

Review Article

UNDERSTANDING OF MALARIA AND ITS THERAPEUTIC REGIMENS – THE WAY FORWARD

ABSTRACT

Aim: Malaria is a very serious deadly disease that has attracted the attention of many researchers all over the world. Because a lot of work has been done in the area of malariology, there is need to understand advance pattern and its therapeutic regimens.

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Methods: Past and recent literatures on malaria were searched for information on history, global situation, classification, biology, pathology, pathogenesis, diagnosis, treatment and control of malaria to assess the progress made so far in the area of malariology.

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Results: Malaria is an ancient disease recognized by Hippocrates over 2413 years ago, caused by Plasmodium species, first identified by Charles-laveran 123 years ago affect 300 – 500 millions human worldwide, responsible for 3 deaths in every 30 seconds. The knowledge of classification, biology, pathology, pathogenesis, diagnosis and treatment of malaria is a tremendous achievement towards the control of the disease.

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Conclusion: But complete elimination of malaria perhaps will still take another time, since a lots need to be known about the molecular biology of antigenic shift and drift, nature and mechanisms of action of the parasite toxin, in order to have basis for definite vaccine development. By so doing, radical cure and total eradication of malaria can be achieved.

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Keywords; Malaria, Hippocrate, Laveran, antigenic shift, radical care, eradication.

1.0 INTRODUCTION

Malaria is an infectious disease caused by a protozoan of the phylum: *Apicomplexa*, class: *Sporozoea*, subclass: *Coccidia*, suborder: *Haemosporina*, family: *Plasmodidae*, genus *Plasmodium* and transmitted by the female mosquito of the genus *Anopheles* when it feeds by sucking human blood and whose life cycle alternates between man and mosquito.^[1] An

34 anopheline mosquito inoculates plasmodium sporozoites to initiate human infection.
35 Circulating sporozoites rapidly invade liver cells. Exoerythrocytic stage tissue schizonts
36 mature in the liver and invade erythrocytes. Only erythrocytic parasites cause clinical illness.
37 Repeated cycles of infection can lead to the infection of many erythrocytes and serious
38 disease. Sexual stage gametocytes also develop in erythrocytes before taken by mosquitoes
39 where they develop into infective sporozoites ^[2,3]. The means of infection are through
40 infective mosquito bites, contaminated syringes and vertical transmission from mother to
41 foetus through placenta ^[4,5]. Malnutrition, splenomegaly, and anaemia are the expected
42 complications of repeated attacks of malaria ^[1,2].

43 The emergence of resistant malaria in addition to the toxicity of drugs currently used
44 as anti-malarials has created a major concern and an urgent need for development of new
45 anti-malarial agents. Throughout the world, herbs have sustained man not only as source of
46 food but also as medicines utilized in various ways for varied purposes. In the last decade,
47 people have become increasingly aware of the use of medicinal plants for the treatment of
48 diseases ^[6]. In developing countries, it is important to know the therapeutic potentials of
49 substances from natural sources, since local drugs could be of great value and substitute for
50 the more sophisticated and expensive drugs. Therefore, there is need to find cheaper and
51 pharmacologically active substances from natural products and this has defined the
52 research goals of developing nations as encouraged and recommended by the World Health
53 Organization ^[7].

54 Traditional healers have made various efforts to control diseases including malaria-
55 using herbs. Few of these plants have been properly identified and documented. Only a very
56 small percentage of the plants with ethnopharmaceutical potentials have been subjected to
57 scientific analysis hence their safety and efficacy are questionable ^[8]. World Health
58 Organization (WHO) in recognition of the increased value of herbal medicine in primary
59 health care, especially in developing countries has advocated for the proper identification,
60 sustainable exploitation, scientific development and appropriate utilization of herbal
61 medicines, which provide safe and effective remedies in medicine ^[9]. Investigation on the
62 risks associated with prolonged and improper use of some herbal drugs revealed a potential
63 for toxic and teratogenic effects in biosystem ^[10], yet scientific information and the results
64 of comparative studies are scarce on the effectiveness and safety of most traditional
65 remedies and techniques ^[11]. Of the estimated 300,000 plants species acclaimed worldwide

66 as possible pharmaceutical candidates, only about 5% have been investigated scientifically
67 for medicinal properties ^[8].

68

69 1.1 JUSTIFICATION

70 Malaria is the worst human problem at the moment. There were an estimated 247
71 million malaria cases among 3.3 billion people at risk in 2006, causing nearly a million
72 deaths, mostly children under 5 years and 109 countries were endemic for malaria in 2008,
73 but 45 countries are within African region. More than 1 reported cases per 1000 population
74 per year was reported in 2006. Nigeria accounts for a quarter of all malaria cases in the
75 African region and almost all cases are caused by *P. falciparum* with recorded 57,506,430
76 malaria cases and 225,424 deaths in 2006. In 2007, Nigeria was the 7th malaria country.
77 Treatment is ~~one of the recommended policies and strategies~~ for malaria control ^[12]. The
78 disease causes ~~wide spread~~ death and suffering, ~~imposes financial hardship on poor and~~
79 ~~household, holds retards~~ economic growth and improvement in living standard ^[13]. Between
80 10 and 13% of maternal deaths are caused by malaria in endemic countries and
81 spontaneous abortions are reported in up to 60% of maternal malaria cases ^[14]. The rapid
82 spread of resistance to antimalarial drugs present a potentially devastating threat to
83 effective, safe and affordable treatment. Chloroquine was the main drug used for decades,
84 but increasing resistance forced its replacement with other antimalarial drugs ^[13], 40 – 60%
85 of malaria cases in Nigeria have been reported not to respond to treatment with the drug
86 ^[15]. Toxicity of antimalarial drugs and lack of vaccine against malaria have compounded
87 problems in malaria chemotherapy ^[15]. While large number of people in the rural areas of
88 developing countries still consume crude decoctions and concoctions of medicinal herbs ^[16].
89 Scientific and technological advances in the field of chemotherapy will boost malaria control
90 ^[17].

91 Since prehistoric times, plants based medicines have been in use for treatment of
92 diseases until synthetic drugs were developed in the 19th century. Today the use of herbs
93 continue to exist throughout the developing world, while 40% of prescription drugs are still
94 herb based remedies for treatment of illnesses ^[18, 19]. Phytochemicals are protective,
95 disease preventing plant substances ^[20]. Natural products in several developing countries
96 are still the mainstay of all medicines ^[21]. The most commonly used sources of drugs are
97 herbs, plant extracts, seeds, leaves, barks of certain plants, tubers and roots. Noteworthy in

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this regard is the use of single remedy or plant extract to treat more than one disease and combination of various plants extracts for broad-spectrum therapy. Within the context of traditional practice, decoctions or infusions of plants have been used commonly to treat malaria and malaria symptoms. There are numerous illustrations of plant based antimalaria drugs. Quinine is an important drug of plant origin with history of long use. This alkaloid occurs naturally in the bark of *Cinchona* tree, and is used in the treatment of malaria apart from its use to relieve nocturnal leg cramps ^[22]. *Artemisia annua* has been in use for more than 2000 years and is found effective in the treatment of malaria ^[23]. The plant, *Azadirachta indica* has been used extensively for malaria treatment in Nigeria and was proven to have antimalarial activity ^[24]. Other plants that have been used include; *Sida acuta*, *Carica papaya*, *Vernonia amygdalina*, *Khaya senegalensis*, *Nuclea latifolia*, *Anacardium occidentale*, *Mangifera indica*, *Scleocarya birrea*, *Spondia mombin*, *Balanites aegyptica*, *Newboldia laevis*, *Commiphora kerstingii*, *Allium sativum*, *Tridilia emetica*, *Phoenix dactylifera*, *Piper guinense*, *Neocarya macrophylla* ^[25], *Achillea millefolium*, *Baccaris trimera*, *Lippia alba*, *Matricaria chamomilla*, *Mikania glomerata*, *Tanacetum pathenium* ^[25], *Duguetia furfuracea*, *Xylopia emarginata* ^[27], *Centella asiatica* ^[28], *Bupleurum montanum*, *Bupleurum plantagineum* ^[29], *Ferula opoda* ^[30], *Cynodon dactylon* ^[30], *Setaria magaphylla* ^[32], *Momordica foetida* ^[33], *Momordica charantia*, *Curcubita maxima* ^[31,4], *Phyllanthus amarus* and *Phyllanthus niruri* ^[35]. [The alkaloids lysicamine, trivalvone, palmatine, jatrorrhizine and columbamine from *Annickia kummeriae* showed strong to moderate antiplasmodial activities with IC₅₀ value of 2.8 – 14.3 µg/ml](#) ^[36]. [Two stilbenes, longistylin A and C and betulinic acid showed a moderately high in vitro activity against p. falciparum strain 3D7](#) ^[37]. Tropical plants that are used for the treatment of malaria in over 100 underdeveloped and developed countries of the world are provided in table 1.

Many plant genera were found to be used either alone or in combination with each other for the treatment of malaria. The plants are mainly of the families *Rubiaceae* and *Apocynaceae* and a few from the families *Bombaceae*, *Loganaceae*, *Rutaceae*, *Solanaceae*, *Meliaceae* and *Gramniae*. Plants used for malaria medicines vary enormously from one community to the other, in both the choice of plant and methods of preparations. Complementary to oral therapy is steam treatment, where the patient is covered with a thick blanket or cloth and subjected to the vapours from a steaming pot of herbs (ingredient of this hot pot include the leaves of lemon grass, paw-paw, mango, and guava). Sometimes

the leaves of these plants are used for the preparation of “teas” typical teas are made from lemon grass (*Cymbopogon citratus*), lime (*Citrus aurantifolia*) and sometimes guava leaves. This form of treatment is recommended usually for mild attacks of malaria ^[16]. Coker and Adesegun compiled a list of over 200 medicinal plants claimed by traditional healers and communities to have antimalarial activity^[386].

In spite of several pitfalls encountered in the medicinal plant research, the prospects of developing indigenous drugs for health care delivery systems should be viewed positively ^[37,3839, 40]. In a broader perspective, plants are economic source of a number of important drugs such as morphine, atropine and digoxin. The perpetual biodiversity in nature will continue to provide newer species of plants for production of newer drugs. However, species of plants yielding better quantity of the desired chemicals such as active principles can be developed through genetic engineering while their production can be accelerated through tissue culture techniques ^[3739]. The objective of producing affordable, potent and safer drugs from plants can be met to certain extent by promoting formulations of medicines in their natural or semi-processed form (powder or extracts) from plants as used in traditional medicine for some disorders. Standardization especially in respect of dosages will be necessary through controlled clinical trials to prove their efficacy and safety ^[39]. Research on medicinal plants need to be conducted across all geographical regions of the world, this will highlight the effect of climate, soil chemistry and other environmental factors on the quality of the plant products ^[39, 4041, 42]. The Nupe ethnic group from Bida emirate have been using *Abrus precatorius* leaf for the treatment of both acute and chronic malarial symptoms. The use of *Abrus* leaf in the treatment of malaria among Nupes is sometimes either the last option after drugs have failed or due to poverty ^[4344]. High cost, increased toxicity level and emergence of parasites resistant to antimalarial drugs (e.g. chloroquine) have made eradication of malaria by chemotherapy difficult and threatened to render current antimalarials obsolete ^[442].

2.1 HISTORICAL BACKGROUND OF MALARIA

Human malaria has been recognized since the earliest period, and the occurrence of mosquitoes trapped in amber suggests its prevalence in prehistoric times ^[453]. Malaria is an ancient disease recognized by Hippocrates about 400 BC. He described the three characteristic stages of malaria attack as chills, high fever and profuse sweating ^[464].The first

evidence that *plasmodium* was the aetiological agent of malaria was recognized by Charles Laveran in 1890 as he scanned a live mount of a febrile soldier's blood at Constantine University Hospital in Algeria ^[475]. Laveran noted pigment granule containing red blood cells in various forms of elongated or crescent shape disfigurement. Translucent round cells with pigmented granules were also seen, and most notably, amoeboid-like cells possess long whipping strands that dramatically interacted with and were capable of "drawing in" neighbouring red blood cells. Laveran understood that he was looking at the malaria pathogen and this observation stands as a singular historical event in providing support for a protozoan basis of disease. Twenty years later, MacCallum ^[46, 4748, 49] described exflagellation the whipping motions of the sinuous flagella as the extrusion of male gametes after emergence from within red blood cells a process, which occurred in the gut of the mosquito vector ^[48, 4950, 51]. A variety of names were used to describe the disease and they include the shakes, march, noman, jungle, intermittent fever, ague and chills ^[520]. The work of Laveran, Ross, MacCallum ^[45 4947 - 51], and some other malariologists ^[520] showed the occurrence of developmental cycle in the blood corpuscles and the transmission through mosquitoes. By the early part of the last century, it was believed generally that the broad outlines of the life cycle was known fully, with sporozoites injected by a mosquito bite, thought to enter the cells directly and undergo schizogony. However the actual penetration of a corpuscle was described by Schaudin ^[4446] who observed that sporozoites, on entering the blood did not directly enter red blood cells as formerly thought but within half an hour were carried to reticuloendothelial system (usually, the liver) where they underwent a schizogony circle ^[4345].

2.2 MALARIAL GLOBAL SITUATION

According to World Health Organization (WHO), each year 300 to 500 million people living in the tropics and subtropics are infected with malaria parasites with nearly 3 million (mostly children) dying ^[5453]. About 1.5 billion people are known to live in the regions where malaria is endemic. The regions are central and northern South America, tropical Africa, North Africa including the Nile valley, parts of Middle East, Central Indian Subcontinents and South East Asia excluding Hong Kong and Macao and East Indies. Malaria is imported into the United Kingdom with 1500 – 2000 cases reported each year, and 10 – 20 death. Approximately three-quarters of reported malaria cases in the UK are caused by

plasmodium falciparum^[5254]. About 93% of the 550 million people living in Africa are at risk of malaria and over 90% of the 300-500 million clinical cases reported from Africa^[5355]. Malaria occurs in 100 countries with about 40% of the world's population at risk^[5456]. Malaria epidemics are on the increase due to fabricated conflicts and climate associated disasters causing the movement of non-immune populations to malaria endemic areas^[5557]. Urban and periurban malaria are now substantial problems in certain areas of Asia and Africa. Malaria is becoming more difficult to manage because of multi-drug resistance ~~since effective drugs are unavailable~~^[5658]. Malaria is directly responsible for one in five childhood deaths in Africa and its resurgence in Africa contrasts dramatically with the global decline in mortality since 1900^[13]. Nigeria accounts for a quarter of all malarial cases in the WHO African region. Transmission in the south occurs all-year round and is more seasonal in the north^[12]. In Nigeria malaria affects more people than it did in the 1960s^[5759]. Fifty percent (50%) of Nigerian population experience at least one episode of malaria every year. The Federal Ministry of Health reported that one in four people suffer from malaria at one time or the other^[2]. Transmission in tropical countries is highly heterogenous spatially and seasonally. Plasmodium falciparum is known to cause the majority of severe clinical disease^[5960].

About 110 million Nigerians are at risk of infection from malaria parasites^[5861] and malaria is responsible for deaths before the age of 5 years in 1/5 and 1/3 of children in urban and rural areas respectively^[6062]. In Nigeria and probably in other parts of West Africa, the predominant parasite is *Plasmodium falciparum* (75%). Others are *Plasmodium malariae* (15%) and *Plasmodium ovale* (3%) with *Plasmodium vivax* probably not found in West Africa (James and Gilles, 1985). Funding for malaria control in Nigeria was increased from US\$ 17 million in 2005 to US\$ 60 million in 2007, provided by the government, the Global Fund and the World Bank^[12]. False positivity under reporting of mixed infections and a significant number of species mismatch needs attention and should be improved for appropriate diagnosis. The detection of substantial of false positive results by molecular methodologies may provide the accurate incidence of circulating plasmodium species in the geographical regions and has important repercussions in understanding malaria epidemiology and subsequent control^[63]. More systemic, timely, and empirically based approaches are urgently needed to track the rapidly evolving landscape of malaria transmission in Africa^[64].

226

227 2.3 CLASSIFICATION OF MALARIA

228 Malaria fever has been categorized as benign, simple or tertian (caused by
229 *Plasmodium vivax*) or aestivo-autumnal, malignant tertian, pernicious quotidian, subtertian
230 or tropical (caused by *Plasmodium falciparum*) or quartan ague or quartan malaria (caused
231 by *Plasmodium malariae*) or ovale tertian malaria (caused by *Plasmodium ovale*).
232 *Plasmodium vivax* shows the widest distribution, being prevalent throughout the tropics and
233 many temperate regions and characterized by relapses: reappearances of symptoms after a
234 latent period of up to 5 years, as is infection with *Plasmodium ovale*, which occurs chiefly in
235 tropical Africa. Such relapses are due to the sudden activation of hypnozoites (sleeping
236 merozoites) in liver cells. *Plasmodium malariae* is much less common than *Plasmodium*
237 *vivax* and *Plasmodium falciparum*. Although falciparum malaria and malariae malaria do not
238 show relapses, they are subjected to 'recrudescence' repeated manifestation of infection
239 after a relatively short latent period between 3 months and 1 year^[4345]. Malaria genetics
240 reveal many peculiarities. There is immunity amongst Africans living in endemic areas that
241 are exposed to repeated reinfection (premonition). There are racial differences in
242 susceptibility; and resistance is associated with certain genetic factors; e.g. haemoglobin S,
243 which is common amongst Africans with sickle cell anaemia trait with lethal effect^[2].
244 ~~Nevertheless, confers resistance to falciparum malaria, just as in those whose erythrocytes~~
245 ~~are deficient in glucose 6-phosphate dehydrogenase enzyme^[2]. The means of infection are~~
246 ~~through infective mosquito bites, contaminated syringes and vertical transmission from~~
247 ~~mother to fetus through placenta^[5].~~

248

249 2.4 BIOLOGY OF MALARIA PARASITES

250 The plasmodium life cycle is complex with a number of different forms that differ in
251 microscopic appearance and antigenicity. In the human host, sporozoites, the infectious
252 form injected by the mosquito, are carried by the blood stream to the liver, where they
253 infect liver cells. In these cells, each parasite enlarges and subdivides, producing thousands
254 of merozoites, which are then released into the bloodstream and establish the cycle
255 involving the erythrocytes. The parasite grows and divides in the erythrocytes of the host.
256 The earliest form resembles a ring, with a large pale food vacuole in the central area, with
257 the nucleus and cytoplasm being pushed to the periphery. This develops into a larger motile

