Greener Journal of Biomedical and Health Sciences

Submitted: 18/10/2016
Accepted: 22/10/2016
Published: 08/11/2016

DOI: http://doi.org/10.15580/GJBHS.2016.1.101816180

Artemisia annua (Qing Hao): Solved and Adaptively Met the Drug Resistance Challenge by *Plasmodium* Malaria Parasite. It's other Chemotherapeutic attempt against Cancer; and Overall Implications on Public Health

By

Ozurumba LN
David J
Ukoh V

Research Article (DOI: http://doi.org/10.15580/GJBHS.2016.1.101816180)

Artemisia annua (Qing Hao): Solved and Adaptively Met the Drug Resistance Challenge by *Plasmodium* Malaria Parasite. It's other Chemotherapeutic attempt against Cancer; and Overall Implications on Public Health

***[1]Ozurumba LN, [2]David J and [3]Ukoh V**

[1]School of Public Health, College of Health Sciences, Walden University, Minneapolis, United States of America.
[2]Department of Biological Sciences (Parasitology), Abubakar Tafawa Balewa University ATBU, Bauchi, Bauchi State, Nigeria.
[3]Department of Medical Microbiology and Parasitology, College of Health Sciences/Medicine, University of Uyo, Uyo, Akwa Ibom State, Nigeria.

*Corresponding Author's Email: leo.ozurumba @waldenu. edu; leon_ozurumba @yahoo .com;
Phone: +2347036018070.

ABSTRACT

The plant herb *Artemisia annua* (Qing Hao) has been used in China for over 400years to treat malaria disease, which has a mostly higher prevalence in the tropics where it is more endemic. Also, it has been used to kill parasitic worms, as anti-microbial agents, and has found non-medicinal uses in the United States and Europe. The active anti-malarial compound in *A. annua* called Artemisinin was isolated in the 1970s.

Evidence of drug resistance by malaria parasite to Artemisinin based monotherapy in some Southeast Asian countries propelled development and introduction of Artemisinin based combination therapies (ACTs) which the WHO now encourages over monotherapy.

A research team in the United States appear to have pioneered a "chemotherapeutic research revolution in Cancer treatment" involving use of Artemisinin based compounds, with reported successes on human breast cancer cells in-vitro-from bench work, as the cancerous cells were killed within some hours on treatment with an Artemisinin based compound.

With work on the first genetic map of *A. annua* done and published by a United Kingdom based research team, and on-going funded studies to develop more effective non-synthetic and semi-synthetic analogues of Artemisinin underway, a plethora of more opportunities stand to become available to be exploited and utilized in other investigations; but whether this would translate to authenticated successes that could do well or/and pass anti-cancer drug screening yardsticks of related National Drug approving and standardization agencies remains the real task.

Worthy of note is the discovery and use of some new and other herb plants which have been screened and found to show anti-cancer properties to battle cancer. This should complement efforts through studies on use of artemisinin and its derivative compounds to battle cancer.

These efforts are part of the multi-faceted attempts by man against "these strange and deranged cells that grow for the sake of growth but with no clearly constituted means of modulating the growths".

The historical developments in use of *Artemisia*/artemisinin and its various derivatives, the active chemical compounds, shortcomings and attempts and improvements in relation to malaria and cancer treatment have been elucidated in this article.

Key words: Artemisinin, combination therapy, anti-cancer, *Plasmodium*, genetic map.

INTRODUCTION

Artemisia annua is a short day-plant possessing a shoot and root system and could attain a height of around 2metres (Ferreira et al, 1995a; McVaugh, 1984). Historically, Artemisia plants have been traditionally grown in China, and have been found to be a component of the plant flora in Asia– with notable presence in countries like China, Vietnam and India (Gray 1959; CDC 2012). The chromosome number of *A. annua* is derived from the genetic equation 2n = 36.

In recent years, the plant has been found to now grow wild in America and Europe, and Artemisia annua has also been introduced for cultivation in high altitude African Nations in East and Central Africa (Bui *et al*, 2 0 1 1) , in

addition to the cultivated form of the plant (crops) in countries where they are utilized for health purposes – particularly in Asia. *Artemisia annua* is a plant and a herb which is grown as a Crop. It has several medicinal and non-medicinal uses (Klayman, 1993; Wright, 2002).

Ethno-botanical and ethno-pharmacological engagements has reported its usage for treating other ailments such as inflammation, bleeding, certain bacterial and fungal infections, certain helminthic worm infections, cold, diarrhea, certain ulcerations, some reproductive related problems in females and to reduce effects of fever. Also, it is utilized as aromatic wreath and for flavouring beverages. Methods such as solvent based extraction procedures has been successfully employed to extract Artemisinin. Historically in 1971, an extraction procedure in which aerial parts of *A. annua* was extracted in low-boiling point solvents such as Diethylether was discovered and this has been vital to the technology of Artemisinin extraction and production (Efferth, 2006).

It was also discovered that *Artemisia* naturally synthesizes and stores Artemisinin in special glands called Glandular trichomes (GT) which are seen as structures that bulge out from the epidermal surfaces of the leaves, stems and flowers of plants (Woerdenberg *et al*, 1994). Artemisinin concentration in the plant is normally highest close to the period of flowering. In 1984, scientists at the Walter Reed Army Institute of Medical Research in the United States successfully crystallized Artemisinin.

