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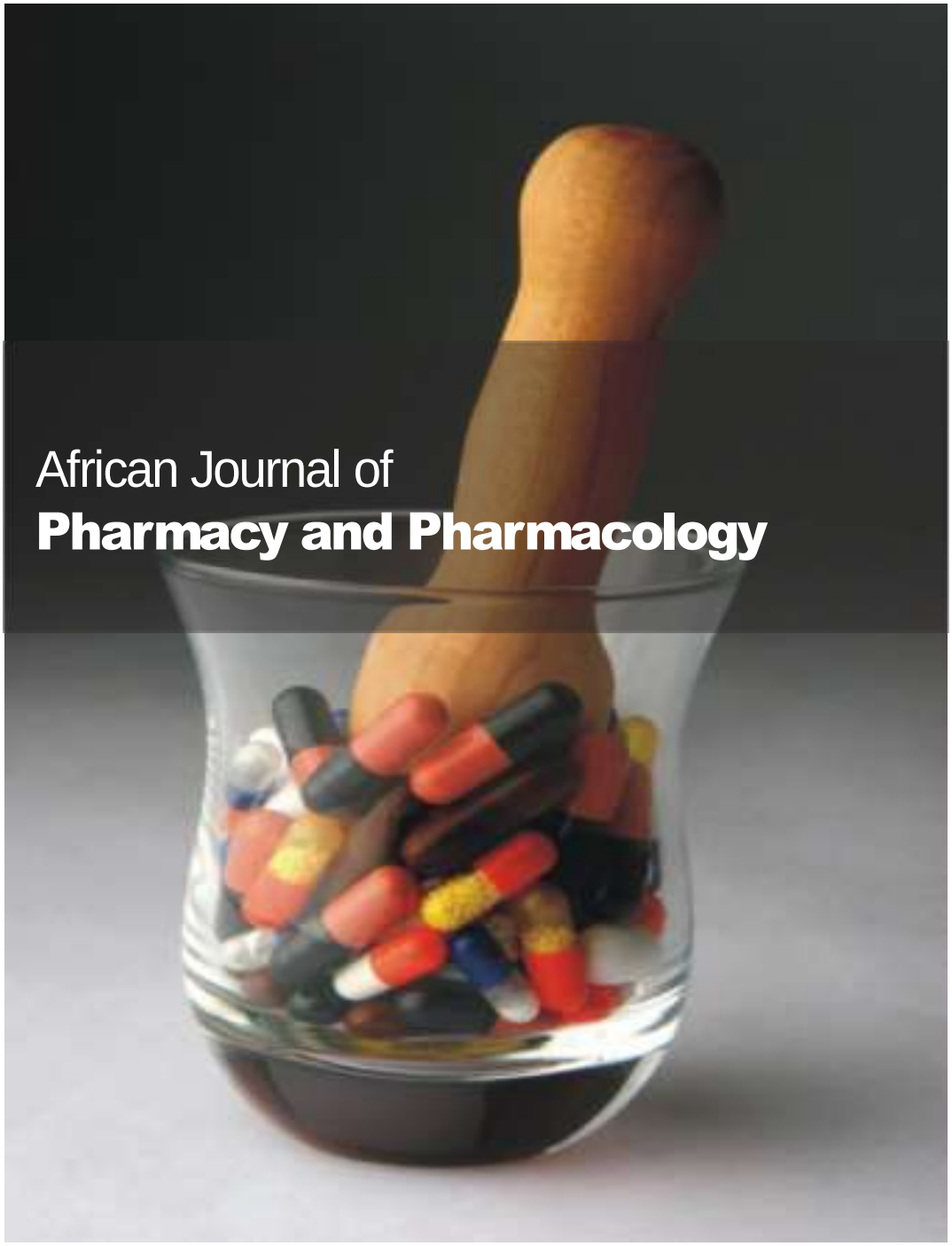

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Review

Modern approach of treatment on destroyable pathogenicity of malaria parasite: A review article