258 trophozoites, which goes on to subdivide, producing a schizont. The infected erythrocytes
 259 then break open, and the offspring of the division called merozoites (6 – 32) which after 5 –
 260 16 days, months or years ^[654] are released into the plasma. The duration of this cycle varies
 261 with species of plasmodium, *P. falciparum* (6 days), *P. ovale* (9 days), *P. vivax* (8 days) and *P.*
 262 *malariae* (14 days). The merozoites then enter new erythrocytes and multiply, repeating the
 263 cycle. The erythrocytic cycle takes 2 days for *P. falciparum*, *P. vivax* and *P. ovale* and 3 days
 264 for *P. malariae*. The attack of fever occurs at the rupture of the erythrocytes and release of
 265 the merozoites ^[6062]. The symptoms last for 12 to 24 hours ^[6266]. Some merozoites that enter
 266 erythrocytes develop into gametocytes, which are specialized sexual forms. Male and
 267 female gametocytes transforms into about half dozen tiny whip-like gametes that swim
 268 about until they unite with the female gamete. The resulting zygote transforms into a motile
 269 form that burrows into the wall of the midgut of the mosquito and forms a cyst, which
 270 enlarges as diploid nucleus that undergoes meiosis, dividing asexually into numerous
 271 offspring. The cyst then ruptures into the body cavity of the mosquito, and the released
 272 sporozoites find their way to the mosquito's salivary gland and saliva, from which they must
 273 be injected into a new human host ^[63, 6467, 68]. The incubation period for malaria is between
 274 10 – 35 days ^[6465]. Mosquito is the definitive host. The only function of human is to enable
 275 the parasites infect more mosquitoes, so that further sexual recombination can occur.
 276 Asexual cycle takes place in man while sexual cycle takes place in mosquito ^[6569]. Although
 277 malaria can be transmitted by transfusion of infected blood, congenitally, and by sharing
 278 needles, infection usually is transmitted by the bite of infected female Anopheline
 279 mosquitoes. Once the tissue schizonts burst in *P. falciparum* and *P. malariae* infections, no
 280 forms of the parasite remain in the liver. High prevalence of placental malaria has been
 281 reported in Nnewi, South Eastern Nigeria ^[70]. However, in *P. vivax* and *P. ovale* infections,
 282 tissue parasites (hypnozoites) persist that can produce relapses of erythrocytic infection
 283 months to years after the primary attack. Once plasmodia enter the erythrocytic cycle, they
 284 cannot reinvade the liver; thus, there is not tissue stage of infection for malaria contracted
 285 by transfusion. The merozoites invade more erythrocytes to continue the cycle, which
 286 proceeds until death of the host or modulation by drugs or acquired partial immunity. For
 287 erythrocyte invasion, merozoites bind to specific ligands on the red cell surface ^[6671]. *P.*
 288 *falciparum* has a family of binding proteins that can recognize a number of host cell
 289 molecules, including glyophorins A, B, and C, as well as band 3. It is able to invade all stages

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of erythrocytes and therefore can achieve high parasitemias, *P. vivax* is more selective in its binding; it needs to recognize the Duffy chemokine receptor protein as well as reticulocyte-specific proteins; thus, it will not establish infection in Duffy-negative individuals and will only invade reticulocytes. Because of this restricted subpopulation of suitable erythrocytes, *P. vivax* rarely exceeds 1% parasitaemia in the bloodstream. But in Asia and the America, *P. vivax* is a more common cause of malaria^[72]. The Fy (a-b-) phenotype is most common in the area where there is little *P. vivax* malaria^[73]. *P. ovale* is similar to *P. vivax* in its predilection for young red blood cells, but the mechanism of its erythrocyte recognition is unknown. *P. malariae* recognizes only senescent red cells, maintains a very low parasitemia, and typically cause an indolent infection^[6774]. *P. falciparum* assembles cytoadherence proteins (the PfEMP3s encoded by a highly variable family of var genes) into structures called knobs on the erythrocyte surface. This allows the parasitized erythrocyte to bind to the vascular endothelium, to avoid the spleen, and to grow in a lower oxygen environment. For the patient, the consequences are microvascular blockage in the brain and organ beds and local release of cytokines and direct vascular mediators such as nitric oxide, leading to cerebral malaria^[6875]. Recently, *Plasmodium cynolphi* a monkey *Plasmodium* species has been discovered in a 39-year-old woman from malaria free area with no previous history of malaria or travel to endemic area^[76].

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2.5 PATHOGENESIS OF MALARIA

Plasmodium falciparum is not only the most common in Africa but also is the most virulent, and enjoys the reputation as the greatest killer of mankind being particularly dangerous to children^[2] and responsible for all severe complications and deaths^[3]. Infective female Anopheles mosquito injects saliva containing plasmodia sporozoites, which enter the parenchyma cells of the liver usually within 1 hour^[1]. The merozoites rupture out from the liver into blood stream and invade erythrocytes^[6977]. Each species has a specific receptor on erythrocytes it attaches. For example *Plasmodium vivax* attaches to the duffy blood group antigen and many natives of West Africa lack this antigen and therefore are resistant to *Plasmodium vivax*^[7978]. Genetic resistance to malaria occurs through both modifications of the immune system that enhance immunity to this infection and also by dangers in human red blood cells that hinder the malaria parasite's ability to invade and replicate within these cells. Host resistance involves Blood cell genes, abnormal

322 hemoglobins ^[79]. Several inherited variants in erythrocytes have become common in
 323 formerly malarious parts of the world as a result of selection exerted by this parasite ^[80].
 324 Persons with α -thalassemia HBC and HBE have some degree protection against the parasite
 325 ^[81]. South-East Asian ovalocytosis offers protection against cerebral malaria in children by
 326 reducing sequestration of erythrocytes parasitized by *P. falciparum* in the brain
 327 microvasculature ^[82]. Adhesion of *P. falciparum* – infected red blood cells to CD36 is
 328 enhanced by the trait and higher efficiency of sequestration could determine a different
 329 organ of distribution of sequestered infected red blood cells ^[83]. Endogamy along caste and
 330 ethnic lines appear to have confined malaria resistance via multiple genes to many
 331 community of Nepal and India ^[84]. Humoral and cell-mediated immune response limit
 332 malaria parasite multiplication and many cytokines contribute to pathogenesis and
 333 resolution of malaria ^[85]. The infections in the millions of different red blood cells nearly
 334 become synchronous, rupture and release daughter protozoa at the same time. For *P.*
 335 *malariae* the cycle takes 72 hours so that fever appears every third day ^[6468]. In other
 336 species of plasmodia, rupture occurs every 48 hour. The liberated merozoites rapidly infect
 337 a new population of erythrocytes initiating the next cycle of fever and chills ^[7078]. The
 338 merozoites enter red cells and differentiate into male and female gametocytes, which are
 339 ingested by blood sucking female Anopheles mosquito. *Plasmodium vivax*, *Plasmodium*
 340 *malariae* and *P. ovale* parasitaemia are of relatively low grade because the parasites favour
 341 either young or old red cells; *Plasmodium falciparum* invades red cells of all ages including
 342 the erythropoietic stem cells in bone marrow, so parasitaemia may be very high ^[6977].
 343 *Plasmodium vivax* and *Plasmodium ovale* prefer young red cells and *Plasmodium malariae*
 344 prefer aged red cells. *Plasmodium falciparum* has no secondary phase and the infection is
 345 resolved in 3 years (usually within 1 year) ^[7078]. *Plasmodium malariae* had occurred as long
 346 as 10-53 years in the infected humans after initial exposure especially after splenectomy.
 347 The spleen appears to be involved in the prevention of maturation of parasites thereby
 348 preventing reinfection ^[7486]. *Plasmodium malariae* with its prolonged latency is the most
 349 common cause of transfusion malaria in non-endemic areas, whereas *Plasmodium*
 350 *falciparum* and *Plasmodium vivax* are the most common cause of malaria worldwide ^[70].
 351 Patients with malaria often exhibit laboratory abnormalities due to an acute phase
 352 response. Lipid profile changes are characteristic for malaria ^[7287]. Changes in high-density
 353 lipoprotein and very low-density lipoprotein in human serum are related to lipid metabolism

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of plasmodium vivax^[7388]. [Dilated cardiomyopathy related cytomegalovirus –induced myocarditis has been reported in vivax malaria in an Amazonian child](#) ^[89].

2.6 PATHOLOGY OF MALARIA

The most characteristic symptom of malaria is the occurrence of paroxysm of fever with temperatures of up to 40-41°C at regular intervals-every 48 hours (*Plasmodium falciparum*, *Plasmodium ovale* and *Plasmodium vivax*) or 72 hours (*Plasmodium malariae*) tertian or quartan fever – alternating with good periods of no fever ^[2, 9074]. The periodicity of parasitaemia and febrile manifestation is preceded by headache, lassitude, loss of appetite, muscle pain and chills, resulting in violent uncontrollable shivering with teeth chattering, accompanied by thirst, nausea, vomiting and in severe cases sometimes by delirium and convulsion in children frequently ending in death. These signs are more pronounced usually in falciparum malaria ^[2]. [There is temporal lagged association between meteorological factors and malaria which depend on the climatic condition. Therefore, the lag pattern for meteorological factors should be considered in the development of malaria early warning system](#) ^[91]. Malaria was perceived as the world's worst health problem ^[7592]. More people are dying each year from malaria than 30 years ago and malaria is returning to areas from where they had been eradicated. High level of malaria parasitaemia has been observed in African children with symptomatic HIV infection. These children have been found to be protected against cerebral malaria and invariably deaths due to cerebral malaria. This has been attributed to lower levels of tumor necrosis factor, which boost antibodies against malaria in HIV infected children ^[76—7893-95]. [However, concurrent infections with *P. falciparum* and *W. bancrofti* or *M. perstans* has been reported in children and young adults in Mali](#) ^[96]. [Hemozoin-dependent induction of matrix metalloproteinases-g \(MMP-9\) expression and activity has been demonstrated in mononuclear and endothelial cells](#) ^[96] and so MMP₅ should be taken into account as potential new targets for an innovative and adjunctive therapy for severe malaria ^[98].

Malnutrition, splenomegaly and anaemia are the expected complications of repeated attacks of malaria. However, acute falciparum malaria produces complications collectively known as pernicious or malignant malaria. This arises from interruption of blood flow in the capillaries that interferes with oxygen supply causing anoxia and may eventually lead to rupture of the capillaries and bleeding into the tissues, invariably resulting in death

[1, 2]. There are two main types of pernicious malaria: cerebral malaria, which causes brain damage resulting from the clogging of the brain capillaries with symptoms as severe headache, convulsions, delirium and other psychotic signs with temperature rising up to 42°C. Cerebral malaria frequently ends in death and is the most lethal of all the malaria. The other is agid malaria, involving other organs of the viscera: the signs in the patients are cold clammy skin, with high internal temperature as well as severe vomiting, diarrhea and sweating. The consequences are never as severe as in cerebral malaria, but extreme exhaustion may lead to prostration and unconsciousness [2]. In Africa, 30 million women living in malaria-endemic area become pregnant each year, with up to 200,000 new born deaths each year as a result of malaria in pregnancy [99].

2.7 DIAGNOSIS OF MALARIA

Malaria is a disease of many facets with symptoms that trigger most of the diseases of man. Jeffery [797100] divides the parasitaemia of man into four phases: preclinical, clinical, terminal (asymptomatic), and relapse (asymptomatic and symptomatic). Bray [808101] designated another prior to the preclinical as the pre-erythrocyte phase, which lasts only 24 hours, as a period of cytoplasm fission of a multinucleate mass. Preclinical period follows the appearance of the parasite in the peripheral blood and which is the time when frank manifestations appear. Periods of chill alternating with longer febrile intervals are the classical manifestations [818102].

Malaria parasites in blood sample stored at 4°C are viable for at least a period of one week. *Plasmodium falciparum* can remain viable for a period of 2 weeks [74786]. A definite diagnosis of malaria infection is established on the finding of parasites in the blood. Malaria should be suspected in all cases of fever in endemic areas or in persons who have been exposed to the infection. In drug resistant core endemic region, anti-inflammatory effect on white blood cells is demonstrated using a simple: economic monocular microscopic that can be used in day light or with aid of lamp [103]. Microscopically diagnosis is only as reliable as the competence of the workers who prepare the blood slides and examine such slides. Diagnosis of human malaria is mainly by the detection of plasmodium species from microscopic examination of the blood. One should remember that the presence of malaria parasites in the blood is a sign of infection but not necessarily a cause of the disease [54, 5956, 61]. Although various modern methods ranging from density high-speedcentrifugation, with

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monoclonal antibodies to the application of magnetic separation techniques, DNA probes and even the newer amplification technique such as the polymerase chain reaction (PCR) have been tried, in order to detect scanty parasitaemias. It appears that the time honoured thin-and thick film blood examination by a competent microscopist remains unchallenged when it comes to simplicity and convenience ^[5961]. But the flow cytometry method is a simple robust, and efficient method for detecting *P. vivax* – infected reticulocytes ^[104]. But PET-PCR, a new molecular diagnostic tool with similar performance characteristics as commonly used PCR methods that is less expensive, easy to use and amiable to large scale – surveillance studies in developing country settings ^[105]. The pLDH antigen in three RDTs, used in combination with HRP2 provides added diagnostic specifically of malaria parasitaemia and may be useful to distinguish acute infection from recently treated infections where diagnostic specifically is desirable (e.g. for selection of malaria infected participants in clinical trials) a three-band RDT should be considered in sub-Saharan African ^[106].

Malaria rapid diagnostic tests (RDTs) are qualitative immune-chromatographic lateral flow tests in dipstick (strip), cassette or card form that detect malaria antigen in peripheral blood. Malaria antigen from a lysed blood sample is reacted with anti-malarial monoclonal antibody conjugated to colloidal gold (pink-mauve) particles. The antigen-antibody colloidal gold complex migrates along the nitrocellulose membrane where it becomes bound (capture) by a line of specific monoclonal antibody, producing a pink line in the test result area. The line can be seen after a washing buffer has removed the background haemoglobin. A further pink line, i.e. inbuilt positive control, is produced above the test line indicating that the test reagents have migrated satisfactorily (it is not a malaria antigen control) ^[5860].

Radioimmunoassays have also been tried for malaria diagnosis. Antibodies to malaria can be detected using enzymatic immunoassays or immune-fluorescence techniques. The antibodies to the asexual blood stages appear days to weeks after the infection and may persist for months. Although useful in survey work or for screening blood donors and reducing wastage, they are of little value in the “acute” malarial situation ^[5456].

Solid-phase inhibition radioimmunoassays have been used to demonstrate parasite antigens. These assays use solubilized erythrocytes infected with *P. falciparum* and are based on the ability of washed infected red blood cells to inhibit the binding capability of radio-or enzyme-labelled antibody on a plastic of microtitre plate precoated with crude

450 extracts of malaria antigen obtained from *in-vitro* cultures of *P. falciparum*. Such test
451 systems are useful where low parasitaemias in the range 5-50 asexual parasites/ μ l of blood
452 are found. An inhibition radioimmunoassay test based on a monoclonal antibody labeled
453 with a radioisotope, iodine -125, and used in an antibody 'sandwich', has also been
454 described. In field trials it produced a detection level of > 1 asexual parasites of *P.*
455 *falciparum*/ μ l of blood; better than one would expect from routine light microscopy^[5456].

456 Serological methods of diagnosis of malaria have become of practical value since
457 1962 when the indirect fluorescent antibody test (IFAT) was introduced. In the IFAT
458 procedure the antigen consists of a film of infected blood on a microscope slide. The slide is
459 covered first with one of the serial dilutions of the test serum; then it receives a solution of
460 antihuman globulin labeled with fluorescein isothiocyanate; after washing and drying, the
461 slides are examined in a fluorescence microscope. Antibody in the test serum reacts with
462 antigen of the malaria parasites and the antiglobulin reaction with the antibody is indicated
463 by the fluorescence of the parasites. Fluorescence of the last serial dilution is given as a 'titre'
464 of the antibody present^[5456].

465 In recent years a number of new techniques based on the "dipstick" format, have
466 become available for the diagnosis of malaria. These include the ICT-Malaria PF, OptiMALr
467 and the Kat-Quick kits. The methods are based on the principle of the detection on
468 plasmodial histidine rich protein-2 (HRP-2) or parasite-specificities lactate dehydrogenase
469 (PLDH) which is present in *P. falciparum* and other Plasmodial infections. A number of
470 reports claim sensitivities and specificities approaching 100% while other reports have
471 claimed up to 6% cross reactivity with sera positive for rheumatoid factor. Some of these
472 "dipstick" methods have been extended to include screening for other forms of malaria but
473 to date results have not been quite impressive^[5860]. The performance of HRP-2 test in
474 detecting asymptomatic carriers of *P. falciparum* varies by age and parasite density. Its low
475 sensitivity may limit its utility in pre-elimination interventional settings. So loop-mediated
476 isothermal amplification in combination with cost effective HRP-2 test may be worth
477 exploring in such setting^[107]. But Luciferase-expressing *plasmodium berghei* parasites to
478 measure pre-patent period of malaria infection in rodents using a bioluminescence assay is
479 novel, simple, fast and sensitive. The sensitivity and accuracy of this new method is
480 comparable to standard PCR and microscopy-based techniques respectively^[108].

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481 Dipstick tests have the potential of enhancing the speed and also the accuracy of
482 diagnosing *P. falciparum*, particularly in non specialized laboratories where inexperienced or
483 junior staff may be involved, since very little training is required for these techniques. A
484 potential problem with these methods is that the circulating antigen may be detected for
485 many days up to 2 weeks in a laboratory after the elimination of viable parasites from the
486 circulation. It must therefore be remembered that a positive test may not always be due to
487 an active infection. The dipstick methods should be regarded as useful additional tests to
488 the long established diagnostic method of examining thick and thin blood films regarded as
489 the standard, not as replacement methods ^[5860].

490 Molecular biological detection tests have also been used for diagnosis and are
491 known to use DNA and RNA probes. DNA probe is based on principle of hybridization with
492 two complementary strands of the DNA helix separated (denatured) by chemical means, or
493 heat treatment. The separated strands of DNA are then put into contact with a DNA probe.
494 This probe has been obtained using recombinant DNA techniques, or produced
495 synthetically. Most of the available DNA probes are specific to *P. falciparum* and sensitivities
496 as low as 5 asexual parasites/μl of blood have been reported, but unfortunately, these
497 results have only so far been obtained with radioisotopic method using iodine 125 or
498 phosphorus 32. Enzyme-based systems with biotin and others are rather less sensitive
499 although new probes specifically designed for enzymes detection may improve these levels
500 considerably ^[5456].

501 Ribonucleic acid (RNA) probes have also been evaluated with promising results.
502 Unfortunately, RNA is less stable and cross-species reactivity could occur. RNA probes have
503 been developed for all four human malarias and show an increased sensitivity due to the
504 high number of target sequences which occur in RNA. Detection techniques using 12-hour
505 autoradiography exposure have reportedly produced detection levels as low as few
506 parasites/μl of blood. No effective non-radioactive label has yet been reported ^[5456].

507 Other methods of diagnosis include the QBC II, Becton-Dickinson's Quantitative Buffy
508 Coat (QBC) method. This involves centrifuging the patient's blood in special capillary tubes
509 precoated with Acridine Orange (AO) in which parasite DNA is stained with AO. A small
510 precision moulded plastic float presses the parasitized red cells (which occupy the upper
511 most part of the red column) against the wall of the tube, where they can be viewed by ultra
512 violet light microscopy. The sensitivity of this method is claimed to be very high with

experienced users, although some reports suggest that young trophozoites of *P. falciparum* and *P. vivax*, could not be distinguished with any degree of certainty and that confirmatory blood films should always be examined. Additionally special equipment is required, which may preclude the method from being used in smaller centres ^[5456].

