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A REVIEW ON TRADITIONALLY USED ANTI-MALARIAL PLANT DRUGS

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ABSTRACT
Malaria as insect-borne disease is a global problem. The World Health Organization (WHO) estimates that a large number of people (between 300 to 500 million) are infected with malaria, and more than 2 million people die annually. Malaria is transmitted from man to man through the bite of female Anopheles mosquitoes. Malaria disease is still a major problem in the world. In allopathic system of medicine, the drug used in the treatment of malaria is less effective or either sensitive to drug used for malaria treatment. Most of the world population is going to use plant drugs or herbal medicines for treatment of malaria. Hence it is needed to explore natural source drug for malaria, because the drugs have less side effects, low cost and easy availability.

KEYWORDS: Malaria parasite, Anopheles Mosquitoes, Plasmodium, Mortility and anti-malarial.

INTRODUCTION

Malaria as insect-borne disease is a global problem, especially in tropical and subtropical regions. The World Health Organisation (WHO) estimates that a large number of people (between 300 to 500 million) are infected with malaria, and more than 2 million people die annually. Today, Africa country alone accounts for 90 % of malaria mortality, because the malaria mosquito, *Anopheles gambiae*, is the most widespread in this part of world and is very difficult to control. The earlier researchers estimate that 40% cases of malaria are only due to *Plasmodium falciparum* than any other species. Malaria is an endemic disease in this region mainly due to the multidrug resistance developed by *Plasmodium falciparum.* Malaria remains the leading cause of death due to parasitic diseases with approximately 300 million clinical cases annually resulting in an estimated 2,300,000 deaths, primarily in children (Sudhanshu et al, 2003., Sachs and Malaney, 2002., WHO, 1966). The use of herbal drugs is very common in many of African countries. In India, malaria is responsible for around 20 lacs of the clinical cases and about 500 deaths in a year. In West Bengal alone, malaria is responsible for around 28,500 clinical cases in a year, of which 10% cases are of falciparum parasite (Roy and Saha, 2005). As a result, it is a major public health problem in India. The name malaria had its origin from Italian words mal (bad) and aria (air). In early days, it was believed to be caused by bad air. It is a protozoan disease caused by the parasite '*Plasmodium'* and transmitted by the bite of female *Anopheles* mosquitoes (Talib, 2001). The causatic agent is a unicellular protozoan known as the Plasmodium, belonging to the class Sporozoa. There are four species of Plasmodia, which infect man. They are *Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale and Plasmodium malariae.* Out of these four, *Plasmodium falciparum* is the dreaded one and is associated with high mortality (Cox, 1993).

In nature, malaria is transmitted from man to man through the bite of female Anopheles mosquitoes, and through accidental inoculation by intramuscular or intravenous injection of blood or plasma e.g. by blood transfusion or unintentional infection in drug addicts and transmission from mother to foetus may give rise to congenital malaria. The most pronounced clinical manifestations of malaria are periodic chills, fever, usually accompanied by frontal headache, myalgia. Fever may persist for several days before the typical periodicity develops. Additional symptoms include malaise, nausea, anorexia and abdominal pain. Vomiting may also develop and can be quite intense (Katz et al, 1982). Untreated, all forms of malaria tend to become chronic and repeated attacks are caused by recrudescence or relapses.

Brief of *Plasmodium* Parasites and Anopheles Mosquitoes

The plasmodium genus of protozoal parasites (mainly *Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale* and *Plasmodium malariae*) have a life cycle which is split between a vertebrate host and an insect vector except of *Plasmodium malariae* (which may affect the higher primates) these species are exclusively parasite of man. The vector is always an Anopheline mosquito, although out of the 380 species of Anopheline mosquito,

only 60 can transmit malaria. Only female mosquitoes are involved as the males do not feed on blood.

Life cycle of malarial parasites

When an uninfected female Anopheles mosquito bites an infected person, the mosquito takes up parasites in her meal of blood. Once they are safely inside the mosquito, some of these parasites reproduce sexually in the gut of mosquito. The parasite then travels to the salivary glands of the mosquito where they mature into sporozoites. At the next meal, the mosquito injects a small amount of saliva into her victim to stop the blood clotting and the sporozoites are passed into a new host. The sporozoites are carried along in the blood of the new host until they reach the liver. In the host liver cells, the parasite multiplies repeatedly and after about 5 days, there are around 40,000 new parasites called merozoites. At this state the liver cells burst and released merozoites attack red blood cells. In red blood cells, the parasite divides again, forming about 16 new merozoites which are released to invade new red cells and from time to time some merozoites form gametocytes which can be taken up by a mosquito with a blood meal. Malarial parasites mature into sporozoites in the salivary glands of a mosquito and enter a human when the mosquito bites.