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Plasmodium **is the malaria parasite that completes the life cycle between two different hosts, such as human and** ***Anopheles*** **mosquito. These parasites go through several developmental stages like exo-erythrocytic stage that is absent in** ***Plasmodium falciparum*****, so relapses do not occur. The drugs which contain three P's like proguanil, primaquine, and pyrimethamine kill schizonts in the liver. Due to prolonged treatment of high dose of chloroquine, there may be serious side effects named as Bull's eye maculopathy. Atovaquone is rapidly acting blood schizonticide that acts by collapsing the parasite's membrane. Artemisinins are the fastest acting drugs against malaria. Mepacrine is an anti malarial drug which concentrates in collagen tissue. Infection by** ***P. falciparum*** **is the most lethal form of malaria, in this case agglutination of the infected RBC occurs and these agglutinised RBCs block the capillary vessels of the internal organs. Tafenoquine is a single dose medication for radical cure of** ***P. vivax*** **malaria. People with an enzyme problem G6PD deficiency can cause severe anaemia. At least two genes affecting red cells which are resistant to** ***P. falciparum*** **are autosomal gene for haemoglobin S (HbS) and the gene linked to sex G6PD variant gene. Anaemia is the main result due to malaria by haemolysis of infected and uninfected erythrocytes, dyserythropoiesis, splenomegaly and depletion of folate stores. Cerebral malaria is the most urgent complication that is manifested by confusion or coma by clusters of parasitized red blood cells to form large size cells of the capillary circulation which adhere to the vascular endothelium and block the circulation causing cerebral hypoxia and resulting to neurological symptoms and diagnosed cerebral malaria. Blackwater fever associated with falciparum malaria is mostly common with individuals that have taken antimalarial treatment irregularly or deficient in G6PD deficiency. Tropical splenomegaly is another symptom in falciparum malaria. HbAS was the genetic variant which associated with protection against malaria incidence and other variants such as alpha thalassemia, G6PD deficiency, polymormhism of genes encoding NOS_2A and TNF, as well as protection against uncomplicated malaria.**

Key words: Malaria, pathogenicity of malaria, parasite of malaria.

INTRODUCTION:

The innumerable microscopic and macroscopic forms which after attacking the human body manifest different diseases are known as pathogens and their activity are known as pathogenicity. Over the century, malaria has been the sustained thread to the urban areas of so many countries. Though according to the Greek mythology, it was so believed that this diseased condition accompanied by high fever and inflammation in spleen was often seen in local communities with poor hygienic condition, with this disease highly communicable. The term originated from Greek word *mal'aria*, which refers to polluted environment (Ali et al, 2011). Later on, in the year 1880, the Charles Louis Alphonse Laveran discovered that the disease was caused by protozoan parasite (*Plasmodium vivax*) infection which is transmitted by female *Anopheles* species mosquitoes.

Eventually, microbiological research revealed that five different species of *Plasmodium* genus protozoas, namely, *P. falciparum, P. vivax, P. ovale, P. knowlesi, and P. malariae* have been identified as causes of malaria in human (Anne et al, 2013). Among them it was reported that *P. falciparum* and *P. vivax* registers majority (>60%) of death cases in human. As per the WHO malaria report 2015, African countries are prone (70-80%) to be affected by malaria; whereas the south Asian countries registers (10%) of overall deaths worldwide. In 2015 worldwide, 214 million cases of malaria were identified, and 438 000 malaria deaths were reported in this survey (Beatriz et al, 2015). According to a survey report conducted in Ethiopia, malaria was considered the most common communicable disease in the country, as 75% of the total population are reportedly victims of malaria (Clark et al, 2004).

The parasite named as plasmodium genus can manifest the malaria in the human body in a serious manner. The rate of manifestation of the malaria depends on how fast the parasite replicates. Over 100 types of plasmodium parasites are able to spread the diseases in various species. Five different types of parasite named plasmodium can spread the diseases in human (Clark et al, 2004, Doolan et al, 2009; Francis et al, 2010).

MALARIAL LIFE CYCLE

Plasmodium genus parasites are transmitted into human blood stream after a bite from female *Anopheles* species mosquitoes; this parasite initiates the infections which thereafter travel to the liver and attacks hepatocytes, of thousands of merozoites in the blood stream. Merozoites in the bloodstream undergoes another asexual multiplication invading the RBCs (Red Blood cells) and forms mature schizont, which in turn further releases merozoites that attacks new erythrocytes (Doolan et al, 2009; Smith et al, 1995). The highest mortality rate of malaria is reportedly by *P. falciparum* and *P. vivax*, where *P. vivax* causes benign malaria, whereas *P. falciparum* causes most of the malignant malarias among young people (Eastman et al, 2011; Eltahir et al, 2010; Cox, 2010). *P. falciparum* contains trophozoites rings formed by cytoplasm and two chromatin dots, which is responsible for erythrocyte damage and facilitates malignant malaria.