Another relatively new method is the polymerase chain reaction (PCR) which uses a non-isotopically labeled probe following PCR amplification. It is possible to detect less than 10 parasites in over 10 µl of blood. PCR may yet prove to be a valuable addition to the examination of blood films for the diagnosis and speciation of malaria. Again, the special equipment required precludes all but the larger centre. Some researchers have claimed that PCR (and ELISA) techniques are as sensitive as blood films, however they are infinitely more expensive, require specialized equipment and take a longer time to complete ^[5961]. The RDTs detected plasmodium in P. knowlesi-infected blood samples has poor sensitivity and specificity. Patients with P. knowlesi could be misdiagnosed as P. falciparum with OptiMal-TT, P. vivax with paramax-3 and more correctly as nonP. vivax/non-P.falciparum with Binax Now® malaria. Therefore, there is a need for a sensitive and specific RDT for malaria diagnosis in settings where P. knowlesi infections predominate ^[109].

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2.8.0 TREATMENT OF MALARIA

Malaria is the classical example of a disease that affects the productivity of individuals, families and the entire world due to morbidity and mortality ^[11082]. A key component of any transmission reduction strategy must be methods to attack the parasite as it passes from man to mosquito (and vice versa). The understanding of such methods should be rationally based on molecular, cellular, population to the evolutionary levels ^[111]. But no single intervention will significantly lower the burden of imported malaria ^[112]. The first antimalarial drug was quinine isolated from the bark of cinchona specie (Rubiaceae) in 1820. In 1940, chloroquine was synthesized and until recently was the only drug used for the treatment of malaria. Chloroquine resistant *P. falciparum* is treated with alternative drugs or drugs combinations, which are expensive and sometimes toxic ^[83113]. Chloroquine and hydroxychloroquine have been proven to have antiretroviral activity both *in-vivo* and *in-vitro* hence could be used to treat co-infection of malaria and HIV ^[84114]. Mechanism of action of chloroquine remains controversial, the agent probably acts by concentrating in parasite food vacuoles, preventing the polymerization of the haemoglobin break down

product, haemozoin and thus eliciting parasite toxicity due to the abundance of free haem. Resistance in *Plasmodium falciparum* has been attributed to mutations in a putative transporter PFCRT, however the clinical value of resistance-reversing drugs is not established. Chloroquine remains the drug of choice for the treatment of sensitive *P. falciparum* and other species of human malaria parasites. It rapidly terminates fever (in 24-48 hours) and clears parasitaemia (in 48-72 hours) caused by sensitive parasites. It is safe, cheap and many partially immuned individuals respond to chloroquine treatment [3]. Artemisinin and its derivatives are effective against drug-resistant *Plasmodium falciparum* and so they are of utmost important in the current antimalarial campaign [82][110]. Artemisinin or Qinghaosu is a sesquiterpene lactone endoperoxide isolated from Chinese herb *Artemisia annua* L. (Asteraceae) that has been in use in traditional treatment for chills and fevers for more than 2000 years [85][115]. Artemisinin was isolated pure in 1972 and its structure was determined in 1979 [86][116]. Quick reduction of fevers, fast clearing of parasites from blood (90% of malaria patients recovered within 48 hours) are characteristics of artemisinin. WHO recommended that all countries experiencing resistance to conventional monotherapies should use combinations containing artemisinin derivative (artesunate) [81] and other agents such as amodiaquine and fansidar [86][116]. Lapdap that contains chloroguanol hydrochloride and dapsone is one of the safest antimalarials in use [87][117]. Terkuile *et al.* strongly recommended household level treatment for presumed malaria [88][118].

Fansidar® may be used against chloroquine-resistant and presumptive *falciparum* malaria. [Intermittent preventive treatment during the pregnancy with optimal doses of sulphadoxine-pyrimethamine protects pregnant women from malaria related adverse outcomes](#) [119]. A number of antibiotics in addition to the folate antagonists and sulphonamides are modestly active antimalarials but their mechanisms of action are unclear [3, 88][118]. The sulphadoxin/pyrimethamine combination had been used to treat uncomplicated *falciparum* malaria for more than 30years. Non-silent mutations in dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) genes are responsible for the resistance to pyrimethamine and sulphadoxine respectively [73][88]. The discovery of techniques for continuous maintenance of human *Plasmodium falciparum* *in vitro* has led to practical assays of susceptibility of these organisms to antimalarial drugs [90][120]. The biology of malaria infection must be appreciated for understanding of action and therapeutic uses of antimalarial drugs [42][44].

577 Malaria is the most important of the transmissible diseases. The incubation period of
578 malaria is 10-35 days and since there are no effective drugs against sporozoites, infection
579 with the malaria parasite cannot be prevented. Sporozoites develop into merozoites after 5-
580 16 days and after months or years are released from liver into circulation. But *Plasmodium*
581 *falciparum* has persistent hepatic circle. Primaquine, proguanil and tetracyclines (tissue
582 schizonticides) act on this site and are used for radical cure. Chloroquine, quinine,
583 mefloquine, halofantrine, proguanil, pyrimethamine and tetracyclines kill these asexual
584 forms. These drugs are used to treat and prevent acute attacks called suppressive
585 prophylaxis. Quinine, mefloquine, chloroquine, artesunate, artemether and primaquine
586 (gametocides) prevent the transmission of infection ^[62]. But artemisinin combination
587 therapy (ACT) is currently being used as the first line therapy for falciparum malaria^[7388].
588 [With improvements in surveillance systems linked to improved diagnosis of malaria. The use](#)
589 [of satellite imagery and mobile phone have complimentary and contemporary benefits in](#)
590 [infectious disease control and elimination](#) ^[121].

591

592 2.8.1 CLASSIFICATION OF DRUG TYPES USED IN TREATMENT OF MALARIA

593 The drugs which are effective in the treatment of malaria may be divided into two
594 groups; drugs which act on the asexual stage of the malarial parasite in the blood-quinine,
595 chloroquine, proguanil, halofantrine, mefloquine and pyrimethamine and drugs which act
596 on the exo-erythrocyte stage in the liver and gametocytes-primaquine. Doxycycline is
597 effective against resistant *P. falciparum* and has been used with success in the far East. It
598 should be taken after meals with copious fluids. There are two ways in which malaria can be
599 attacked by drugs-chemosuppressive and treatment of established disease. Suppressive
600 treatment means the regular administration of a drug to prevent the clinical manifestation
601 of the disease. The best drug for this purpose varies in different parts of the world. *P.*
602 *falciparum* strains from many parts of the world are resistant to one or more antimalarial
603 drug^[94122]. Drugs for prevention of malaria include chloroquine (500mg weekly), mefloquine
604 (250mg weekly), doxycycline (100mg daily), malarone 1 tablet (250mg atovaquone/100mg
605 proguanil) daily, primaquine 26.3mg (15mg base) daily for 14 days and proguanil (200mg
606 daily) as an alternative to mefloquine. Drugs that eliminate developing or dormant liver
607 forms are called tissue schizonticides (e.g. primaquine and tafenoquine), those that act on
608 erythrocytic parasites are blood schizonticides (e.g. quinine, chloroquine, halofantrine,

609 arteflene, artesunate) and those that kill sexual stages and prevent transmission to
610 mosquitoes are gametocides (e.g. primaquine, chloroquine, quinine). No one available agent
611 can reliably effect a radical cure that is eliminate both hepatic and erythrocytic stages. Few
612 available agents are causal prophylactic drugs that are capable of preventing erythrocytic
613 infection. All effective chemoprophylactic agents kill erythrocytic parasites before they grow
614 sufficiently in numbers to cause clinical disease. Fansidar is commonly used to treat
615 uncomplicated falciparum malaria^[3]. Combination drug therapy, administered
616 concomitantly or consecutively, is common with antimalarial drugs ^[92123]. Proguanil,
617 pyrimethamine, sulphadoxine and dapsone are antimetabolites whereas tetracycline,
618 doxycycline and minocycline are antibiotics ^[6266]. Causal prophylactics (e.g. proguanil,
619 primaquine) attack pre-erythrocytic phase; suppressive prophylactics (e.g. chloroquine,
620 mefloquine) suppress the erythrocytic phase; suppressive cures are a form of radical cure by
621 extended suppressive therapy (e.g. chloroquine 300mg weekly for 10 days). It may involve
622 slow action on hypnozoites. Clinical cure involves the use of erythrocytic shizonticides (e.g.
623 atovaquone, artemisinin, halofantrine) to terminate episode of malarial fever. But radical
624 cure involves the use of drugs (e.g. primaquine 15mg daily for 2 weeks) to attack the
625 hypnozoites given together with a clinical curative to achieve total eradication of the
626 parasites ^[66,9371,124].

627 The aims of using drugs in relation to malarial infection are: to prevent and treat
628 clinical attack of malaria; to completely eradicate the parasite from the patient's body; and
629 to reduce the human reservoir of infection-cut down transmission to mosquito. These are
630 achieved by attacking the parasite at its various stages of life cycle in the human host.
631 Antimalarial drugs exhibit considerable stage selectivity of action. A single 45 mg (0.75
632 mg/kg) dose of primaquine is employed immediately after clinical cure of falciparum malaria
633 to kill the gametes and cut down transmission to mosquito ^[93124].

635 2.8.2 CHEMICAL CLASSIFICATION OF ANTI-MALARIAL DRUGS

636 There are several major chemical classes of antimalarial drugs. These include 4-
637 aminoquinoline used for treatment and chemoprophylaxis of infection with sensitive
638 parasites (e.g. chloroquine, hydroxychloroquine, amodiaquine), quinoline methanol (e.g.
639 quinidine, mefloquine and cinchona alkaloid (quinine) used to treat chloroquine resistant *P.*
640 *falciparum*, 8 – aminoquinoline used for radical cure and terminal prophylaxis of infections

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641 with *P. vivax* and *P. ovale* (e.g. primaquine, bulaquine), biguanides (folate antagonist) for
 642 chemoprophylaxis (e.g. proguanil)^[62], tetracyclines for treatment of infections with *P.*
 643 *falciparum* and chemoprophylaxis (e.g. tetracycline, doxycycline), phenanthrene methanol
 644 (e.g. halofantrine) for treatment of infections with some chloroquine-resistant *P. falciparum*,
 645 amyl alcohol (lumefantrine) for treatment of *P. falciparum* in fixed combination with
 646 artemether (coartem)^[65], sesquiterpene lactone endoperoxides (artesunate, artemether,
 647 arteether) for treatment of infection with multidrug resistant *P. falciparum* and
 648 quinonefolate antagonist combination (e.g. malarone: atovaquone/proguanil) for treatment
 649 and chemoprophylaxis of *P. falciparum* infection^[3]. Other classes; are
 650 Hydroxynaphthaquinone (atovaquone) has activity against *plasmodium* species,
 651 diaminopyrimidines (e.g. pyrimethamine) exhibited potent antimalarial activity. Antimalarial
 652 activity of proguanil is ascribed to cycloguanol, a cyclic triazine metabolite and selective
 653 inhibitor of the bifunctional plasmodial dihydrofolate reductase thymidylate synthetase,
 654 sulphonamides (e.g. sulphadoxine) and sulphones (e.g. dapsone) have antimalarial activity
 655 but are slow acting schizonticides that are more active against *P. falciparum* than *P. vivax*.
 656 As para-aminobenzoate analogues that competitively inhibit the dihydropteroate synthase
 657 of *P. falciparum*. The sulphonamides are used together with an inhibitor of parasite
 658 dihydrofolate reductase to enhance their antiplasmodial action. Dapsone given with the
 659 chloroquinil also has been effective for therapy of chloroquine-resistant *P. falciparum*
 660 malaria^[64]. Acridine (e.g. mepacrine), an erythrocytic schizonticide, more toxic and less
 661 effective than chloroquine^[60, 9562, 126]. The efficacy of artemisinin based combination therapy
 662 has been established. Artemether + lumefantrine, Artesunate + sulphamethoxypyrazine-
 663 pyrimethamine, Artesunate + Amodiaquine and sulphadoxine – Pyrimethamine +
 664 amodiaquine have almost same efficacy. Defervescence was faster with Artesunate +
 665 Amodiaquine than Artesunate + Lumefantrine. Fatigue was more frequent in patients
 666 receiving Amodiaquine than by those treated with Artesunate + Sulphamethoxypyrazine –
 667 pyrimethamine or Artesunate and Lumefantrine^[127]. OMARIA the antimalarial said to be
 668 effective against *P. falciparum* and *P. vivax* uses ellagic acids and tannins. But alkaloids may
 669 have deleterious effects on the placental parenchyma and ellagi-tannins seem to up-
 670 regulate healthy conditions and post partum^[128]. All these point the fact that workers
 671 across the globe are making intense efforts to combat malaria^[129, 130]. Firstever White
 672 House Summit on malaria focuses on life-saving initiatives announced the president's

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[malaria initiative \(PMI\), a five year, \\$ 1.2 billion programme for combating malaria in 15 of the hardest-hit countries in Africa. Aid has already reached 6 million Africans from Angola, Tanzania and Uganda](#) ^[131].

Chloroquine and mefloquine (Long-acting quinolines) are used for chemotherapy and chemoprophylaxis of malaria, although widespread resistance is now associated with chloroquine while mefloquine treatment is associated with toxicity and resistance development. Quinine a short acting quinoline is effective in the treatment of severe and drug resistance malaria, but has a potent effect on the cardiovascular system ^[22]. [The protective efficacy of tafenoquine \(200mg daily for 3 days followed by 200mg weekly maintenance doses is similar to that of weekly standard of care \(methoquine, 250mg\)](#) ^[132].

Primaquine, a quinoline active against hepatic phase of some malaria parasites is contraindicated in glucose 6-phosphate dehydrogenase deficiency and pregnancy ^[96133].

Atovaquone, which is given in combination with proguanil, is not effective for *P. vivax* malaria, so it is not used for children under 11 kg, pregnant women or those breast-feeding, and is contraindicated in patients with severe renal impairment ^[97138]. [P. vivax malaria can no longer be considered a benign condition. WHO guide line for treatment of P. vivax need to be reinforced](#) ^[139]. Diaminopyrimidines used in combination with sulpha drugs (e.g.

pyrimethamine-sulphadoxine) in the treatment of chloroquine resistant malaria, however, it is known that sulphonamides are potentially toxic and resistance to the antifolates is prevalent ^[98140]. Sesquiterpene lactone endoperoxide derivatives such as artemisinin, dihydroartemisinin, artemether and artesunate obtained from *Artemisia annua* a Chinese plant although has been in use for more than three decades, no report of systemic human toxicity study on the plant. However, in the pre-clinical toxicity study, lesions occurred in the brain, liver, bone marrow and fetus ^[23]. [Findings revealed that about 95.4% of the plant showed in vitro antiparasmodial activities are from African and Asian continents. But only 2.9% of the plants were studied in vivo. However, 19.5% of the plants showed promising in vitro antiparasmodial activities \(IC₅₀ > 5.0 µg/ml\). However one in every four plants showed promising in vivo antiparasmodial activities \(cleared at 25 – 50 mg/kg between 50 – 99% parasites from the blood in 4 days\). There is no correlation between in vitro and in vivo antiparasmodial activities of medicinal plant extracts and phytochemical principles \(Saganuwan, 2013\). Sulphadoxine-pyrimethamine remains effective at clearing existing infections when provided as intermittent preventive therapy in pregnancy](#) ^[141].

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708 2.9 IN VITRO ANTIPLASMODIAL ASSAY

709 The testing of new anti-malarial drugs requires that at least two steps are
 710 undertaken before testing in human may take place. In the first step, the new drug is tested
 711 in vitro and then-if promising results are obtained – it is tested in vivo ^[99142].

712 In the first step of process, assays have been developed that focus on the drug's
 713 ability to affect parasite growth in red cells. In these assays, *P. falciparum* is the parasite
 714 used if the drug is intended for humans ^[99142]. *P. falciparum* drug sensitivity assays are
 715 performed by monitoring the ~~accumulation~~ accumulation of the parasite protein, Histidin –
 716 Rich protein 2. (HRP 2) in the culture after lysis of the parasite cells. Quantification of HRP2
 717 is assessed by a double-site antigen capture ELISA as described by Robin et al. ^[400143]. The
 718 photometric reading obtained and the corresponding log drug concentrations are fitted to a
 719 dose response curve model using an automated curve-fitting analytical software (Table
 720 curve 2D version 4). The results are expressed as the drug concentration resulting in 50%,
 721 90% and 99% inhibition of parasite growth (IC₅₀, IC₉₀, IC₉₉) ^[401144]. The development of a
 722 continuous in vitro culture system for *P. falciparum* by Trager and Jensen has provided an
 723 extremely useful system for analysis of the effects of drugs on *P. falciparum* ^[94145]. But
 724 several constraints limit the use of this system for drug screening (Timothy et al., 1983) ^[102].

725 Modification of existing continuous in vitro culture methods for *P. falciparum*
 726 involves the maintenance of the parasite in RPMI/640 medium supplemented with human
 727 or rabbit serum or with the H-hypoxanthine supplemented bovine serum. The antiparasite
 728 effect of the test drug can be screened routinely against *P. falciparum* growth in bovine
 729 serum supplemented with H-hypoxanthine. Drug effect may be rapidly and accurately
 730 determined by monitoring the incorporation of H-hypoxanthine into parasite nucleic acids
 731 ^[402145]. OMARIA is highly potent against all field isolates. Lethal dose on vero cells indicate a
 732 selective index of 13 for *P. falciparum* strains FCB. Hence OMARIA can be used in searching
 733 African phyto parables for use in Africa with similar results as in India and in New drug
 734 design ^[146].

735 Another modification of in vitro assay is green fluorescent protein (GFP) system in
 736 which the *P. falciparum* protein binds to GFP, which produces a fluorescence that can

normally be detected by a microplate reader. However, fluorescence activated cell sorter (FACS) has been used to assess the parasite growth. Also, GFP-fluorescence needs to be performed in live parasites, besides the fact that ring-form stages of the parasite containing GFP are difficult to distinguish from unaffected cells, which are estimates. Therefore, to be able to quantify parasite growth, luciferase protein can be used in place of microplate reader. Luciferase reporter protein system is used. The luciferase protein is also the result of light-emitting reaction. To build a DNA construct, the Luciferase gene is strategically engineered next to a specific DNA sequence known as a promoter, which is a gene-specific sequence that triggers transcription. The luciferase system is used to investigate whether a promoter of interest is working. The working promoter transcribes the luciferase gene that results in the production of the luciferase protein which then emits light that can be quantified using a microplater. But to estimate parasite growth, cell lines are built that are infected with DNA constructs carrying the luciferase system. In each of the cell lines a specific promoter is added to the luciferase system, either the *ama-1* promoter that is schizont-specific and therefore to be active only in schizont-stage parasites, or the *eef1 aa*, which is a constitutive promoter that is expected to be working all times. The first system (*ama-1* promoter) is an in vitro assay used to evaluate a drug effect on schizont growth, whereas a second system (*eef 1 aa*) is an in vivo test evaluated through analyzing drug effects on parasite growth during all stages ^[99142].