1. Sporozoites invade liver cells and reproduce asexually many times, forming large number of merozoites.
2. The infected liver cells burst to release merozoites.
3. Merozoites invade red blood cells and continue to produce asexually. Each red blood cell produces an average of 16 to 20 merozoites. Sometimes 32 merozoites are seen. This is because the red blood cell was originally infected with two parasites.
4. Infected red blood cells rupture; release the parasites and the toxin that cause fever and chills. Some of them parasites are able to form gametocytes.

A female Anopheles mosquito picks up gametocytes when she bites an infected person. The gametocytes become gametes. Sexual reproduction of the parasites occurs in the gut of mosquitoes. The sporozoites from the mosquito salivary gland are injected into the human as the mosquito must inject anticoagulant saliva to ensure an even flowing meal. Once in the human blood stream, the sporozoites arrive in the liver and penetrate hepatocytes, where they remain for 9-16 days, multiplying within the cells. Then they return to the blood and penetrate red blood cells, in which they produce either merozoites, which re-infect the liver, or micro and macro gametocytes, which have no further activity within the human host. Another mosquito arriving to feed on the blood may suck up these gametes into its guts, where exflagellation of microgametocytes occurs and microgametes are produced. The micro and macrogametes fuse to form the zygote. The resulting ookinete penetrates the wall of a cell in the midgut, where it develops into an oocyst. Sporogony within the oocyst produces many sporozoites and when the oocyst ruptures, the sporozoites migrate to the salivary gland, for injection into host by the next blood meal of the mosquito. This highly specialized life cycle requires specialized on the part of the *Plasmodium* species.

The reason that not all mosquitoes are vectors for the Plasmodium parasites is that those refractories possess substances toxic to *Plasmodium* within their cells. A higher trypsin-like activity was also found in the midgut of the resistant species, possibly inhibiting ookinete development. Plasmodium parasites are capable of adapting to any suitable Anopheline mosquito, given sufficient time and contact. Once injected into the human host, most of the Plasmodium species penetrate hepatocytes. However, *Plasmodium falciparum* and *Plasmodium malariae* sporozoites trigger immediate schizogony whereas *Plasmodium ovale* and *Plasmodium vivax* sporozoites may either trigger immediate schizogony or have a delayed trigger, resulting in the dormant hypnozoites. Some strains such as the North Korean strain seem to consist of sporozoites with universally delayed trigger, so they all form long lasting hypnozoites. *Plasmodium vivax* may have an incubation period up to 10 months. Gametocytes produced in the primary attack seem to contain all the genetic information required to create sporozoites of several different activation times. The same seems true for gametocytes produced in relapses where the hypnozoites become activated. The sexual development of *Plasmodium* begins as the merozoites invade the erythrocytes after their release from the liver. In erythrocytes, shizogony occurs to produce either more merozoites (in case of *Plasmodium berghei* taken 22 ½ hours) or the sexual micro and macrogametocytes (taking 26 hour). In Plasmodium falciparum, erythrocytic schizogony takes 48 hours and gametocytogenesis take 10- 12 days. Normally a variable number of cycles of asexual erythrocytic schizogony occur before the gametocytes are produced. The immune system may produce antibodies to the gametocytes at this stage. Once dig into the mosquito, the gametocytes increase in volume and escape the erythrocyte. Microgametes are formed by 3 mitotic divisions. Within the microgametocyte are expelled explosively and no further changes affect the female macrogametocyte until fertilization where the plasmalemmas of the male and female gametes fuse and the nucleus of the microgamete enters the female cytoplasm. After the fertilization, the zygote is a motionless globular cell, but after 18 to 24 hours it becomes elongated and motile, containing micronemes and pellicle. The cell invades the microvillus border, passes through the midgut cells and lies beneath the basement membrane. The ookinete then becomes a static oocyte between the basal lamina and the basement cell membrane, bounded by a thick plasmalemma. The chief source of nutrients is the heamolymph in which the oocyte develops. Sporoblast form and sporozoites bud off. After the cyst ruptures, the sporozoites escape into the body cavity of the mosquito and migrate to salivary gland cells where they lie in

vacuole for up to 59 days. These sporozoites develop and become upto 1000 times more infective than when in the oocyst. They are more antigenic and bear circumsporozoites polypeptide on their plasmalemma. Sporozoite motility is involved in their invasion of the cells and escape from the salivary gland. The sporozoites are about 12 µm long and 1 µm across with a single nucleus, anterior to which lie micronemes and posterior to which lie endoplasmic reticulum and mitochondria. They possess a complex pellicle, which is responsible for motility and this pellicle contains circumsporozoites protein. The apical penetrating region contains extensions of the microneme ducts which release an agent which interacts with host cell plasma membrane during penetration. A biting mosquito transfers about 10% of its sporozoite load into the capillaries or perivascular tissue. Now the sporozoite must begin their evasion of the host defences, possibly by binding serum proteins for 'camouflage'. Some are destroyed by macrophages or by antigen-specific antibodies in immune individuals but in non-immune individuals. They reach the hepatocytes and initiate schizogony or become hypnozoites depending on their deley trigger. All sporozoites leave the peripheral circulation system within 45 minutes.