Usually, all type of malaria is characterized by the incidence of anaemia, as it causes destruction of RBCs. A survey was carried out in Ethiopian young subjects who were admitted in hospital; the results obtained from the respective disciplines showed that the subjects with *P. falciparum* malaria had a high level of lymphocytes, other WBCs (White Blood cells) were within range, but the hemolysis was greater in patients having *P. falciparum* type of malaria when compared to other malarial parasites attacks. Due to impaired cytokine level, the healing of tissue damage also takes more time than the merozoites attack to the new cells (Clark et al, 2004).

SEVERITY AND THREATS FEATURED BY MALARIAL PARASITE

Apart from conventional and regular diseased state in vulnerable population living in poor hygienic places, there are several more severe threats accomplished with the attack of *Plasmodium* parasite specie. Blood circulation comprises RBC movement through the heart followed by passing through the spleen. Therefore, spleen hygiene is majorly dominated by blood cells, as it regulates the filtration of impaired or infected RBCs. However, focussing the pathogenicity of *Plasmodium* species on RBC, gives rise to the *P. falciparum* Erythrocyte Membrane Protein 1 (PfEMP1) in the iRBC membrane surface, resulting to elicitation of different inflammatory responses (Su et al, 1995; Baruch et al, 1995). Among them, TNF-α plays a key role as a cytokine, facilitates ICAM-1 expression, and enables followed by asexual multiplication resulting to production cytoadhesion of pRBC. Apart from TNF-α, (IL)-1b, IL-6 and IL-10 and endogenous NO (Nitric Oxide) also involves in the pathogenesis of malaria. NO is subjected to developing the host defence, as well as maintaining both the vascular permeability and microenvironment of organs. Splenomegaly, considered as the marker of *P. falciparum* transmission of infected areas indicates severe malaria caused by parasite, which in turn results to spleen enlargement. During the acute infection phase, uRBC,

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knob positive and negative iRBC accumulated in spleen (Prommano et al, 2005, Imbert et al, 2010) Moreover, *P. falciparum* infection causes cerebral malaria; a neurological disorder found in African countries. Generally, according to previous reports, children are the most vulnerable to the brain injury which can even lead to coma, caused by neurological disruption infected by *P. falciparum* parasite (Henry et al, 2012).

ANTIMALARIAL DRUGS AND DRUG RESISTANCE

The biggest threat to counteract malaria has been the drug resistance shown by parasites (more specifically by *P. falciparum*). The first line treatment against malaria parasite was designed by giving chloroquine with sulfadoxine/pyrimethamine combination. Chloroquine enters the haemoglobin, followed by protonation, causing acidification and binds with heme group, and ultimately causes lysis of parasite cell (Geleta and Ketema, 2016; Giha et al, 2005). Sulfadoxine/pyrimethamine causes enzyme (DHFR) inhibition in parasite cell, resulting to DNA damage. However, the recent manifestation against anti malarial treatment regimen is resistance to chloroquine. From a genetic point of view, *P. falciparum* parasites become spontaneously multigenic and are conferred primarily by mutations in a transporter (PfCRT) gene (Hall AP et al, 1975). This genetic postulation for resistance by *P. vivax* is not employed because the genetic mutation does not occur like PfCRT gene. Resistance to few more drugs belonging to quinine derivatives like Amodiaquine, Mefloquine, Piperaquine have developed resistance evidentially by *P. falciparum* (Hart and Naunton, 1964; Heinonen et al, 1977). A treatment schedule was designed by China and that attempt as anti malarial therapy was awarded Nobel prize in 2015, with the application of Artemisinin derivatives along with quinine derivatives and Sulfadoxine/ pyrimethamine. Artemisinin causes protein damage of parasite cell by activating free radicals in heme group of erithrocytes. The therapy facilitates a better efficacy against *P. falciparum* parasites, because Artemisinin have shorter half life whereas quinine derivatives as combination therapy have longer elimination half-life. However, from a recent survey, acceptance of this therapy is still debatable, because among people from the south east Asian countries, and due to low immunity level in community and greater risk associated with mutation of parasite genotype have conflicted so many arguments (Hodder et al, 2009; Kaiser et al, 2004; Kochar et al, 1995).