2.10 IN VIVO ANTIPLASMODIAL ASSAY

In the second step of the process, animal models, usually rodents (mice, young rats) are used to test the drug efficacy. In this step, species-specific parasites such as *P. berghei* are used according to a 4-day suppressive test. The experimental groups are treated with antiplasmodial agent at 0, 24, 48, and 72h post-infection of the animal models with *P. berghei*. Tail blood is usually taken to determine parasitaemia and haematological parameters are monitored daily during the first 7 days and thereafter every 2 days interval for a period of 2 weeks ^[101]. Percentage parasitaemia, packed cell volume, hemoglobin, red blood cells count, white blood cells count and differential leucocyte count are monitored during the period. Rodent malaria parasites have been proven to be analogous to the malaria parasites of man and other primates in most essential aspects of structure, physiology and life cycle ^[103147].

2.11 ANTI-MALARIAL RESISTANCE

In Madagascar, there has been a shift with indoor residual spraying from DDT to pyrethroids, despite the two having similar efficacy. The two greatly decreased the vector-human contact with an associated decrease of the plasmodial index^[148]. But the indoor biting behavior of *Anopheles farauti* documented 20 years ago in Guadalcanal still exist due to the failure of eradication programme^[148].

The rapid spread of resistance to antimalarial drugs present a potentially devastating threat to effective safe treatment with effective and affordable options quickly running out. The discovery of new antimalarial drugs is not keeping pace. For decades chloroquine was the main drug of choice for treatment, however increasing resistance forced its replacement in parts of Asia and South America during the 1980s and in the African countries in the 1990s^[13]. In Eastern Nigeria 40-60% of malarial cases have been reported not to respond to treatment with the drug. There is evidence that chloroquine-resistant *Plasmodium falciparum* accumulates significantly less chloroquine than susceptible parasites by an accelerated drug efflux^[104–106, 149–151]. Various drugs, including calcium channel blockers (e.g. verapamil) and tricyclic compound (e.g. desipramine) have been shown to reverse or modify chloroquine resistance *in vitro*^[102–104, 145–149]. The decline in efficacy of Artesunate and Mefloquine concern the Thai-Cambodia and Thai-Myanmar borders. High prevalence of chloroquine and mefloquine-resistant *P. falciparum* isolates was observed during 2006 – 2009 in the area. Artesunate sensitivity declined and quinine sensitivity improved. *Pfmdr1* and *Pfmdrp1* are the key genes that modulate multi-drug resistance in *P. falciparum*^[152]. The persistence of malaria as a public health problem is partly as a result of resistance of malarial parasites to antimalarial drugs and to insecticides by *Anopheles* mosquitoes. Unfortunately, progress in the field of vaccine production has been slow although, a breakthrough by Patarroyo *et al.* has raised some hopes, however its usefulness to malaria endemic third world countries is yet to be determined^[15].

2.12 CONTROL OF MALARIA

2.12.1 DEVELOPMENT OF MALARIA VACCINES

Malaria vaccines are considered among the most important modalities for potential prevention of malaria diseases and reduction of malaria transmission. Upon all the intensive effort being made toward this area, there is currently no licensed malaria vaccine^[153].

Attempts are now being made to improve the immunogenicity of antisporeozoite vaccines by taking into account, the requirement for T-cell as well as B-cell stimulation. Hitherto vaccines have been designed with blocking antibody in mind, but it has recently been shown that cytotoxic T cells can also be effective against the liver stage. However, the T cells of many patients living in endemic areas respond poorly or not at all to sporozoite antigens, presumably because parasites have selected antigenic variants that lead to their own survival^[7486]. Genetic studies have identified several loci correlated with severity of malaria^[154]. Polymorphisms at the HLA loci which encode proteins that participate in antigen presentation, influence the course of malaria. In West Africa an HLA class I antigene (HLA Bw 35) and HLA class II haplo type (DRB1*1302 – DQBI*0501) are independently associated with protection against malaria (Hill et al., 1991). However, HLA correlations vary according to genetic constitution of polymorphism and geographic location^[154].

Vaccine produced against *Plasmodium falciparum* injected intramuscularly into 40 volunteers produced antibody response only in 9 persons. The challenge of the 9 persons by mosquito bites indicated that only 2 were protected. Unfortunately, since a single surviving sporozoite can initiate clinical malaria, protection against this stage has to be “all or nothing”^[495150].

In another trial, a Colombian group was tested with a more complex antigen made by hybridization and then polymerising three separate peptides from the asexual blood parasites, which is the stage associated with the symptoms and lesions of malaria. Three of 9 volunteers, when challenged with parasites intravenously, had only transient low-level parasitaemias while the others required chemotherapy when their parasitaemia reached the previously agreed level of 0.5%^[15]. The experiment highlights the ethical difficulties of testing this type of vaccine. A much larger trial of this strategy is now in progress with the precise role of T-cell stimulation under close scrutiny and there is no universal agreement about the sort of immunity that should be aimed for^[495150]. One worrying aspect is that many of the most promising parasite surface antigens are extremely polymorphic, so that a vaccine might have to contain antigens from numerous strains (as with the pneumococcal

polysaccharide vaccine). It is interesting to note that, as with many parasites, some of the protective antigens are functional enzymes, whose aminoacid sequences may be expected to be less variable. An advantage of the blood stage is that protection does not have to be 100% effective to benefit the patient. Moreover there are a very large number of antigens to choose from, by no means all of which have been explored ^[106151]. Due to the role that malaria parasite P₁₂ and P₃₈ proteins seem to play during invasion in P. species, added to the PV₁₂ and PV₃₈ antigenic characteristics and the low genetic diversity observed these proteins might be good candidates to be evaluated in the design of a multistage/multi-antigen vaccine^[155].

Two other approaches, not yet tried in human populations, should also be mentioned. The first is the “transmission-blocking” vaccine, aimed at preventing the development of the sexual stage of the parasite in the mosquito. Vaccines consisting of gamete- derived antigens are surprisingly effective in animal models though there are many problems to overcome, one being the hint that suboptimal levels of immunity may actually enhance the production of infective sporozoite in the mosquito. This type of vaccine can only be evaluated at the population level, and both uptake and effectiveness would probably need to be high for any impact on the level of transmission ^[107156].

The principal idea is to vaccinate against the disease rather than the parasite, rather in the same way as one does against tetanus and diphtheria, where it is the toxin and not the bacterium that causes the damage^[106]. No direct toxin has been isolated from the malaria parasite, but there is growing evidence for indirect toxicity via the overinduction of cytokines, particularly tumour necrosis factor (TNF), which has been implicated in the pathological changes in the brain, lung, liver, and other organs in severe malaria. If the molecules that induce TNF production can be identified, antibodies against them might form the basis of an “anti-disease” vaccine ^[106151]. In summary, it seems certain that several more field trials will be necessary to evaluate the various strategies now under consideration, and it may be that in the end some kind of “cocktail” of the strongest antigens of each kind will give the best all-round results^[105150]. Unfortunately, Malaria Vaccine Technology Roadmap has been trying to actualize its visionby developing effective vaccine against P. falciparum^[151]. Can it make a landmark by developing and licensing a first generation malaria vaccine that will have a protective efficacy of more than 50% and lasts longer than one year by 2030? If not, the strategic goal of developing and licensing a malaria vaccine

that has a protective efficacy of more than 80% against clinical disease and lasts longer than four years can not be achieved!. However, about 70 malaria vaccines have been reported, 7 (SR. 11.1, Pfs 25-EPA, CSVAE, ChAd63/MVA ME-TRAP + Matrix MTM polyepitope DNA EP1300 PfCellTOS FMP 012, and ChAd63 AMA/MVA AMAI +AI/CP67909) at the level of phase 1a, whereas 8 (Ad35.CS/RTS.S-A OI, Ad35.C5/Ad26.C5, ChAd63/MVA (CS; ME-TRAP), PfSPZ, PfGAPP52-/P32, ChAd63/MVA MSPI, ChAd63/MVA AMAI, FMP2.1 – ASOIB (AMAI 3D7), NMRC. M3V.Ad. PFEA, and NMRC. M3V.D/Ad pfCA) are at the phase 2a, but 6 (AD 35.C5, AMAI-CI-Alhydrogel + CPG 7909, SE36, BSAM-2Alhydrogel + CPG 7909, EBA175.R2, and CSP, AMAI (PEV 301, 302) at phase 1b level and so those at phase 2b level are GMZ2, MSP3 [181-276], and ChAd63/MVA MF-TRAP. Phase 3 vaccine being developed is RTS.S, A501 ^[153]. Development and phase 3 testing of the most advanced malaria vaccine, RTS,S/ASOI, indicates that malaria vaccine R & D is moving into a new phase that will impact host-parasite relationship through vaccine-induced immune responses to multiple antigenic targets using different plat forms ^[158].

2.12.2 CAMPAIGN AGAINST MALARIA

Despite concerns that the feasibility of text-messaging interventions targeting caregivers may be compromised in rural high malaria risk areas in Kenya, very favourable conditions were found with respect to mobile network, access and ownership of phones, use of text-messaging and minimum literacy levels required for successful intervention delivery. More there was a high level of willingness of caregivers to receive text-message reminders. Impact evaluations of carefully tailored text-messaging interventions targeting caregivers of children with malaria are timely and justified ^[159].

In some parts of Africa, e.g., South-Sudan, the observed high level of malaria prevalence could be due to low levels of coverage and utilization of interventions coupled with low knowledge levels. Therefore, access and utilization of malaria control tools should be increased through scaling up coverage and improving behavior change communication ^[160]. Which types of behaviour change communication that can be accepted by all the endemic malaria countries?

In jiangsu province of China, there was a consistent increase in the number of malaria cases imported from other countries while the number of locally acquired cases sharply declined. This trend may be ascribed to the increasing investment from China to

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Africa and the rising number of Chinese labourers working in Africa. Therefore preventive efforts should be targeted on this high-risk group and the surveillance and response system should be strengthened to prevent local resurgence ^[161]. In Tanzania, there is a major shift in *Anopheles gambiae* S.l. sibling species composition combined with decline in overall vector density in the area. The decline has been most marked for *Anopheles gambiae* S.S., and least for *Anopheles arabiensis*. Due to differences in biology and vectorial capacity of *Anopheles gambiae* S.l. Complex, the change in sibling species composition will have important implications for the epidemiology and control of malaria and lymphatic filariasis in the study area ^[162].

Clusters of AMA-1 seroprevalence or parasite prevalence that are predictive of malaria infection after one year can be identified using geospatial models kernel smoothing using 1km window and spatial scan statistics both provided accurate prediction of future infection ^[163].

In addition to the availability of subsidized artemisinin-combination therapy, the intensity of communication campaigns may contribute to reported levels of the affordable medicines facility-malaria awareness and knowledge among private for-profit providers. Future subsidy programmes for antimalarials should similarly include communication activities ^[164]. Although, the malarial epidemiological and control status has changed markedly since 2006 when the Roadmap was originally launched ^[165].

The necessity of re-energizing basic research of malaria life-cycle and plasmodium developmental biology to provide the basis for promising and cost-effective vaccine approaches and to reach eradication goals is more urgent than previously believed. The focus of the field must be shifted to the basic research efforts including findings on the skin stage of infection ^[166]. A significant obstacle to malaria elimination in Asia is the large burden of *Plasmodium vivax* which is more difficult to eliminate than *plasmodium falciparum*. Persistent *P. vivax* liver stages can be eliminated only by radical treatment with a > seven-day course of an 8-aminoquinoline, with the attendant risk of acute haemolytic anaemia with G6PD deficiency. In Azerbaijan, Tajikistan, North Afghanistan and DPR Korea 8,270,185 people received either a 14-day “standard” or a 17-day “interrupted” primaquine preventive treatment to control post-eradication malaria epidemics. Despite G6PD prevalence of up to 38.7%, the reported frequency of severe adverse reactions related to primaquine was very low ^[167].

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2.12.3 THE USE OF INSECTICIDE

Insecticide resistance is well established in malaria vectors throughout Africa and represents a threat to malaria control. In agriculture areas, the massive usage of pesticides from various families appears to select for metabolic and cuticle resistance mechanisms to a wide range of insecticides including pyrethroids and carbamates^[168].

Several anopheline species occur in the northern Kruger National Park and their densities fluctuate between seasons. Species abundance and relative proportions within the Anopheles gambiae complex varied between collection method. There is a perennial presence of Anopheles arabiense in Malahlapanga site which declined in density during the dry winter months^[169]. The use of pyrethroids to impregnate mosquito nest has had a good impact on the incidence of morbidity and mortality from malaria. These nets are therefore likely to be used on a large scale as an important strategy of malaria control in the future. In Malawi and Cameroon, the per house hold expenditure for impregnated mosquito nets compares favourably with the cost of malaria. The economic losses from malaria would be reduced by 37.83% over 3-year period in Malawi and in Cameroon savings 9.3% and 11.2% in two places resulted as a consequence of a diminished need for case treatment^[170]. Both Kitibina and Folonzo chromosomal forms of Anopheles funestus are formidable malaria vector in Burkina Faso. However, the significantly greater tendency for the Kiribina form to rest outdoors despite its pronounced anthropophily suggests that uniform exposure of the overall Anopheles funestus population to indoor-based vector control tools can not be expected. Kiribina is more likely to evade indoor intervention and escape unharmed outdoors, reducing the efficacy of malaria control^[169]. But vaccinating Malawian children with RTS, S vaccines was very cost effective^[171].

Insecticide-treated bed nets are preeminent malaria control means: though there is no consensus as to a best practice for large scale insecticide-treated bed net distribution. Studies revealed consistent inequalities between urban and rural populations; which were most effectively alleviated through a free-insecticide-treated bed net delivery and distribution framework^[172].

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2.12.4 THE USE OF SYNTHETIC AND HERBAL BASED DRUGS

The major MSP-1₁₉ haplotypes of *P. falciparum* population in all endemic populations in Thailand were identified, providing basic information for malaria vaccine development^[173]. Idiopathic myocarditis has been reported during treatment for controlled human malaria infection^[174].

Mass antimalarial drug administration should be undertaken just before and during the rainy season when community members are less mobile^[175]. The world's first potential malaria vaccine proved only 30% effective in African babies in crucial trial, calling into question whether it can be a useful weapon in the fight against the deadly disease^[176].

OMARIA is prophylactic and therapeutic active against stage of the parasite development and in patients having multiple infections. It has synergistic and buffering roles^[177].

In the ancient Hindu scriptures, there had been mention of OMARIA which is widely available and is very cheap to produce^[178]. Because women are more aware of children's vulnerability to malaria, they are more inclined than men to want to buy permethrin impregnated bed nets^[179].

Punica granatum L. fruit is used in the India for treatment of *P. falciparum* and *P. vivax* malaria^[180]. Elagitannins have been responsible for inhibition of the proinflammatory mechanisms involved in the onset of cerebral malarial^[181]. OMARIA-T cleared haemoprotozoa and wane of myalgia within 36 hours and conferred prophylaxis for months thereafter. But OMARIA-P completed the year prophylaxis with 99% success devoid of side effects^[182].

The *in vitro* antiplasmodial activity of *P. granatum* support its folkloric uses in the Asian continent as antimalarial plant^[183]. The sun dried dermis powder of *Punica granatum* has been in continuous use by Indian Red Cross, Koraput since June, 1998. The plant has prophylactic activity at the dose 1 gramme and therapeutic activity at the dose of 2 gramme^[184].

The cytokine approach to disease pathogenesis can be said to have eventually reconciled Claude Bernard's opinion that all disease conditions were disturbances of patients' internal cellular environment and Louis Pasteur's subsequent view that each disease was, instead, the direct result of specific microbial invaders and toxins^[185] as seen in the case of malaria infection.

993 Since malaria is changing its facet from time to time: with the change of human
994 factors and the natural causes, the control efforts must be adapted accordingly. *P.*
995 *falciparum* malaria is the cause of all the mortality and most of morbidity in malaria. It can
996 present with a typical features, cause dramatic complications and treatment may be
997 rendered difficult by resistance to antimalarial drugs^[186]. Also, the additional demonstration
998 of microstatelite loci in *P. vivax* as neutral markers capable of distinguishing the origin of the
999 recurrent parasite (new infection or originating from the patient) lends support to their use
1000 in assesement of treatment outcomes^[187].

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1004 3.0 CONCLUSION

1005 Because of the long recognition of malaria through anthropology, a lot was known
1006 about control and treatment of malaria. But ~~developing~~ development of vaccines is not
1007 keeping pare due to antigenic shift of all the stages of Plasmodium, in vitro and vivo
1008 antiplasmodial assays need to be improved upon with a view to proffering solution to
1009 episode of malaria resistance. In the local areas where malaria is sporadic and endemic,
1010 there is need to combine chemotherapy with ethnomedicine in addition to the new
1011 available vaccines, since many malaria patients from developing countries cannot afford
1012 costlier effective and less toxic antimalarials-

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- 1014 **REFERENCES:**
- 1015 1. Ukoli FMA. *Introduction of Parasitology in Tropical Africa*, Chichester: John Wiley and
- 1016 Sons Ltd. 1984. 404.
- 1017 2. Ukoli FMA. The biology and natural history of malaria. Proceedings of the fifth
- 1018 annual convention and scientific assembly. *Arch Ibad Med* 2003, **1**(2): 35-36.
- 1019 3. Katzung B. *Basic and Clinical Pharmacology*. International edition. London: McGraw
- 1020 Hill London. 2004: 864 – 873.
- 1021 4. Bruce-Chwat LJ. *Essential Malariology*. London: William Heinemann Medical Books
- 1022 Ltd. 1980: 354.
- 1023 5. Brabin BJ. Malaria in pregnancy. Its importance and control. *Postgrad Doc. Afr*
- 1024 *1989*, **2**: 57-59.
- 1025 6. Abdu-Aguye I. Medicinal herbal research in West Africa. In proceedings of the
- 1026 24th Annual Regional Conference of the West Africa Society for Pharmacology (WASP):
- 1027 22 - 25 October, 1997, Usmanu Danfodiyo University, Sokoto. 1997. 2-3.
- 1028 7. WHO. Promotion and development of training and research in traditional medicine.
- 1029 *Technl Report Geneva*. 1997. 622.
- 1030 8. Rabo ET, Sanusi SS. *An Inventory of Medicinal Plants of the Nigerian Savannah*,
- 1031 Lagos: Levithan Books. 2001. 21-24.
- 1032 9. Wambebe C. Development and production of standardized phytomedicines. *West*
- 1033 *Afr J Pharm*. 1998, **12**(2): 13-24.
- 1034 10. WHO. The promotion and development of traditional medicine. *Techn Research Ser*
- 1035 Geneva 1992. 143.
- 1036 11. Ghiretti M. The possible role of ethnoveterinary medicine in the delivery of more
- 1037 effective animal health services in tropical and sub- tropical areas. *Giornate Italiane*
- 1038 *Dimedicine Tropicale* 1996, **1**: 34 -39.
- 1039 12. WHO. World malariareport. *WHO Bull*. 2008. 99.
- 1040 13. WHO. Rolling back malaria. *The World Health Report*, 1999. 49.
- 1041 14. The Health Exchange. Roll Back Malaria Facing The Challenge in Complex
- 1042 Emergencies. 2001. pp 62.

