. Considering the many antiplasmodial

activities observed for all crude extracts and natural compounds described here, it can be stated that in fact there are optimistic perspectives on the continuing investigation of plants used in traditional medicines for the treatment of malaria, and they will certainly lead the scientific community to the discovery of more new efficient molecular templates and phytomedicines for this disease. Since people suffering from these diseases have not offered a market lucrative enough to attract any notable investment in research and development for new drugs. Thus non-alkaloidal antimalarial drug Rufigallol (anthraquinone derivatives) active against the parasites *Plasmodium falciparum*, this work also intends to stimulate and bring together new and intensive efforts from all research communities of the world to the quest of efficient phytomedicines and novel potential drug candidates both for malaria and other neglected diseases.

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