ANTI MALARIAL DRUG IN PREGNANCY

Evidently,anti-malarial drug Chloroquine causes impaired fetal toxicity during third trimester, due to slow clearance rate from plasma (Korenromp et al, 2003, Lewis and Ponnampalam, 1975). It is also relatable that the awful thread to the African and SE Asian countries as the Chloroquine is becoming resistant to *P. falciparum* parasites, the breakdown of erythrocytes may worsen the fetal health; thus, treatment options are becoming much intricated (Li et al, 2002). Quinine was the first invented anti-malarial drug, without having any reported teratogenicity, but the patient compliance is very much poor after the completion of total course because it causes hypoglycaemia. This can be indirectly harmful to pregnancy (Marsh et al, 1998, Matuschewski et al, 2002) also, some study report on animals revealed that the quinine dose may cause nerve damage in cranial nerve (Miller et al, 2002). Another drug combination which have been popular over the years (sulfadoxine and pyrimethamine), have also shown some dose related embryo toxicity in pregnant rats in animal study. This is a fundamental fact that 5-methyl tetrahydrofolate demethylated to form the active forms of folate (tetrahydrofolate) is independent of enzyme dihydrofolate reductase which is inhibited by pyrimethamine (Mutabingwa et al, 1991; White et al, 1985). However, several studies on human female volunteers clinically postulated that the treatment procedure resulted to an increased risk of malformations, kernicterus or any other severe effects on the fetus (Paufique and Magnard, 1969; Phillips-Howard and Wood, 1996; Phillipson, 1991). Artemisinin derivatives are the recently innovated group of drugs which has been very popular in SE Asia and part of Africa due to the fact that till now there has not been any noticeable resistance by parasites. These derivatives include Artesunate, Artemether, and Arteether used in severe or complicated malaria. But the biggest concern of this drug is regarding the susceptibility towards pregnant population. Few animal studies reported that the high dose formulation produced embryo-fetal toxicity, cardiovascular malformations and skeleton abnormalities (Plowe et al, 2003).

GENETIC MODIFICATION AS AN APPROACH FOR MALARIA TREATMENT

One of the recent advanced approach to treat malarial parasite involves determination of specific genes responsible for encoding in protozoan cell and present during pre-erythrocyte and liver stage. The salient feature of this attempt would be tricky and advantageous avoiding drug resistance and minimizing the probable toxicity caused by combination therapy. Few genes (e.g. UIS) are expressed in pre-erythrocytic stage in sporozoites which causes infections in erythrocytes in the mammalian host. However, it can be postulated that, targeting the UIS proteins at erythrocyte levels could be a sharp approach which may lead to attenuation of the liver-stage parasite. In an independent study, a protein

UIS3 was identified which encodes a transmembrane of parasite sporozoites. The protein structure was altered and the alteration could be checked by RT-PCR. This will contribute to the inability of the host-cell invasion capacity (Rustaiyan et al, 2009; Baragaña et al, 2015). Another study was carried out in Kenya, where an attempt was taken to find out genetic diversity and prevalence of malaria drug-resistant mutations in different geographical regions (Schlagenhauf et al, 2004). Different patients, suffering from malaria were randomly chosen based on different treatment groups they are getting. Different genes were analysed (like Poly a, Pfg377, 2490, TA 81, TA 87, Ara2, TA1, PfPK2, Ta109, and TA42) isolated from *P. falciparum* positive samples (Schultz et al, 1994). PCR was carried out during the analytical phase in specific DNA template, specific volume and given temperature, to obtain proportion of multiclonal infections and number of infections with more than one allele at ≥8. Different mutations were observed emphasizing the drug resistant malaria mutations (Bala et al, 2018). Nine codons in four genes for resistance to chloroquine and Sulfadoxine/ pyrimethamine: pfcrt (K76T), pfmdr1 (N86Y, N1042D, and D1246Y), pfdhfr (N51I, C59R, and S108N), and pfdhps (A437G and K540E). Genomic DNA from *P. falciparum* clones HB3, W2, and Dd2 (MR4, Manassas, VA) were used as positive control. The overall genetic diversity was studied and compared, and the obtained result showed that, Sulfadoxine/pyrimethamine-resistant mutants at the *pfdhfr* codon 51, the *pfdhps* codons 437 and 540 were significant (Schlagenhauf et al, 2004). However, modification in the mutation could be a remarkable approach to counter drug resistant malaria Schultz LJ et al, 1994- Sourav et al, 2018).