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- 1043 15. Pattaroyo ME et al., Amador R, Clarjo P, Moreno A, Guzman F, Romero P: A synthetic
1044 vaccine protects human against challenging with asexual blood stage of plasmodium
1045 falciparum malaria. *Nature* 1988, **332**: 158 – 161.
- 1046 16. Iwu MM: Handbook of African Medicinal Plants. London; CRC Press, Boca Raton,
1047 1993: 12-14.
- 1048 17. Saganuwan SA, Yatswako S: Malaria parasites of clinical and laboratory importance –
1049 an update. *J Med Pharmaceut Sci* 2006, **2**(3): 96 – 105.
- 1050 18. Hackskaylo MM: Culinary garden. In *The National Herb Garden*. Edited by Ober R.
1051 Springfield; The Herb Society of America; 1996: 79 – 93.
- 1052 19. Davidson A: The Oxford Companion to Food. Oxford:Oxford University Press; 1999.
- 1053 20. Remilard RL, Wynn SG: Herbal medicines In *Textbook of Veterinary Internal*
1054 *Medicine: Diseases of the Dog and Cat*. 6th edition. Edited by Ettinger, SJ, Feldman FC.
1055 Philadelphia: Elsevier; 2005: 524-526.
- 1056 21. Hoareau L, Edgar JD: Medicinal plants: A re-emerging health aid. *Electr J Biotechnol*
1057 1999, **2**(2): 56 – 70.
- 1058 22. Bateman DN, Dyson EH: Quinine toxicity: adverse drug reaction. *Acute poison Rev*.
1059 1986, **5**: 215- 233.
- 1060 23. Johann-Liang R, Albracht R: Safety evaluations of drugs containing artemisinin
1061 derivatives for treatment of malaria. *Clin Infect Dis* 2003, **36**: 1626 -1627.
- 1062 24. Tella A: The effects of Azadirachta indica in acute Plasmodium berghei malaria. *Nig*
1063 *Med J* 1965; **7** (3): 258 –263.
- 1064 25. Mann A, Gbate M, Nda Umar A: Medicinal and Economic Plants of Nupeland, Bida:
1065 Jube Evans Books and Publications; 2003: 275.
- 1066 26. Luize PS, Tiuman TS, Morello LG, Maza PK, Ueda Na Kamura T, Filho BPD, Cortez
1067 DAG, de Mello CP, Nakamura CV: et al. Effects of medicinal plant extracts on growth
1068 of Leishmania (L.) amazonensis and Trypanosoma cruzi. *Braz J Pharmaceut Sci* 2005,
1069 **14**(1): 85 – 94.
- 1070 27. de Mesquita ML, Grellier P, Mambu L, de Paula JE, Espindula LS: et al In vitro
1071 antiplasmodial activity of Brazilian Cerrado plants used as traditional remedies. *J*.
1072 *Ethnopharmacol* 2007, **110**(1): 165 – 170.
- 1073 28. Devkota A, Jha PK: Biology and medicinal characteristics of Centella asiatica. In: Jha,
1074 P.K., Karmacharya, S.B., Chettri, M.K., Thapa, C.B. and Shrestha, B.B.

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- (eds) ~~Medicinal~~ Medicinal plants in Nepal: An Anthology of Contemporary Research Ecological Society (ECOS), Kathmandu. Edited by Karmachary SB, Chettri MK; Thapa CB, Shrestha BB. 2008.
29. Laouer H et al., Hireche Adjai Y, Prado S, Boulaacheb N, Akkal S, Singh G, Singh P, Laidorov VA, Sziparniak L: Chemical composition and antimicrobial activity of essential oil of Bupleurum montanum and Bupleurum Plantagineum. Nat Prod Commun 2009, **4**(11): 1605-1610.
30. Esmaeili S, ~~Naghbi F, Mosaddegh M, Sahramaward S, Ghafari S, Abdullah NR: et al.~~ Screening of antiplasmodial properties among some traditionally used human plants. J Ethnopharmacol 2009, **121** (3): 400-404.
31. Dhar ML, ~~Dhar MM, Dhawan BN, Mehrotra BN, Ray C: et al.~~ Screening of Indian plants for biological activity. Ind J Exper Biol 1968, **6**(4): 232 – 247.
32. Okokon JE, Ubulom PM, Udokpoh AE: Antiplasmodial activity of Setaria megaphylla. Phytother Res 2007, **21**(4): 366 – 368.
33. Waaka PJ, ~~Gumede B, Smith P, Folb PJ: et al.~~ The in vitro and in vivo antimalarial activity of Cardiospermum halicacabum L. and Momordica foetida Schundi Et Thonn. J Ethnopharmacol 2005, **99**(1): 137 – 143.
34. Amorim CZ, Marques AD, Cordeiro RS: Screening of the antimalarial activity of plants of the Cucurbitaceae family. Mem Inst Oswaldo Cruz 1991, **86**(2): 177 – 180.
35. Mustofa, Sholikhah EN, Wahyono S: **In vitro and in vivo antiplasmodial activity and cytotoxicity of extract of phyllanthus niruri L. herbs traditionally used to treat malaria in Indonesia.** Southeast AS J Trop Med Public Health 2007, **38**(4): 609 – 615.
36. Malebo HM et al. Antiprotozoal activity of aporphine and protoberberine alkaloids from Annickia Kummeriae (Eng. & Diets) Setten & Maas. Complement Alternat Med 2013, 13: 48. Doi: 10.1186/1472-6882-13-48.
38. Coker HAB, Adesegun SA. The malaria scourges the place of complementary traditional medicine. Nig Med Pract 2006, 49(5): 126-132.
39. Gupta SS. Prospects and perspective of natural products in medicine. Ind J Pharmacol 1994, 26:1-12.
39. Duker-Eshun G et al. Antiplasmodial constituents of Cajanus cajan. Phytother Res 2004, 8(2): 128 – 130. Doi: 10.1002/ptr.v18:2/issuetoc.

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1107 40. Saganuwan SA. Some tropical plants with antihypertensive, antiasthmatic and
1108 antidiabetic value. *J Herb Spice Med Plant* 2009, **15**(1):24-44.

1109 41. Geidam YA. Antibacterial and toxicological studies of aqueous leaf extract of *Psidium*
1110 *guajava* (guava) in Chickens. *Ph.D. Thesis*, University of Maiduguri, Maiduguri, Nigeria
1111 2008

1112 42. Saganuwan SA, Gulumbe ML. Evaluation of in-vitro antimicrobial activities and
1113 phytochemical constituents of *Cassia occidentalis*. *ARI* 2006, **3**(3):566 – 569.

1114 43. Saganuwan SA. Toxicological and antimalarial effects of aqueous leaf extract of *Abrus*
1115 *precatorius* (Jecquirity bean) in Swiss albino mice. *Ph.D. Pharmacology Thesis*,
1116 Sokoto: Usmanu Danfodiyo University 2012: 242.

1117 44. Tracy JW, Webster. Drugs used in the chemotherapy of protozoal infections. In
1118 *Goodman and Gilman's The pharmacological Basis of Therapeutics*. Edited by
1119 Hardman JG, Limbird LE, Mohinstt PB, Ruddon RW, Gilman AG. Ninth edition.
1120 McGraw Hill Companies 1996. 1905.

1121 45. Smyth JD. *Animal Parasitology*. Cambridge low price edition. Cambridge: University of
1122 Cambridge Press 1996, 126-136.

1123 46. Bradley DJ. The last and the next hundred years malariology. *Parasitologia* 1999,
1124 **41**:11-18.

1125 47. Laveran C. Pludism. In *Trans*. Edited by Martins JW. London: *The New Sydenham*
1126 *Society* 1983, 197.

1127 48. MacCallum WG. On the flagellated form of the malaria parasite. *Lancet* 1897, **2**:1240-
1128 1241.

1129 49. MacCallum WG. On some peculiar pigmented cells found in two mosquitoes fed on
1130 malaria blood. *Br Med J* 1987, **2**:1786-1788.

1131 50. Ross R. On the haematozoan infections of birds. *J Exp Med* 1897, **3**: 117-136.

1132 51. Ross R. Researches on malaria. *JR Army Med Corps* 1905, **4**: 474.

1133 52. Kettle DS. *Medical and Veterinary Entomology*, Wallingford: CAB International 1993:
1134 513-541.

1135 53. WHO. Malaria actions: programme, severe and complicated malaria. *Tran Royal Soc*
1136 *Med Hyg* 1986, **80**: 1-50.

1137 54. Lalloo DG et al. UK malaria treatment guidelines. *J Infect* 2006, **54**: 111 – 121.

1138 55. [WHO.Roll back malaria: a global partnership. WHO Geneva 1995.](#)

1139 56. [Cheesebrough M.District Laboratory Practice in Tropical countries Part 1. Low price](#)
1140 [edition. Cambridge University Press 2005: 434.](#)

1141 57. [Disease Watch.Malaria. TDR Nature Reviews MicrobiologyInDistrict laboratory](#)
1142 [practice in Tropical Countries. Edited by Cheesebrough M. Cambridge: Cambridge](#)
1143 [University press 2004, 454.](#)

1144 58. [Dellacollete C.Malaria epidemic response: What the clinician needs to know.Mera](#)
1145 [2004: 3.](#)

1146 59. [Ukoli FMA Prevention and Control of Parasitic Diseases in Tropical Africa: The Main](#)
1147 [Issues, Ibadan: University Press Plc 1992 192.](#)

1148 60. [Supargiyano S et al Seasonal changes in the antibody responses against plasmodium](#)
1149 [falciparum merozoite surface antigens in areas of differing malaria endemicity in](#)
1150 [Indonesia. Malaria J 2013, 12: 444.](#)

1151 61. [Gilles HM.Diagnostic methods in malaria. In Bruce-Chawtt Essential Malariaology.](#)
1152 [Third edition. Edited by Gilles HM, Warrell DA, Great Britain: Division of Holder](#)
1153 [Stoughton 1993: 78-95.](#)

1154 62. [Akubue PI.Malaria. In Textbook of Pharmacology. Edited by Akubue PI. Onitsha:](#)
1155 [Africana first publishers limited; 2006: 536.](#)

1156 63. [Kebede S et al. Re-evaluation of microscopy confirmed Plasmodium falciparum and](#)
1157 [plasmodium vivax malari by nested PCR detection in Southern Ethiopia. Malaria J](#)
1158 [2014, 13: 48. Doi: 10.1186/1475-2875-13-48.](#)

1159 64. [Gething PW et al. Declining malaria in Africa: improving the measurement of](#)
1160 [progress: Malaria J 2014, 13:39. Doi: 10.1186/1475-2875-13-39](#)

1161 65. [Bennett PN, Brown MJ. Protozoal infection. Clinical Pharmacology Edited by Bennet](#)
1162 [PN, Brown MJ. New Delhi: Churchill Livingstone 2005, 789.](#)

1163 66. [Nester EW, et al.Microbiology: A Human Perspective. Fourth edition, New York;](#)
1164 [McGraw Hill 2004, 731-738.](#)

1165 67. [Shapiro TA, Goldberg DE. Chemotherapy of protozoal infections \(Malaria\). In:](#)
1166 [Goodman and Gilman's, The pharmacological Basis of Therapeutics. Edited by](#)
1167 [Brunton LL, Lazo JS, Parker KL, New York: McGraw Hill Medical Publishing 2006: 1021](#)
1168 [– 1045.](#)

1169 68. Rang HP et al.: Rang and Dale's Pharmacology. 6th edition. Philadelphia: Churchill
1170 Livingstone, 2008: 829.

1171 69. Sibley L, Sipe TA, Koblinsky M. Does traditional birth attendant training improve
1172 referral of women with obstetric complications: a review of the evidence. *Soc Sci*
1173 *Med* 2004, **59**(8): 1757-1768.

1174 70. Okolie VE et al. prevalence and risk factor for placental malaria in Nnewi, South East
1175 Nigeria. *Int. J Trop Healt Dis* 2014, **4**(3): 374 – 383.71. Brooks GF, Butel JS, Nurse
1176 SA. *Jawetz, Melnick & Adelberg's Medical Microbiology*. International 23rd edition.
1177 London: McGraw Hill 2004, 677-683.

1178 72. van Buskirk KM, Sevova E, Adams JH. Conserved residues in the plasmodium vivax.
1179 Duffy-binding protein ligand domain are critical for erythrocyte receptor recognition
1180 *Proc Natl Acad Sci USA* 2004, **101**:15754-9. PMC free article: PMCS24844, PubMed:
1181 15498870.

1182 73. Livingstone FB. The Duffy Blood groups, vivax malaria and malaria selection in human
1183 population: a review. *Human Biol* 1984, **56**: 413 – 425. PubMed: 6386656.

1184 74. Barbara JAJ. *Microbiology in Blood Transfusion*, London: Wright. PSG 1983, 97-103.

1185 75. Craig A, Scherf A. Molecules on the surface of the Plasmodium falciparum infected
1186 erythrocytes and their role in malaria pathogenesis and immune evasion. *Molecul*
1187 *Biochem Parasitol* 2001, **115**: 129-143.

1188 76. Ta TH et al. First case of naturally acquired human infection with Plasmodium
1189 cynomolgi. *Malaria J* 2014, **13**: 68. doi:10.1186/1475-2875-13-68.

1190 77. Stanier RY et al. *The Microbial World*. Fifth edition. New Jersey: prentice-hall,
1191 Englewood Cliffs 1986, 647 - 656.

1192 78. Conrad ME. Diseases transmissible by blood transfusion: Viral hepatitis and other
1193 infectious diseases. *Semin Haematol* 1981, **18**:122-146.

1194 79. Lopez C et al. Mechanisms of genetically based resistance to malaria. *Gene* 2010,
1195 **467**(1-2): 1 – 12. Doi:10.1016/j.gene.2010.07.008

1196 80. Anstee DJ. The relationship between blood groups and disease. *Blood* 2010, **115**(23):
1197 4635-4643. PMID 20308598 (<http://www.ncbi.nlm.gov/pubmed/20308598>).

1198 81. May et al. 200786. Hardman JG et al Goodman and Gilman's. *The*
1199 *Pharmacological Basis of Therapeutics* 9th edition. London: McGraw Hill; 1996: 1905.

1200 82. Allen SJ et al. Prevention of cerebral malaria in children in Papua New Guinea by
1201 South East Asian ovalocytosis band 3". *Am J Trop Med Hyg* 60(6): 1056 – 1060.
1202 [PMID10403343](#)

1203 83. Cortes A et al. Adhesion of plasmodium falciparum-infected red blood cells to CD36
1204 underflow is enhanced by the cerebral malaria-protective trait South-East Asian
1205 ovalocytosis". *Mol Biochem Parasitol* 2005, 142(2): 252 – 257. [PMID 15978955](#).

1206 84. Terrenato L et al. Decreased malaria morbidity in Tharu people compared to
1207 sympatric people populations in Nepal. *Ann Trop Med Parasitol* 1988, 82(1): 1 – 11.
1208 [PMID3041928](#).

1209 87. Viser BJ et al. Serum lipids and lipoproteins in malaria-a systematic review and meta-
1210 analysis. *Malaria J* 2013, 12: 442.

1211 88. Lau TY, Sylri M, William, T, Mutational analysis of Plasmodium falciparum
1212 dihydrofolate reductase and dihydropteroate synthase in the interior division of
1213 Sabah, Malaysia. *Malaria J* 2013, 12: 445.

1214 89. Martins AC et al. Vivax malaria in an Amazonian child with dilated cardiomyopathy.
1215 *Malaria J* 2014 13:61. Doi: [10.1186/1475-2875-13-61](#).

1216 90. Philips RS. Current status of malaria and potential. *Clin Microbiol Rev* 2001, **14**(1):
1217 [208-226](#).

1218 91. Zhao X et al. The temporal lagged association between meteorological factors and
1219 malaria in 30 countries in South-West China: a multilevel distributed lag non-linear
1220 analysis. *Malaria J* 2014, 13: 57. Doi: [10.1186/1475-2875-13-57](#).

1221 92. Witworth J et al. Effect of HIV and increasing immunosuppression on malaria
1222 parasitaemia and clinical episodes in rural Uganda adults: a cohort study. *Lancet*
1223 [2000, 356:1051-1056](#).

1224 93. Francesconi et al. HIV, malaria parasites and acute febrile episodes in Ugandan
1225 adults: a case control study. *AIDS* 2001, **15**:2445-2450.

1226 94. Bastos F et al. Co-infection with malaria and HIV in injecting drug user in Brazil: a new
1227 challenge to public health. *Addict*. 2004, **94**(8): 1165-1174.

1228 95. Jeffery GM. Infectivity to mosquitoes of *Plasmodium vivax* and *plasmodium*
1229 *falciparum* under various conditions. *Amer J Trop Med Hyg* 1960, **9**: 315-320.

1230 96. NIH National Institute of Health Clinical Centre. Medical Implications of Co-Infection
1231 with Malaria and Filariasis Parasites-Full Text View-Clinical Trials. Gov processed this
1232 record on February 13, 2014. <http://clinicaltrials.gov/NCT00471666>

- 1233 [97. Lewin, 2004](#)
- 1234 [98. Prato M, Giribaldi G, Matrix metalloproteinase-9 and haemozoin: Wedding rigs for](#)
 1235 [human host plasmodium falciparum parasite in complicated malaria. J Trop Med](#)
 1236 [2011, 1 – 11. Doi:10.1155/2011/628435.](#)
- 1237 [99. WHO Lives at Risk: Malaria in pregnancy, 2014, 1 – 3. Available at](#)
 1238 [www.who.int/feature/2003/04b/en.](#)
- 1239 [100. Bray RS.Observations on the cytology and morphology of the mammalian malaria](#)
 1240 [parasites. A process of apparent plasmotomy in the preerythrocytic phase of](#)
 1241 [Laveranian falciparum.Riv Parasit. 1960, 21: 267-276.](#)
- 1242 [101. Horsefall WR.Medical Entomology: Arthropods and Human Diseases; New York: The](#)
 1243 [Ronald press Company 1962, 338-347.](#)
- 1244 [102. White NJ. In Manson's Tropical Diseases Edited by Cook G. London: WB Saunders;](#)
 1245 [1996: 1087-1164.](#)
- 1246 [103. Bhattacharya D. Relevance of economic field microscope in remote rural regions for](#)
 1247 [concurrent observation of malaria and inflammation. Adv Infect Dis 2012, 1\(2\): 13 –](#)
 1248 [18. Doi:10.1016/52222 – 1808\(11\) 60055-8.](#)
 1249 [http://www.apitem.com/zz/2011jun/13.pdf](#)
- 1250 [104. Ratovonjato J et al. Entomological and parasitological methrin in the Western forthill](#)
 1251 [area of Madagascar. Malaria J 2014, 13: 21. Doi: 10.1186/1475-2875-13-21.](#)
- 1252 [104. Roobsoong W et al. A rapid sensitive, flow cytometry-based method for the](#)
 1253 [detection of plasmodium vivax-infected blood cells. Malaria J 2014, 13: 55. Doi:](#)
 1254 [10.1186/1475-2875-13-55.](#)
- 1255 [105. Talundzic E et al. Field evaluation of the photo-induced electron transfer fluorogenic](#)
 1256 [primers \(PET\) real-time PCR for the detection of plasmodium falciparum in Tanzania.](#)
 1257 [Malaria J 2014. 13:31 http://www.malariajournal.com/content/13/1/31](#)
- 1258 [106. Hawkes M et al. Use of a three-band HRP2/PLDH combination rapid diagnostic test](#)
 1259 [increases diagnostic specificity for falciparum malaria in Uganda children. Malaria J](#)
 1260 [2014, 13: 43. http://www.malariajournal.com/content/13/1/43](#)
- 1261 [107. Tiono AB et al. lesson slearned from the use of HRP-2 rapid diagnostic test in](#)
 1262 [community-wide screening and treatment of asymptomatic carriers of plasmodium](#)
 1263 [falciparum in Burkina Faso. Malaria J 2014, 13:30. doi: 10.1186/1475 – 2875 – 13- 30.](#)

1264 108. Zuzarte-Luis V, Sales-Dias J, Mota MM. simple, sensitive and quantitative
1265 bioluminescence assay for determination of malaria prepatent period. *Malria J*,
1266 2014, 13:15. <http://www.malariajournal.com/content/13/1/15>

1267 109. Foster D et al. evaluation of three rapid diagnostic tests for the detection of human
1268 infections with plasmodium knowlesi. *Malaria J* 2014, 13:60.doi:10.1186/1475-2875-
1269 13-60.