Diagnosis

The malaria diagnosis is confirmed by examination of blood smear slide testing under the microscope, after special staining.

Treatment of malaria

1. The best approach of malaria treatment is the diagnosis and treatment on the same day.
2. Drug resistance foci are prevalent in the country but Chloroquine is still safest, effective, cheapest antimalarial and easy to administered.
3. Any fever in endemic areas during transmission season without any other obvious may be considered as malaria and treated accordingly (Roy and Saha, 2005; Leech et al., 1988; James and Gilles, 1985).

Plant used traditionally Showing Anti-malarial Activity

Plant	Part used	Plasmodium sp.and strain	Extract	Dose efficiency	References
Picralima nitida	Root Stem bark	P.falciparum NF 54	Methanol water Methanol water	1.629 10.914 1.792 > 50	Francois et al, 1996
Uapaca nitida	Root bark	P.falciparum KI	Ethanol Chloroform Methanol	45 ng/ml 25 µg/ml 18 µg/ml	Kirby et al, 1993
Morinda lucida	leaves	P. berghei	Pertroleum ether	6.25- 50 mg/kg/day	Mankinde et al,1994
Hernandia voyronii	Stem bark	P.falciparum FCM-29C1	ethanol	3.53 mg/kg	Ratsimamanga- Urverg et al, 1994
Cochlospermum tinctorim	Tubercle	P.falciparum F32 and FCBI	Infusion in water Decoction in Water	0.93 and 1.31 1.35 and 0.92	Benoit et al, 1995
Cassia abberviata	Roots	P.falciparum	Methanol	7.07	Connelly et al, 1996
Croton guatemalensis	Cortex leaves	P.falciparum NF 54 and KI	Dichloromethene	27.8 and 23.1 19.8 and 22.1	Franseen et al, 1997
Bidens pilosa	Whole plant	P.falciparum BH 26/86	Ethanol Butanol	90 NT	Brandao et al, 1997
Alnus incana	Stipes	P.falciparum D6 and W2	Ethyl acetate	8.7 and 7.3	Grzybek et al, 1997
Swertia chirata	Stem and leaves	P.falciparum FCK2	PE,Methanol,Ethanol, Aqueous	53.17, >100, 21.69, > 1000	Bhat and Surolia, 2001
Pterocarpus erinaceus	Leaves and Bark	P. falciparum	PE, Methanol, Ethanol, Aqueous	7.38, 1.93, 95.13, 103.35	Karou et al, 2003
Sida acuta	Whole plant	Fresh clinical isolates of P. falciparum	PE, Methanol, Ethanol, Aqueous	57.04, 0.87, 0.92, 4.37	Karou et al, 2003
Funtumia elastica	Stem bark	P.falciparum FCB1	Ethanol	3.3 ±0.9	Zirihi et al, 2005
Boerhaavia erecta	Stem	P.burghei	Aqueous	564.95 ±6.23	Hilou et al, 2006

L.					
Amaranthus spinosus L.	Stem	P.burghei	Aqueous	789.36 ±7.19	Hilou et al, 2006
Stachytarpheta cayennensis	Leaf	P.berghei	Ethanol	77.42	Jude E.Okokon et al, 2008
Phyllanthus niruri	Stem, leaves, Root	P. falciparum	Ethanol and Water	22±4 and14 ±4, 25±4 and19±3, >50 and > 50	P. Njomnang Soh et al, 2009
Verbena hastata	Leaf	P. berghei berghei	Ethanol	9.66 ±0.53	G.C. Akuodor et al, 2010
Boerhavia elegans and Solanum surattense	Whole plant	P, falciparum and P. berghei	Hydro alcoholic	> 50 >50	Ali Ramazan et al, 2010
Anthocleista djalonensis	Leaf Stem bark	P. berghei	Ethanolic	5.0 and 2.23	Antia S. Bassey et al, 2011

CONCLUSION

Malaria disease is still a major problem in the world. Today, Africa country alone accounts for 90 % of malaria mortality, because the malaria mosquito, *Anopheles gambiae*, is the most widespread in this part of world and is very difficult to control. Malaria is an endemic disease in this region mainly due to the multidrug resistance developed by *Plasmodium falciparum.* Malaria remains the leading cause of death due to parasitic diseases with approximately 300 million clinical cases annually. In allopathic system of medicine, the drug used in the treatment of malaria is less effective or either sensitive to drug used for malaria treatment. Most of the world population is going to use plant drugs or herbal medicines for treatment of malaria. Hence it is needed to explore natural source drug for malaria, because the drugs have less side effects, low cost and easy availability.

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