Approaches with phytomolecules as anti-malarial treatment

Choice of phytoconstituents instead of synthetic compounds was always preferable to treat diseases, as it causes less toxicity and cheaper too (Sourav et al, 2018, Asis et al, 2017, Naskar et al, 2011). Due to geographical variance and genetic manifestation, a lot of synthetic compounds have grown resistance. There are also few groups of drugs which can be harmful to pregnant women (Mohammed et al, 2018) Thus, scientists are in search of such molecule which should have moderate safety profile and also should be new entities that would not show resistance. The basic mechanism of action of the plant extract or molecule should be concentrated on how the growth of parasite is inhibited or the mechanism of transforming the biochemistry which in turn causes death of parasite (Schultz et al, 1994). Previously, in the mid eighteenth century, the revolutionary discovery by French scientist was the isolation of alkaloidial moiety of quinine from Cinchona species of plant (Sutherland et al, 2010). Afterwards, it was found that quinine derivatives developed resistance, in the SE Asian and few parts of African countries. Another invention of active compound of Artemisinin from *Artemisia annua* was a breakthrough in medical research, which was useful in condition where there was chloroquine resistant malaria (Plowe et al, 2003). It was currently found that, in two different studies (Sutherland et al, 2010; Verhoeff et al, 1998) *Artabotrys hexapetalus,* a plant along with another plant found in Iran (*Artemisia diffusa*) contains endoperoxide; a compound from sesquiterpene group is present which provides a synergistic action as anti malarial treatment when used in combination with chloroquine. However, the chloroquine induced resistance against *P. falciparum* can be overcome and several *in vivo* studies revealed that it showed relatively low toxicity (West and Wichita, 1938; Naskar et al, 2011).

Modern emerging tools to treat malaria

New therapeutics invention has sparked spontaneous interest among scientists, and still there is so much scope on malarial drug research. As a new therapeutic tool, a specific papain-like proteins SERA and its analogs was targeted. From a background study, the *P. falciparum* invades erythrocytes very rapidly, where specific proteins play a key role in parasite life cycle. A specific antigen SERA, is expressed in malarial cell parasitophorous vacuole, which protects parasites from host cell phagolysosome. SERA5 an analogue of SERA is broken down by SUB1 enzyme during asexual blood stage (White et al, 1999; White et al, 2004; Ruecker et al, 2012). Disruption of both SERA4 and SERA5 proteins causes impaired replication, as well as invaded rupture of host cell (World Health Organisation, 2015). This strategy of modification of SERA proteins could be a significant tool to control malaria.

Another approach was attempted (Wright et al, 2009) where a new molecule was designed (DDD107498), whose molecular mechanism of action was unique from other anti malarial drugs. This reportedly can show activity against different life cycle stages of different malarial parasites. The molecule targets a specific translation of protein elongation factor 2 (eEF2), which enables translocation of ribosome analogue messenger RNA, which is an important tool for protein synthesis.

Conclusion

As medical research is developing rapidly by the course of time, new molecules and strategies are being employed to explore more opportunities. Malarial research has been one of such concern for so many years. The different species of parasites is modifying their genetic morphology predominantly, and is randomly challenging the older treatment options. Drug resistance

have also been observed as another issue. Some drugs cause toxicity in individuals. Thus, new treatment remedies with phytocompounds or gene-based therapy would be beneficial.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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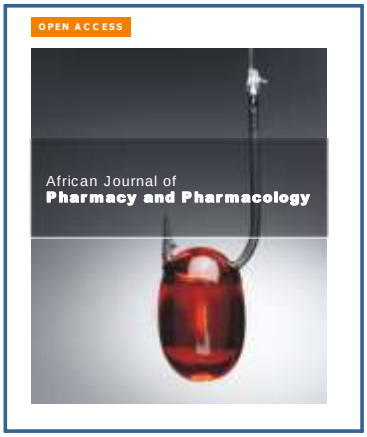

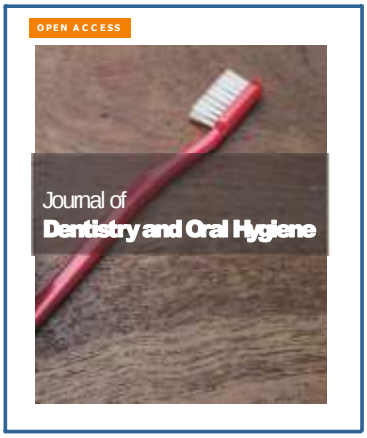

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