1270 110. WHO. *Quality Control Method for Medicinal Plants Materials*, Switzerland; 1998: 115.

1271 111. Sinden RE et al. The biology of sexual development of plasmodium: the design and
1272 implementation of transmission blocking strategies. *Malaria J* 2012, 11:70.
1273 <http://www.malariajournal.com/content/11/1/70>.

1274 112. Neave PE, Jone COH, Behrens RH, Challenges facing providers of imported malaria –
1275 related healthcare services for Africans visiting friends and relatives (VFRs). *Malaria J*
1276 2014, 13: 7. Doi:10.1186/1475 – 2875-13-17.

1277 113. Adeoti OM et al. Presumed malaria and human immunodeficiency disease: a
1278 challenge to health planners. *J Med Pharmaceut. Sci.* 2007, 3(3): 75-80.

1279 114. Klayman DL. Qinghaosu (artemisinin): an antimalarial drug from China. *Sci* 1985,
1280 228:1049-1055.

1281 115. Namdeo AG, Mahadik K, Kadam SS. Antimalarial drug – *Artemisia annua*.
1282 *Pharmacogn Magaz* 2006, 2(6): 106-111.

1283 116. Jimmy ED et al. Haematologic responses in comparative doses of chloroquine,
1284 fansidar, lapdap, amalar and cotexicin. *J Med Pharmaceutic Sci* 2006, 2(4): 1-4.

1285 117. Terkuile FO et al. The burden of co-infection with human immunodeficiency virus
1286 type 1 and malaria in pregnant women in sub-Saharan Africa. *Am J Trop Med Hyg*
1287 2004, 71: 41-54.

1288 118. Rosenthal PJ. *Basic and Clinical Pharmacology*. Ninth edition, New Delhi: MC Graw
1289 Hill 2004, 1202.

1290 119. Tragar W, Jensen JH. Human malaria parasites in continuous culture. *Sci* 1976, 193:
1291 673-675.

1292 119. Saganuwan SA. Palaver of in vitro – in vivo antiplasmodial activities correlation. BIT's
1293 3rd Annual World Congress of Microbes – 2013, July 30 – August 7, 2013, 345.

- 1294 [119. Exavery A et al. Factors affecting uptake of optimal doses of sulphadoxine-](#)
1295 [pyrimethamine for intermittent preventive treatment of malaria in pregnancy in six](#)
1296 [districts of Tanzania. Malaria J 2014, 13: 22. Doi: 10.1186/1475-2875-13-22.](#)
- 1297 [120. Greenstein B, Gould D. Trousseau's Clinical Pharmacology for Nurses, 18th edition.](#)
1298 [Edinburgh: Churchill Livingstone 2009, 483.](#)
- 1299 [121. Tatem AJ et al. Integrating rapid risk mapping and mobile phone cell record data for](#)
1300 [strategic malaria elimination planning. Malaria J 2014, 13: 52. Doi:10.1186/1475-](#)
1301 [2875-13-52](#)
- 1302 [122. Singh J et al. Clinical manifestations, treatment and outcome of hospitalized patients](#)
1303 [with plasmodium vivax malaria in two Indian states: A retrospective study. Malaria](#)
1304 [Res Treat 2013, 1 – 5. <http://dx.doi.org/101155/2013/341862>](#)
- 1305 [122. Abrams AC. Clinical Drug Therapy, 7th edition, Philadelphia: Lippincott Williams and](#)
1306 [Wilkins, A. Wolters Klower Company 2004, 1032.](#)
- 1307 [123. Tripathi KD. Essentials of Medical Pharmacology. 5th edition: New Delhi: Jaypee](#)
1308 [Brothers Medical Publishers \(p\) Ltd. 2003: 735-748.](#)
- 1309 [124. Carson PE, Flanagan CL, Ickes CE, Alving AS. Enzymatic deficiency in primaquine](#)
1310 [sensitive erythrocytes *Sci* 1956, **124**: 484 -485.](#)
- 1311 [125. White N. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R*](#)
1312 [Soc](#) 1997, 354: 739-749.
- 1313 [126. Bjorkman A, Phillips-Howard PA. Adverse reactions to sulfa drugs: implications for](#)
1314 [malaria chemotherapy. *Bull WHO* 1991, **69**: 297-304.](#)
- 1315 [127. Djalle D et al. Efficacy and safety of artemether + lumefantrine, artesunate +](#)
1316 [sulphamethoxypyrazine-pyrimethamine and artesunate + amodiaquine and](#)
1317 [sulphadoxine-pyrimethamine in the treatment of uncomplicated falciparum malaria](#)
1318 [in Bangui, Central African Republic: a randomized trial. Malaria J 2014, 13: 9.](#)
1319 [Doi:10.1186/1475-2875-13-9](#)
- 1320 [128. Soh PN et al. in vitro and in vivo properties of ellagic acid in malaria treatment.](#)
1321 [Antimicrob Agent Chemother 2009, 53\(3\): 100 – 106. doi:10.1128/AAC.01175-08.](#)
- 1322 [129. Drug One, Why Fight Malaria? Chandigarh, India, May 2007, Vol 2, Issue – 9 pp. 30 &](#)
1323 [36.](#)
- 1324 [130. GFATM. The Global Fund to Fight Aids, Tuberculosis and Malaria, 2010. Available at:](#)
1325 [www.fightmalaria.org/uc-Dublin-2012](#)

1326 131. UNICEF. White House Summit on Malaria New York, 2006. Available at:
1327 http://www.unicef.org/health/index_37773.html

1328 132. Dow SG et al. A retrospective analysis of the protective efficacy of tafenoquine and
1329 mefloquine as prophylactic anti-malarials in non-immune individuals during
1330 development malaria-endemic area. *Malaria J* 2014, 13: 49. Doi: 10.1186/1475-2875-
1331 13-49

1332 133. Franke-Fayard B et al Simple and Sensitive antimalarial drug screening in vitro and in
1333 vivo using transgenic luciferase expressing plasmodium berghei parasites. *Int J*
1334 *Parasitol* 2008, **20**: 1 – 5.

1335 138. Bahamontes – Rosa N et al. In vivo anti-malarial effect of β -amino alcohol 1t on
1336 *Plasmodium berghei*. *Parasitol Res* 2009, **10**: 1-9.

1337 140. Timothy GG, Divo AA, Jensen JB. An in vitro assay system for the identification of
1338 potential antimalarial drugs. *J Parasitol* 1983, **69** (3): 577-583.

1339 141. Coulibaly SO et al. Parasite clearance following treatment with sulphadoxine-
1340 pyrimethamine for intermittent preventive treatment in Burkina-Faso and Mali: 42 –
1341 day in vivo follow-up study. *Malaria J* 2014, 13: 41.
1342 <http://www.malariajournal.com/content/13/1/41>.

1343 142. Carter R, Diggs CL. *Plasmodium* of rodents. In *Parasitic Protozoa Volume III*. Edited by
1344 Kreier JP. New York: Academic press 1977, 359-465.

1345 143. Krogstad DJ. Efflux of chloroquine from plasmodium falciparum: Mechanism of
1346 chloroquine resistance. *Sci* 1987, **238**: 1283-1285.

1347 144. Crownman AF, Karcz. Drug resistance and the P-glycoprotein in homologues of
1348 *plasmodium falciparum*: *Semin cellbiol* 1993, **4**: 29-35.

1349 145. Olliaro PL, Trigg PI. Status of antimalaria drugs under development. *Bull WHO* 1995,
1350 **73**(5): 565-571.

1351 146. Lekana-Douki JB et al. Indian antimalarial OMARIA is effective against African drug
1352 resistant *P. falciparum* field isolates and laboratory strains; without toxicity. *Int J Clin*
1353 *Med* 2012, 3:1-8. Doi:10.4236/jcm.2012.31001

1354 147. Bitonti AJ. Reversal of chloroquine resistance in malaria parasite *plasmodium*
1355 *falciparum* by desipramine. *Sci* 1988, **242**: 1301-1303.

1356 148. Schofield L, Grau GE. Immunological process in malaria pathogenesis. *Nature*
1357 *reviews. Immunology* 2005, 5(9): 722 – 735. PMID 16138104.

1358 149. Martins SK, Oduola AMJ, Mkilhous WK. Reversal of chloroquine resistance in
1359 *Plasmodium falciparum* by verapamil. *Sci* 1987, **242**:1301-1303.

1360 150. Playfair JHL, Blackwell JM, Miller HRP. Parasitic diseases. In *Modern Vaccines, Current*
1361 *Practices and New Approaches*. Edited by Moxon ER, Great Britain: Edward Arnold;
1362 1990: 150.

1363 151. Playfair JHL et al. The malaria vaccine: anti-parasite or anti-disease? *Immunol Today*
1364 1990, **11**: 25-27.

1365 152. Phompradit P et al. Four years' monitoring of in vitro sensitivity and candidate
1366 molecular markers of resistance of *Plasmodium falciparum* to artesunate-mefloquine
1367 combination in the Thai-Myanmar border. *Malaria J* 2014, **13**: 23. Doi:
1368 10.1186/1475-2875-13-23.

1369 153. WHO. Malaria Vaccine Rainbow Tables. 2012. Available at:
1370 www.who.int/vaccine_research/en/Rainbowindex.html

1371 154. Malaria Vaccine Technology Roadmap Final Report 2006. Available at:
1372 http://www.malariavaccine.org/files/Malaria_Vaccine_TRM_Final_ooo.pdf

1373 154. Frodsham AJ, Hill AV. Genetics of infectious diseases. *Hum Mol Genet* 13(2): 187 –
1374 194. PMID 15358724.

1375 155. Forero-Rodriguez J, Garzon-Ospina D, Patarroyo MA. Low genetic diversity and
1376 functional constraint in loci encoding *Plasmodium vivax* p12 and p38 proteins in the
1377 Colombian population. *Malaria J* 2014, **13**: 58. Doi:10.1186/1475-2875-13-58

1378 156. Mendis KN et al. Malaria transmission-blocking immunity induced by natural
1379 infections of *Plasmodium vivax* in humans. *Infect Immun* 1987, **55**: 369-77.

1380 158. Schwartz L et al. A review of malaria vaccine clinical projects based on the WHO
1381 rainbow table. *Malaria J* 2012, **22**:22. Doi: 10.1186/1475-2875-11-11.

1382 159. Otieno G et al. The feasibility, patterns of use and acceptability of using mobile
1383 phone text-messaging to improve treatment adherence and post-treatment review
1384 children with uncomplicated malaria in Western Kenya. *Malaria J* 2014, **13**: 44.
1385 Doi:10.1186/1475-2875-13-44

1386 160. Eyobo MB et al. Malaria indicator survey 2009, South Sudan: baseline result at
1387 household level. *Malaria J* 2014, **13**: 43.
1388 <http://www.malariajournal.com/content/13/1/45>

1389 161. Liu Y et al. Malaria in overseas labourers returning to China: an analysis of imported
1390 malaria in Jiangsu province, 2001 – 2011. *Malaria J* 2014, 13:9.
1391 <http://www.malariajournal.com/content/13/1/29>

1392 162. Derua YA et al. Change in composition of the *Anopheles gambiae* complex and its
1393 possible implications for the transmission of malaria and lymphatic filariasis in north-
1394 eastern Tanzania. *Malaria J* 2012, 11:188.
1395 <http://www.malariajournal.com/content/11/1/188>

1396 163. Mosha JF et al. Hot spot or not: a comparison of spatial statistical methods to predict
1397 prospective malaria infections. *Malaria J* 2014, 13: 43. Doi: 10.1186/1475 – 2875-13-
1398 53

1399 164. Willey BA et al. communicating the AMFM message: exploring the effect of
1400 communication and training interventions on private for-profit provider awareness
1401 and knowledge related to a multi-country anti-malarial subsidy intervention. *Malaria*
1402 *J* 2014, 13: 46. Doi:1186/1475 – 2875-13-46

1403 165. Malaria Vaccine Technology Roadmap, November 2013, 1 – 9.

1404 166. Lorenz V, Karams P. malaria vaccines: looking back and lessons learnt. *Asian Pac J*
1405 *Trop Biomed* 2011 1(1): 74 – 78. Doi:10.1016/32221 – 1691 (11) 60072 – 5

1406 167. Kondrashin A et al. Mass primaquine treatment to eliminate vivax malaria: lessons
1407 from the past. *Malaria J* 2014, 13:51. Doi:10.1186/1475 – 2875-13-51.

1408 167. Munhenga G et al. Field study site selection, species abundance and monthly
1409 distribution of anopheline mosquitoes in the northern Kruger National Park, South
1410 Africa. *Malaria J* 2014, 13: 27. Doi:10.1186/1475 – 2875-13-27.

1411 168. Nkya TE et al. Insecticide resistance mechanisms associated with different
1412 environments in the malaria vector *Anopheles gambiae*: a case study in Tanzania.
1413 *Malaria J* 2014, 13:28 <http://www.malariajournal.com/content/13/1/28>

1414 169. Guelbeogo WM. Behavioural divergence of sympatric *Anopheles funestus*
1415 populations in Burkina Faso. *Malaria* 2014, 13: 65. Doi:1031186/1475-2875-13-65.

1416 170. Brinkman U, Brinkmann A. Economic aspects of the use of impregnated mosquito
1417 nets for malaria control. *Bul WHO* 1995, 73(5): 651 – 658.

1418 171. Seo MK, Baker P, Ngo KN-L. Cost-effectiveness analysis of vaccinating children in
1419 Malaria with RTS, S vaccines in comparism with long-lasting insecticide-treated nets.
1420 *Malaria J* 2014, 13: 66.doi:10.1186/1475-2875-13-66.

1421 [172. Sexton AR. Best practices for an insecticide-treated bed net distribution programme](#)
1422 [insub-saharan eastern Africa. Malaria J 2011, 10:157. Doi:10.1186/1475-2875-10-](#)
1423 [157.](#)

1424 [172. Hill AVS et al. Common West African HLA antigens are associated with protection](#)
1425 [from severe malaria. Nature 1991, 353 \(6336\): 595 – 600.](#)

1426 [173. Simpallipan P et al. Diversity and population structure of Plasmodium falciparum in](#)
1427 [Thailand based on the spatial and temporal haplotype patterns of the C-terminal 19-](#)
1428 [KDa domain of merozoite surface protein-1. Malaria J 2014, 13:54,](#)
1429 [doi:10.1186/1475-2875-13-54](#)

1430 [174. Van Meer MPA et al. Idiopathic myocarchitis during treatment for controlled](#)
1431 [human malaria infection: a case report. Malaria J 2014, 13: 38.](#)
1432 [Doi:http://www.malariajournal.com/content/13/1/38](#)

1433 [175. Dial NJ et al. A qualitative study to assess community barriers to malaria mass drug](#)
1434 [administration trials in the Gambia. Malaria J 2014, 13: 47.](#)
1435 [http://www.malariajournal.com/content/13/1/47](#)

1436 [176. Reiland K, Hirschler B. setback for first malaria vaccine in African trial. Fri, Nova 2012.](#)
1437 [http://www.reuters.com/assets/printpaid: USBRE8A801120121109.](#)

1438 [177. Bhattacharya D et al. Transmission blocking of year round resistant malaria in](#)
1439 [Koraput \(India\) by OMARIA – a new antimalarial phytotherapy 2013, 3\(1\): 54 – 77.](#)

1440 [178. BBC News. Indian claims herbal malaria cure. South Asia, Tuesday, 24 October, 2000.](#)

1441 [179. Rashed S et al. Determinants of the epermethrin impregnated bednets \(Pib\) in the](#)
1442 [republic of Benin: the role of women in the acquisition and utilization of pibs. Soc Sci](#)
1443 [Med 1999, 49\(8\): 993 – 1005.](#)

1444 [180. Dell’ Agli M et al. antiplasmodial activity of Punica granatum L. fruit rind. J](#)
1445 [Ethnopharmacol 2009, 125\(2\): 279 – 285.](#)

1446 [181. Dell’ Agli M et al. Ellagitannins of the fruit of Pomegranate \(Pumid granatum\)](#)
1447 [antagonize the host inflammatory response mechanisms involved in the onset of](#)
1448 [malaria. Malaria J 2010, 9\(1\). 208.](#)

1449 [182. Bhattacharya D. Punica granatum’s dermis indicates antimalarial therapeutics and](#)
1450 [prophylaxis. 4th Pan Afrcan Malaria Conf Multilat Initiat on Malaria Yaounde,](#)
1451 [Cameroon 13 – 18 Nov, 2005](#)

- 1452 182. Bugo H et al. The bionomics of the malaria vector *Anopheles farauti* in Northern
1453 Guadal canal, Solomon Islands: Issues for successful vector control. *Malaria J* 2014,
1454 13: 56. Doi: 10.1186/1475-2875-13-56.
- 1455 183. Dell' Agli M et al. Antiplasmodial activity of *Punica granatum* L. fruit rind. *J*
1456 *Ethnopharmacol* 2009 125(2): 279 – 285.
- 1457 184. Bhattacharya D. Tannins, ions, cations and malariasis: observations and theory *Am J*
1458 *Trop Med Heyg* 2007, 77 (5); 27.
- 1459 185. Clark IA et al. Pathogenesis of Malaria and clinically similar conditions. *Clin Microbial*
1460 *Rev* 2014, 17(3): 509 – 539. Doi:10.1128/CMR.17.3
- 1461 186. Panda M, Mohapatra A. Malaria control – an over view in India. *J Hum Ecol* 2004,
1462 15(2): 101 – 104.
- 1463 187. McCollum AM et al. Genetic variation and recurrent paraistaemia in Peruvian
1464 *Plasmodium vivax* populations. *Malaria J* 2014, 13: 67.doi:10.1186/1475-2875-13-67.
- 1465
- 1466 36. Coker HAB, Adesegun SA: The malaria scourges the place of complementary
1467 traditional medicine. *Nig Med Pract* 2006, 49(5): 126-132.
- 1468 37. Gupta SS: Prospects and perspective of natural products in medicine. *Ind J Pharmacol*
1469 1994, 26: 1-12.
- 1470 38. Saganuwan SA: Some tropical plants with antihypertensive, antiasthmatic and
1471 antidiabetic value. *J Herb Spice Med Plant* 2009, 15(1): 24-44.
- 1472 39. Geidam YA: Antibacterial and toxicological studies of aqueous leaf extract of *Psidium*
1473 *guajava* (guava) in Chickens. *Ph.D. Thesis*, University of Maiduguri, Maiduguri,
1474 Nigeria.
- 1475 40. Saganuwan SA, Gulumbe ML: Evaluation of in vitro antimicrobial activities and
1476 phytochemical constituents of *Cassia occidentalis*. *ARI* 2006, 3(3): 566 – 569.
- 1477 41. Saganuwan SA: Toxicological and antimalarial effects of aqueous leaf extract of *Abrus*
1478 *precatorius* (Jecquirity bean) in Swiss albino mice. *Ph.D. Pharmacology Thesis*,
1479 Sokoto: Usmanu Danfodiyo University, 2012: 242.
- 1480 42. Tracy JW, Webster: Drugs used in the chemotherapy of protozoal infections. In
1481 *Goodman and Gilman's The pharmacological Basis of Therapeutics*. Edited by
1482 Hardman JG, Limbird LE, Mohinstt PB, Ruddon RW, Gilman AG. Ninth edition.
1483 McGraw Hill Companies; 1996: 1905.

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- 1484 43. Smyth JD: *Animal Parasitology*. Cambridge low price edition. Cambridge: University
1485 of Cambridge Press, 1996: 126-136.
- 1486 44. Bradley DJ: The last and the next hundred years malariology. *Parasitologia* 1999,
1487 41: 11-18.
- 1488 45. Laveran A: Pludism. In *Trans*. Edited by Martins JW. London: *The New Sydenham*
1489 *Society*; 1983: 197.
- 1490 46. MacCallum WG: On the flagellated form of the malaria parasite. *Lancet* 1897, 2: 1240-
1491 1241.
- 1492 47. MacCallum WG: On some peculiar pigmented cells found in two mosquitoes fed on
1493 malaria blood. *Br Med J* 1987, 2: 1786-1788.
- 1494 48. Ross R: On the haematozoan infections of birds. *J Exp Med* 1897, 3: 117-136.
- 1495 49. Ross R: Researches on malaria. *JR Army Med Corps* 1905, 4: 474.
- 1496 50. Kettle DS: *Medical and Veterinary Entomology*, Wallingford: CAB International 1993:
1497 513-541.
- 1498 51. WHO: Malaria actions: programme, severe and complicated malaria. *Tran Royal Soc*
1499 *Med Hyg* 1986, 80: 1-50.
- 1500 52. Lalloo DG, Shingadia D, Pasvol G, Chiodini PL, Whitty CJ, Beeching NJ, Hill DR, Warrell
1501 Da, Bannister BA: UK malaria treatment guidelines. *J. Infect* 2006, 54: 111-121.
- 1502 53. WHO: Roll back malaria: a global partnership. *WHO Geneva*; 1995.
- 1503 54. Cheesebrough M: *District Laboratory Practice in Tropical countries* Part 1. Low price
1504 edition. Cambridge University Press; 2005: 434.
- 1505 55. Disease Watch: Malaria. TDR Nature Reviews Microbiology In *District laboratory*
1506 *practice in Tropical Countries*. Edited by Cheesebrough M. Cambridge: Cambridge
1507 University press; 2004: 454.
- 1508 56. Dellacollete C: Malaria epidemic response: What the clinician needs to know. *Mera*,
1509 2004: 3.
- 1510 57. Ukoli FMA: *Prevention and Control of Parasitic Diseases in Tropical Africa: The Main*
1511 *Issues*, Ibadan: University Press Plc 1992: 192.
- 1512 58. Supargiyano S, Bretscher MT, Wijayanti MA, Sutanto I, Nugraheni D, Rozqie R,
1513 Kosasih AA, Sulistiyawati S, Hawley WA, Lobo NF, Cook J, Drakeley CJ: Seasonal

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- changes in the antibody responses against plasmodium falciparum merozoite surface antigens in areas of differing malaria endemicity in Indonesia. *Malaria Journal* 2013; 12: 444.
59. Gilles HM; Diagnostic methods in malaria. In *Bruce Chawtt Essential Malariaology*. Third edition. Edited by Gilles HM, Warrell DA, Great Britain: Division of Holder Stoughton; 1993: 78-95.
60. Akubue PI; Malaria. In *Textbook of Pharmacology*. Edited by Akubue PI. Onitsha: Africana first publishers limited; 2006: 536.
61. Bennett PN, Brown MJ: Protozoal infection. *Clinical Pharmacology* Edited by Bennet PN, Brown MJ. New Delhi: Churchill Livingstone; 2005: 789.
62. Nester EW, Anderson DG, Roberts Jr, CE, Pearsall NN, Nester MT, Hurley D; *Microbiology: A Human Perspective*. Fourth edition, New York; McGraw Hill; 2004: 731-738.
63. Shapiro TA, Goldberg DE: Chemotherapy of protozoal infections (Malaria). In: *Goodman and Gilman's, The pharmacological Basis of Therapeutics*. Edited by Brunton LL, Lazo JS, Parker KL, New York: McGraw Hill Medical Publishing; 2006: 1021-1045.
64. Rang HP, Dale MM, Ritter JM, Flower RJ: Rang and Dale's Pharmacology. 6th edition. Philadelphia: Churchill Livingstone, 2008: 829.
65. Sibley L, Sipe TA, Koblinsky M; Does traditional birth attendant training improve referral of women with obstetric complications: a review of the evidence. *Soc Sci Med* 2004, 59(8): 1757-1768.
66. Brooks GF, Butel JS, Nurse SA; *Jawetz, Melnick & Adelberg's Medical Microbiology*. International 23rd edition. London: McGraw Hill; 2004: 677-683.
67. Barbara JA; *Microbiology in Blood Transfusion*, London: Wright. PSG; 1983: 97-103.
68. Craig A, Scherf A; Molecules on the surface of the Plasmodium falciparum infected erythrocytes and their role in malaria pathogenesis and immune evasion. *Molecul Biochem Parasitol* 2001, 115: 129-143.
69. Stanier RY, Ingraham JL, Wheelis ML, Painter PR; *The Microbial World*. Fifth edition. New Jersey: prentice-hall, Englewood Cliffs; 1986: 647-656.
70. Conrald ME; Diseases transmissible by blood transfusion: Viral hepatitis and other infectious diseases. *Semin Haematol* 1981, 18: 122-146.

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71. Hardman JG, Limbird LL, Molinoff PB, Ruddon RW, Gilman AG: Goodman and Gilman's. *The Pharmacological Basis of Therapeutics* 9th edition. London: McGraw Hill; 1996: 1905.
72. Viser BJ, Wieten RW, Nagel IM, Grobusch MP. Serum lipids and lipoproteins in malaria-a systematic review and meta-analysis. *Malaria Journal* 2013; 12: 442.
73. Lau TY, Sylri M, William, T: Mutational analysis of Plasmodium falciparum dihydrofolate reductase and dihydropteroate synthase in the interior division of Sabah, Malaysia. *Malaria Journal* 2013; 12: 445.
74. Philips RS: Current status of malaria and potential. *Clin Microbiol Rev* 2001, 14(1): 208-226.
75. Witworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, Omoding N, Okonge M, Malamba S, Ojiwiya A: Effect of HIV and increasing immunosuppression on malaria parasitaemia and clinical episodes in rural Uganda adults: a cohort study. *Lancet* 2000, 356: 1051-1056.
76. Francesconi, Fabiani M, Dente DG, Lukwiya M, Okwey R, Ouna J, Ochakahom R, Cian F, Decnich S: HIV, malaria parasites and acute febrile episodes in Ugandan adults: a case-control study. *AIDS* 2001, 15: 2445-2450.
77. Bastos F, Barcellos C, Lowndes C, Friedman S: Co-infection with malaria and HIV in injecting drug user in Brazil: a new challenge to public health. *Addict.* 2004, 94(8): 1165-1174.
78. Jeffery GM: Infectivity to mosquitoes of Plasmodium vivax and plasmodium falciparum under various conditions. *Amer J Trop Med Hyg* 1960; 9: 315-320.
79. Bray RS: Observations on the cytology and morphology of the mammalian malaria parasites. A process of apparent plasmotomy in the preerythrocytic phase of Laveranian falciparum. *Riv Parasit.* 1960, 21: 267-276.
80. Horsefall WR: *Medical Entomology: Arthropods and Human Diseases*; New York: The Ronald press Company; 1962: 338-347.
81. White NJ: In *Manson's Tropical Diseases* Edited by Cook G. London: WB Saunders; 1996: 1087-1164.
82. WHO: *Quality Control Method for Medicinal Plants Materials*, Switzerland; 1998: 115.
83. Adeoti OM, Anumudu CI, Adejumbi CA, Siyanbola MF: Presumed malaria and human immunodeficiency disease: a challenge to health planners. *J. Med. Pharmaceut. Sci.* 3(3): 75-80.

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84. Klayman DL;Qhinghaosu (artemisinin): an antimalarial drug from China. *Sci* 1985, **228**:1049-1055.
85. Namdeo AG, Mahadik K, Kadam SS;Antimalarial drug — *Artemisia annua*. *Pharmacogn-Magaz* 2006, **2**(6): 106-111.
86. Jimmy ED, Usoh IF, Etim OE, Nwidi LL;Haematologic responses in comparative doses of chloroquine, fansidar, lapdap, amalar and cotexicin. *J Med Pharmaceutic Sci* 2006, **2**(4): 1-4.
87. Terkuile FO, Praise ME, Verhoeff FH, Udhayakuma V, Newman RD, Vanejik A, Rogerson, Steketee RW;The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-Saharan Africa. *Am J Trop Med Hyg* 2004, **71**: 41-54.
88. Rosenthal PJ; *Basic and Clinical Pharmacology*. Ninth edition, New Delhi: MC Graw Hill; 2004: 1202.
89. Tragar W, Jensen JH;Human malaria parasites in continuous culture. *Sci* 1976, **193**: 673-675.
90. Greenstein B, Gould D: *Trounce's Clinical Pharmacology for Nurses*, 18th edition. Edinburgh: Churchill Livingstone; 2009: 483.
91. Abrams AC: *Clinical Drug Therapy*, 7th edition, Philadelphia: Lippincott Williams and Wilkins, A. Wolters Klower Company; 2004: 1032.
92. Tripathi KD; *Essentials of Medical Pharmacology*. 5th edition: New Delhi: Jaypee Brothers Medical Publishers (p) Ltd.; 2003: 735-748.
93. Carson PE, Flanagan CL, Ickes CE, Alving AS;Enzymatic deficiency in primaquine sensitive erythrocytes. *Sci*. 1956, **124**: 484-485.
94. White N;Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc* 1997: 354: 739-749.
95. Bjorkman A, Phillips Howard PA;Adverse reactions to sulfa drugs: implications for malaria chemotherapy. *Bull WHO* 1991, **69**:297-304.
96. Franke-Fayard B, Djokovic D, Dooren MW, Rameser J, Waters AP, Falade MO, Kranendonk M, Martinelli A, Cravo P, Janse CJ;Simple and Sensitive antimalarial drug screening in vitro and in vivo using transgenic luciferase expressing plasmodium berghei parasites. *Int J Parasitol* 2008, **20**: 1-5.

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- 1610 97. Bahamontes—Rosa N, Bucher K, Held J, Robin A, Hoffmann WH, Flitsch SL, Kremsner
1611 PG, Kun JFJ: In vivo anti-malarial effect of β -amino alcohol 1t on *Plasmodium berghei*.
1612 *Parasitol Res* 2009, **10**: 1-9.
- 1613 98. Timothy GG, Divo AA, Jensen JB: An in vitro assay system for the identification of
1614 potential antimalarial drugs. *J Parasitol* 1983, **69** (3): 577-583.
- 1615 99. Carter R, Diggs CL: *Plasmodium* of rodents. In *Parasitic Protozoa Volume III*. Edited by
1616 Kreier JP. New York: Academic press; 1977: 359-465.
- 1617 100. Krogstad DJ: Efflux of chloroquine from *plasmodium falciparum*: Mechanism of
1618 chloroquine resistance. *Sci* 1987, **238**: 1283-1285.
- 1619 101. Crownman AF, Karcz: Drug resistance and the P-glycoprotein in homologues of
1620 *plasmodium falciparum*. *Semin cellbiol* 1993, **4**: 29-35.
- 1621 102. Olliaro PL, Trigg PI: Status of antimalaria drugs under development. *Bull WHO* 1995,
1622 **73**(5): 565-571.
- 1623 103. Bitonti AJ: Reversal of chloroquine resistance in malaria parasite *plasmodium*
1624 *falciparum* by desipramine. *Sci*. 1988, **242**: 1301-1303.
- 1625 104. Martins SK, Oduola AMJ, Mkilhous WK: Reversal of chloroquine resistance in
1626 *plasmodium falciparum* by verapamil. *Sci* 1987, **242**: 1301-1303.
- 1627 105. Playfair JHL, Blackwell JM, Miller HRP: Parasitic diseases. In *Modern Vaccines, Current*
1628 *Practices and New Approaches*. Edited by Moxon ER, Great Britain: Edward Arned;
1629 1990: 150.
- 1630 106. Playfair JHL, Taverne J, Bate CAW, De Souza JB: The malaria vaccine: anti-parasite or
1631 anti-disease? *Immunol Today* 1990, **11**: 25-27.
- 1632 107. Mendis KN, Munesinghe YD, De Silva YNY, Keragalla I, Carter R: Malaria transmission-
1633 blocking immunity induced by natural infections of *Plasmodium vivax* in humans.
1634 *Infect Immun*. 1987, **55**: 369-77.

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Table 1: ~~Tropical plants~~ Plants that are used for to treat Anti-malaria purpose in Central Tropical Africa in Nigeria

Plant material, family, genus, species & English names	Vernacular names	Plant part(s) used	Therapeutic regimen(s)	Pharmacologic/ toxic principle(s)	
<i>Amaranthaceae</i> <i>Achyranthes aspera</i> (Devils horsewhip)	Hakorinmaciji (H) Aburo (Y) Egyagi (N)	Whole plant	Decoction taken once: Steam relief headache	Alkaloid, potassium salt	Formatted: Font: Italic
<i>Amaranthaceae</i> <i>Alternanthera sessilis</i> (Sessile joyweed)	Maikaidubu (H) Masantogi (N) Dagunro (Y)	Whole plant	Decoction taken orally	Alkaloids	Formatted: Font: Italic
<i>Amaranthaceae</i> <i>Pupalia lappacea</i>	Marin kusu (H) Emaagbo (I) Mamarigbo (N) Ose (Y)	Whole plant	Leaf or root decoction taken orally	-	Formatted: Font: Italic
<i>Poaceae</i> <i>Eleusine indica</i> (Goose grass)	Ciyawarjuji (H) Chinchere (N) Ese-Kannakanna (Y)	Whole plant	Make decoction and take once daily	Elevisine	Formatted: Font: Italic
<i>Guttiferae</i> <i>Garcinia kola</i> (Bitter kola)	Namijin goro (H) Akilu (I) Ewogichi (N) Orogbo (Y)	Seed, stem root	The powder is taken: It can be chewed also	Kolavirone, ametoflavine, tannins	Formatted: Font: Italic
<i>Irvingiaceae</i> <i>Irvingia gabonensis</i> (wild mango)	Goron biri (H) Ogbono (I) Kpeakpea (N) Eso oro (Y)	Leaves	Leaf decoction is made and taken	Protein, fat	Formatted: Font: Italic

<i>Labiatae</i>	-	Leaves	Cold water maceration is taken	-	Formatted: Font: Italic
<i>Ocimum basilicum</i>					
<i>Anacardaceae</i>	Kashew (H)	Stem bark	Decoction taken once daily	Cardol, phenol, gallic acids, resorcinol, anacardic acid	Formatted: Font: Italic
<i>Anacardium occidentale</i> (Cashew)	Okpokpo (I) Kashiwu (N) Kaju (Y)				
<i>Anacardaceae</i>	Mangwaro (H)	Leave, stem bark	Decoction is made with other additives and taken oftenly: boil and inhale steam	Resins, glycoside, quercetin, flavonoids	Formatted: Font: Italic
<i>Mangifera Indica</i> (Mango)	Mangolo (I) Mungoro (N) Mangoro (Y)				
<i>Anacardaceae</i>	Dinya (H)	Stem bark	Dried stem bark decoction is taken twice daily	Tannins	Formatted: Font: Italic
<i>Scleocarya birrea</i>	Jinjere goyi (N)				
<i>Anacardaceae</i>	Tsadar masar (H)	Seed, stem, stem	Decoction or infusion is taken daily for 1-7 days	Gerannin, galloylgerannin, geraniin, galloylgeraniin	Formatted: Font: Italic
<i>Spondias mombin</i> (Hog plum)	Jinkara (I) Jinjerechi (N) Akika (Y)	bark, fruit			
<i>Annonaceae</i>	Uwar banza (H)	Leaf, root	Root decoction is taken once daily	-	Formatted: Font: Italic
<i>Carissa edulis</i>					
<i>Annonaceae</i>	Kasfiya (H)	Twigs, leaves	Decoction from twigs leaf is taken orally	Crossptine, phytosterol, pholobaphene β -quinovine	Formatted: Font: Italic
<i>Crossopteyx febrifuga</i>	Nambi sunsun (N) Ayeye (Y)				
<i>Apocynaceae</i>	Wadda (H)	Stem, leaves	Infusion is taken daily; leaf powder is taken with porridge	Rauwolfine, reserpine, rescinanmine, aijimaline, alstonine, yohimbine, saposterol, serpentine	Formatted: Font: Italic
<i>Rauwolfia vomitoria</i>	Akata (I) Lyalyagi (N) Ira (Y)				

<i>Apocynaceae</i> <i>Alstonia boonei</i>	Ahun (Y)	Root	Make decoction and take twice daily	-	Formatted: Font: Italic
<i>Asteraceae/Compositae</i> <i>Chromolaena odorata</i> (Siam weed)	Ekpe gbakun (N) Akintola-ta-ku (Y)	Whole plant	Make decoction with potash and take once daily	Pinene, limonene, candinene, flavonoids	Formatted: Font: Italic
<i>Asteraceae</i> <i>Acanthospermum hispidus</i> (Star bur)	-	Leaves	Juice from the leaves with potash once daily	Acanthospermolides, inulim	Formatted: Font: Italic
<i>Asteraceae</i> <i>Chrysanthemum indicum</i>	Rariya kasa (H)	Whole plant	Decoction is taken once daily	-	Formatted: Font: Italic
<i>Combretaceae</i> <i>Tridax procumbens</i> (Tridax)	-	Whole plant	Cold water infusion with potash is taken	-	Formatted: Font: Italic
<i>Compositae/Asteraceae</i> <i>Vernonia amygdalina</i> (Bitter leaf)	Tsula (N) Shiwaka (H) Ewuro (Y) Olubo (I)	Stem bark, leaves (Root is very poisonous)	Leaf infusion or stem bark decoction is taken daily	Vernodalin, vernomygdin, vernolepin, vernolide, flavonoid	Formatted: Font: Italic Formatted: Font: Italic
<i>Compositae/Asteraceae</i> <i>Vernonia cinerea</i> (little iron weed)	-	Whole plant	Decoction is taken orally	Vernonin, amyrinacetate, lupeol acetate, vernomoside, β -amyrin, sesquiterpine, β -sitosterol, pene lactine, stigmasterol, luperol, α -spinasterol	Formatted: Font: Italic Formatted: Font: Italic
<i>Compositae/ Asteraceae</i> <i>Vernonia perrottetii</i>	-	Whole plant	Decoction is taken orally	Vernonin	Formatted: Font: Italic
<i>Balanitaceae</i>	Aduwaa (H)	Bark, seed (it	Decoction of either bark	Disogenin, sapogenin,	Formatted: Font: Italic

<i>Balanites aegyptiaca</i> (Desert date)	Adua (N)	causes nephrosis and hepatitis)	or seed is taken 1-3 days	yamogenin, flavonoids, triterpenoid, sterols, carotenoids	
<i>Bignoniaceae</i> <i>Newboldia laevis</i> (Tree of life)	Aduruku (H) Dinberechyamile (N) Ogiris (I) Akoro (Y)	Roots, leaves	Infusion is taken daily	Alkaloids, tannins, flavonoids	Formatted: Font: Italic
<i>Bombacaceae</i> <i>Ceiba pentandra</i>	Rimin (H) Kada (H) Akpu (I) Kuchi (N) Ogun (Y)	Leaves, barks, roots	Decoction is taken oftenly	-	Formatted: Font: Italic
<i>Boraginaceae</i> <i>Heliotropium indicum</i> (Wild clary)	Karkashin korama (H) Etigulu (N) Ogbe-akuko (Y)	Whole plant	Infusion or decoction taken daily	Indicine-N-oxide, saponins, tannins	Formatted: Font: Italic
<i>Caesalpiniaceae</i> <i>Cassia occidentalis</i> (Negro coffee)	Tafasar masar (H) Rere (Y) Gaya (N) Akede ogbara (I)	Leaves (Toxalbumin is destroyed by roasting)	Infusion is taken once daily	Toxalbumin, anthracene glycoside, sennoides, flavonoids	Formatted: Font: Italic
<i>Caesalpiniaceae</i> <i>Chamacrostaphylos rotundifolia</i>	Ilegbere (Y) Damma (N)	Whole plant	Decoction taken daily	-	Formatted: Font: Italic
<i>Caesalpiniaceae</i> <i>Daniellia oliveri</i> (Ilorin balsam)	Maje (H) Ozabwa (I) Danoli (N) Iya (Y)	Stem bark, leaves, bark, leaf buds	Decoction taken daily; powder can also be taken	Alkaloids, tannins, gum	Formatted: Font: Italic
<i>Caesalpiniaceae</i>	Kalgo (H)	Fresh leaves, dried	The decoction of the first	Alkaloid, tannin	Formatted: Font: Italic

<i>Piliostigma thonningii</i> (Thoning's piliostigma)	Okpoatu (I) Bafin (N) Abafe (Y)	stem bark, root bark, fruits	3 is taken; fruit powder infusion is taken daily		
<i>Caesalpiniaceae</i> <i>Tamarindus indica</i>	Tsamiya (H) Darachi (N) Ajagbon (Y) Icheke-oyibo (I)	Leaves, fruits, fresh stem bark	Decoction made with potash or cold water infusion is taken daily	Tartaric acid, citric acid, malic acid, tannins	Formatted: Font: Italic
<i>Capparidaceae</i> <i>Cleome viscosa</i> (Chicken weed)	Egyagi (N) Epira (Y)	Whole plant	Decoction is taken orally	-	Formatted: Font: Italic
<i>Caricaceae</i> <i>Carica papaya</i> (Pawpaw)	Gwanda (H) Konkenii (N) Ojo (I) Ibepe (Y)	Seed, root	Cold water infusion or decoction is made. Half a cup is taken daily	Papain, cryptoxanthin, glycosides polyphenols	Formatted: Font: Italic
<i>Celastraceae</i> <i>Maytenus senegalensis</i>	Namiji tsada (H) Kuku kama (N) Shepolohun (Y)	Roots, leaves	Decoction or infusion is made and taken daily	Maystansine, flavonol	Formatted: Font: Italic
<i>Combretaceae</i> <i>Pteleopsis habeensis</i>	Lallen giwa (H) Shinci (N)	Leaves	Decoction with <i>Xylopia</i> <i>aethiopica</i> and <i>Capsicum</i> <i>frutescens</i> taken orally	-	Formatted: Font: Italic
<i>Canelliaceae</i> <i>Warburgia ugandensis</i> (Fever tree)	-	Dried stem bark, roots, leaves	Decoction or infusion is taken daily	Drimenol, warbugin, warburgiadine, ugandesoline, muzigachial	Formatted: Font: Italic
<i>Solanaceae</i> <i>Withania somnifera</i>	Karama anta (H)	Leaves	Powdered leaf is taken; enema of decorticated root is used on infants	Withanine, withernolide, witherferin	Formatted: Font: Italic

<i>Combretaceae</i> <i>Bryorcapus coccineus</i>	Kimbar maharba (H) Oka (I) Darabagi (N) Ade (Y)	Roots, stem, leaves	Cold water infusion of the root and that of lawsonia inermis; take a tumbler daily in the morning	Alkaloid	Formatted: Font: Italic
<i>Ebanaceae</i> <i>Dicrypyros mespiliformis</i> (West African Ebony)	Faru (H) Musunchi (N) Igududu (Y)	Root bark, stem bark, leaves, roots, (abortifacient)	Decoction is taken once daily	Phembagin, scopolin, tannin	Formatted: Font: Italic
<i>Euphorbiaceae</i> <i>Alchornea cordifolia</i> (Christmas bush)	-	Leaves, stem bark, root	It is used to prepare malaria mixture with other leaves; taken once	Inulin, alchornin, tannin, alkaloid	Formatted: Font: Italic
<i>Euphorbiaceae</i> <i>Jatropha curcas</i> (Fignut)	Binida zugu (H) Olulu-idu (I) Kasha'a (N) Botuje (Y)	Fruits, leaves, root, seeds	Decoction is taken half tumbler daily	Curcin, inulin, tetramethyl- pyrazine, phobolesters	Formatted: Font: Italic
<i>Euphorbiaceae</i> <i>Manihot esculentus</i> (Cassava)	Rogo (N) Rogo (H)	Leaves	Decoction is taken once daily	Hydrocyanide, tannins, alkaloid, saponins	Formatted: Font: Italic
<i>Euphorbiaceae</i> <i>Phyllanthus amarus</i> (Egg noma)	Alambu (H) Sunyegboro – sunzuma (N) Debi-sawo (Y)	Whole plant	Decoction is taken once daily	Tannins, saponins, inulin	Formatted: Font: Italic
<i>Fabaceae</i> <i>Xanthoxylum</i> <i>xanthoxyloides</i> (African satin wood)	Fakuwari (H) Ata (Y) Kosonkori (N)	Roots, stem bark	Decoction is taken once daily	Alkaloids, vanillic acid, xanthoxyloid, 2-hydroxy benzoic acid	Formatted: Font: Italic
<i>Graminae/Poaceae</i>	Eto lemu (N)	Leaves	Tea is prepared and taken	Limonine, neryl, geraniol,	Formatted: Font: Italic Formatted: Font: Italic

<i>Cympogon citratus</i> (lemon grass)	Waape (Y)		oftenly	citronellal, campene, triterpenes, flavonoids
<i>Lamiaceae</i>	Daidoy atagida (H)	Leaves	Decoction taken thrice	Eugenol, thymol, camphor
<i>Ocimum gratissimum</i> (Basil fever plant)	Nehonwu (I)		daily	carryophylline
	Tanmotswagi-wawagi (N)			
	Esinri (Y)			
<i>Liliaceae</i>	Lubasa (N)	Bulb	The leaves are chewed for	Riboflavin, alliin, sulphur ,
<i>Allium cepa</i> (Onion)	Alubasa (H)		10 days	allicin compounds
<i>Liliaceae</i>	Tafarnuwa (H)	Rhizomes	Decoction of fresh or dry	Allicin, alliin, alliinase,
<i>Allium sativum</i> (Garlic)			leaves is taken for 10 days	flavonoides, cyanogenic glycoside
<i>Loganiaceae</i>	Kookiyar (H)	Leaves, fruits (It is	Infusion is taken once	Nigitanin, barterine, kagerine,
<i>Strychnos spinosa</i> (Nux-vomica)	Manvovogi (N)	poisonous)	daily	kribine, strychnine,
	Alako (Y)			lirioresinol
<i>Leguminosae</i>	-	Bark	Decoction is taken twice	-
<i>Entalida plaseoloides</i>			daily	
<i>Malvaceae</i>	Kpami (N)	Fresh fruits, leaves	-	Fernesol
<i>Abelmonchus esculentus</i> (Lady's finger)	Kubewa (H)			
<i>Malvaceae</i>	Sangii ekoti (N)	Whole herb	Decoction is taken orally	Alkaloid, flavonoid,
<i>Sida acuta</i>				prostaglandin, tannins
<i>Ceratonia siliqua</i> (Carob bean)	-	Seeds	Molasses are extracted	Molasses gum
			from seeds and taken	
			accordingly	

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<i>Meliaceae</i>	Dogon yaro (H)	Stem bark, root	Decoction of stem bark or root is taken orally	Nimbin, nimbidion, nimbidin, salanin, meliacin	Formatted ... [1]
<i>Azadirachta indica</i> (Neem tree)					Formatted ... [2]
<i>Meliaceae</i>	Madaaci (H)	Stem bark, leaves	Decoction is taken twice daily	Scopoletin, sterol, limonoid gedunin	Formatted ... [3]
<i>Khaya senegalensis</i> (Mahogany)					Formatted ... [4]
<i>Meliaceae</i>	-	Stem bark, root,	Decoction is taken once daily	-	Formatted ... [5]
<i>Trichila emetica</i>		leaves			Formatted: Font: Italic
<i>Mimosasae</i>	-	Roots, fruits,	A tumbler of hot decoction is taken daily	Tannins, alkaloids	Formatted ... [6]
<i>Dichrostachys cinerrea</i> (Cow thorn)		leaves			Formatted ... [7]
<i>Mimosasae</i>	Dorowa (H)	Leaves, stem bark,	Make decoction and take once daily	Alkaloid, saponin, tannin	Formatted ... [8]
<i>Parkia biglobosa</i> (Niffa)		fruits			Formatted ... [9]
<i>Moraceae</i>	-	Leaves, fruits	Decoction is taken once daily	-	Formatted ... [10]
<i>Ficus thonniigii</i>					Formatted: Font: Italic
<i>Moraceae</i>	-	Leaves, roots,	Decoction is taken orally	-	Formatted ... [11]
<i>Musanga cercropioides</i> (Umbrella tree)		stem			Formatted ... [12]
<i>Myristicaceae</i>	Gwaba (H)	Leaves	Decoction is taken daily	Quarcetin, flavonoids, sapogenins, eugenol	Formatted ... [13]
<i>Psidium guajava</i> (Guava)					Formatted ... [14]
<i>Ochinaceae</i>	Namijin Kade (H), Okopia	Stem, bark, root	The powder is taken with meat when required	Alkaloid, tannin, saponin, resin	Formatted ... [15]
<i>Lochira lanceolata</i> (Iron wood)	(L), Maganchi (N), Iponhon (T)				Formatted ... [16]
<i>Onagraceae</i>	Shashatau (H)	Whole plant	Leaf decoction is taken	-	Formatted ... [17]

<i>Ludwigia octovalis</i> (Willow)			once daily			Formatted ... [18]
<i>Palmae</i>	Kwakwa (H) Akibeka (I)	Bark, root, nut,	Decoction or infusion of	Saponin, tannin, glycerides		Formatted ... [19]
<i>Cocos nucifera</i> (Coconut palm)	Yikunu Kputa (N) Agbon (Y)	leaves, fruit	bark, rook, leaves is taken once daily			Formatted ... [20]
<i>Palmae</i>	Dabbino (H) Dobino (N)	Dried fruits	The fruits are eaten	-		Formatted ... [21]
<i>Phoenix dactylifera</i>	Okun (Y)					Formatted: Font: Italic
<i>Papilionaceae</i>	Idon zakara (H) Ojologbo	Leaves	Cold water maceration or	Abrin, abrine, abricin,		Formatted ... [22]
<i>Abrus precatorius</i> (Jecquirity bean)	(Y) Eyekosun dargii (N)		dried powder is taken for 3days	abricine		Formatted ... [23]
<i>Papilionaceae Pterocarpus</i> <i>erinaceus</i> (African rosewood)	Madobiya (H) Aze eju (I) Zanchi (N) Apepe (Y)	Stem bark, leaves, fruits	Decoction or infusion taken 1-3 times daily	Alkaloid, tannins, resins		Formatted ... [24]
<i>Papilionaceae</i>	Samaci (H) Sabanigi (N)	Whole plant	Decoction is taken once daily	Tephrosin		Formatted ... [25]
<i>Tephrosia bracteolate</i>	Riro (Y)					Formatted: Font: Italic
<i>Piperaceae</i>	Masoro (H) Azeegu (I)	Fruits, leaves	They are used as	Charicine, piperine,		Formatted ... [26]
<i>Piper guinense</i> (West African black pepper)	Masoro (N) Iyere (Y)		adjuvants and taken per os	guinesine, wisanine, dihydrowisanine		Formatted ... [27]
<i>Rosaceae</i>	Gwaza (H) Putu (N)	Fruit, kernel, twig	Decoction is taken orally	2-phytosterol, parinarium,		Formatted ... [28]
<i>Neocarys macrophylla</i> (Neuroli tree)				sterols A and B		Formatted ... [29]
<i>Rubiaceae</i>	Kasfiya (H) Nambi	Root, twig, stem	Decoction is taken orally	Crossoptine pholobaphine, B-		Formatted ... [30]
<i>Cryssopteryx febrifuga</i>	sunsun (N) Ayeye (Y)	bark, leaf		quinovine		Formatted ... [31]
<i>Rubiaceae</i>	Tafashiya (H) Gbashi (N)	Root, fruit, stem	Decoction is taken twice	Naufoline, augustine indole		Formatted ... [32]
<i>Nuclea latifolia</i>	Egbesi (Y)	bark	daily	quinolizidine		Formatted ... [33]

(African peach)						Formatted: Font: Italic
<i>Rutaceae</i>	Lemun tsami (H)	Leaves	Decoction is taken; steam	Flavonoid, ascorbic acid		Formatted: Font: 11 pt, Italic
<i>Citrus aurantifolia</i>	Afofanta (I) Lemu bakagi		from the decoction can be			Formatted: Font: Italic
(Sour orange)	(N) Orombo wewe (Y)		inhaled			Formatted: Font: 11 pt, Italic
<i>Rutaceae</i>	Furuntu (H) Oromo orji	Fruits	Fruits are decocted and	Vitamin C		Formatted: Font: Italic
<i>Citrus paradise</i>	(I) Furuntu (N) Lemi iba		taken orally			Formatted: Font: 11 pt, Italic
(Grape fruit)	(Y)					Formatted: Font: Italic
<i>Rutaceae</i>	Fasa kwabri (H)	Root, stem	Decoction is taken as	Zanthoxylol (antisickling)		Formatted: Font: 11 pt, Italic
<i>Zanthoxylum</i>	Kosonkori (N)		required	inulin, alkaloid, vanillic acid		Formatted: Font: Italic
<i>zanthoxyloides</i>	Ata (Y)					Formatted: Font: 11 pt, Italic
(African satin wood)						Formatted: Font: Italic
<i>Solanaceae</i>	Matsar mama (H)	Whole plant	Decoction is taken as	Alkaloids, glycosides, inulin,		Formatted: Font: 11 pt, Italic
<i>Physalis angulata</i>	Putu (L)		needed	saponin		Formatted: Font: Italic
(Goose berry)	Alasagi (N)					Formatted: Font: 11 pt, Italic
	Koropo (Y)					Formatted: Font: Italic
<i>Sterculiaceae</i>	Kukuki (H)	Stem bark, seed	Decoction is taken thrice	Tannins, rhamnase,		Formatted: Font: 11 pt, Italic
<i>Sterculia setigera</i>	Eso funfun (L)		daily with hot water	galactorumacide		Formatted: Font: Italic
	Kokongiga (N)					Formatted: Font: 11 pt, Italic
<i>Sterculiaceae Theobroma</i>	Cigban koko (N)	Seed	Decoction of dry seed is	Theobromine		Formatted: Font: Italic
<i>cacao</i>			taken			Formatted: Font: 11 pt, Italic
(Cocoa tree)						Formatted: Font: Italic
<i>Sterculiaceae</i>	Harkufa (H)	Whole plant	Cold water infusion or	-		Formatted: Font: 11 pt, Italic
<i>Waltheria indica</i>	Arkufe (N)		decoction is taken daily			Formatted: Font: Italic
	Ewerepo (Y)					Formatted: Font: Italic
<i>Ulmaceae</i>	-	Stem bark, leaf,	Decoction or infusion	Saponins, tannins, inulin		Formatted: Font: 11 pt, Italic
<i>Trema orientalis</i>		twig	taken orally			Formatted: Font: Italic
						Formatted: Font: 11 pt, Italic

(Charcoal tree)						
<i>Zingiberaceae</i>	Turi (N)	Rhizomes, fruits	Decoction is taken with	d-sabinene, aneol, borneol	Formatted: Font: Italic	
<i>Curcuma longa</i>			milk or sugar	zingiberene, bisabolene	Formatted: Font: 11 pt, Italic	
(Turmeric)					Formatted: Font: Italic	
<i>Zingiberaceae</i>	Tsita maiyatsi (H) Tsutafu	Leaves, rhizomes	Rhizome is chewed raw;	Gingerol, phellandren, zingiberene, bisabolene,	Formatted: Font: 11 pt, Italic	
<i>Zingiber zingiber</i>	(N) Atale (Y)		leaf decoction is taken	oleoresin	Formatted: Font: Italic	
Syn: <i>Zingiber officinale</i>			thrice daily		Formatted: Font: 11 pt, Italic	
(Ginger)					Formatted: Font: Italic	
<i>Verbenaceae</i>	-	Fruits, leaves	Make tea with either fruit	Lantadene (toxic)	Formatted: Font: 11 pt, Italic	
<i>Lantana camara</i>			or leaves and take		Formatted: Font: Italic	
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