For over four centuries, *A. annua* has been used in China to treat malaria. Malaria is known to be accompanied by symptoms of which include fever, recalling that malaria was first described in 400BC by Hippocrates. *A. annua* has already been cited in the earliest Chinese medical prescriptions related to the Mawangdui tomb dating back to 168BC. However, a publication dated to 1596 contained a description of the use of *A. annua* to treat chills and fever caused by malaria (Firestone and Sundar, 2009).

In the 1960s, an initiative by the Chinese government under President Mao led to the first isolation and chemical characterization of the active chemical compound in the plant herb *Artemisia*, responsible for its potency in killing *Plasmodium* malaria parasite in 1974 (Efferth, 2006; Efferth 2007). The active compound was called "Qingaosu" in Chinese language. Non-synthetic analogues of the compound were developed one after another. Some of these analogues include: Artemether, Artesunate, and Artenimol.

Malaria is a protozoan parasitic infection caused by a parasite of the generic name *Plasmodium* transmitted mostly by the female Anopheline mosquito, and found to be more endemic in tropical countries of the world, where its resultant effect on morbidity and mortality has more pronounced occurrence in children below five years, and non-immuned individuals (Ozurumba 2011, WHO, 2012) who account for higher burden of the disease. On the other hand, cancer is probably best defined as a group of diseases (more than 100 different diseases) rather than a single bio-phenomenon, characterized by processes of unregulated or uncontrolled proliferation (multiplication) of abnormal cells. Cancer commences when normal cells begin to change and grow uncontrollably, emerging as a mass of abnormally proliferating cells called Tumour. Cancer is also termed Neoplasia and the word "Neoplasm" was derived from "Neoplasia", which connotes "new growth", and described as uncontrolled growth of cells that is not under physiologic control (University of Utah Med Library, 2016). It has been observed that the growth of a neoplasm or cancerous cells may continue despite the cessation of the stimulus which triggered the change (physiological, anatomical and biochemical) of the normal cells to become cancerous cells (also called neoplastic cells). When a cell is cancerous, it means it has the capacity to spread to other parts of the body irrespective of where the cancer has spread; it is still named by what is called its primary site. It should be noted that cancer could also be a secondary cancer. The growth of tumour can generally be described as being benign or malignant (American Cancer Society, 2016; Elyse *et al*, 2016).

A scientist by name Prescott, in the mid 1950s demonstrated that cells often exhibit a remarkable ability to recover from interruptions in their normal processes and cell activities, pointing out the existence of inherent homeostatic mechanism that help return these cells to an equilibrium state. It had been a very important discovery and contribution to cell biology; and to our understanding of some of the fundamental or basic concepts in normal cell activities, growth and transformation into deranged states.

Cancer may be caused by several factors which could be of chemical, physical or biological origins (all called carcinogen in Cancer Biology -Oncogenesis) which possess the capacity to change normal cells into abnormal or deranged or neoplastic cells (Campbell *et al*, 2008; Guenova and Balatzenko, 2015). Typical chemical factors include Aflatoxin, hydrocarbons, nitrosamines, cigarette smoke beyond threshold that the body could tolerate or accommodate, pathogens such as viruses (mostly), radiations such as UV rays and Xrays or Ionizing rays released into the atmosphere and in reported few cases of genetic factors which have been associated with cancer (Mader, 2008; Campbel *et al*, 2008).

The economic burden due to lost productivity, costs associated with illness and therapy, and the long term effects of cancer and its treatment on the quality of life of survivors, all take a combined toll at the population level. Thus, as some cancer incidence rates rises, cancer's impact on public health grows.

Justification and objectives of this review article:

Malaria is a disease resulting from an infection by a Protozoan *Plasmodium* parasite, and it has been found that one of the causes of cancer is through infection by a virus leading to what is called "cervical cancer". Invariably, both malaria and cervical cancer could be treated, except that malaria can not be prevented through usage of a vaccine while a vaccine for cervical cancer exists. Several species of *Plasmodium* exist in both humans and lower animals of which include rodents, reptiles, monkeys, chimpanzee and other animals. The *Plasmodium* species infecting Man include *P. falciparum, P. vivax, P. ovale*, and *P. malariae*; and in recent times, some other species and sub-species have been identified (WHO, 2012), Though the tide of the burden of malaria is been stemmed down in some countries, its incidence may be rising in some other countries while in some countries where it has been previously eradicated, malaria appear re-emerging. Then, the issue of resistance to antimalaria drugs have propelled the need to step up efforts to maintain the presence of potent antimalaria drugs in our drug portfolio. (WHO, 2010; WHO, 2011; Van-Tyne, 2011).

Globally, between 300-500million cases of malaria infection are reported annually, while between 1 to 1.2million deaths are recorded yearly from these cases. One fifth of the world's population is reportedly at risk of being infected (Hollyman, 2015). Between 3.2 and 3.3 billion people live in areas at risk of malaria transmission in 100countries and territories (CDC, 2012; Hollyman, 2015).

In Nigeria the most populous black nation on earth, N132 billion (Naira) is lost to the disease as cost of treatment and loss of man hours, malaria account for 63% of all visits to public health facilities, 29% of childhood death, 25% of infant mortality and 11% of maternal mortality (LSM, 2016).

Malaria is a problem in the 1st and 2nd pregnancies and may cause parturition of babies with low birth weight and other associated problems. About 9 to 10 clinical cases of malaria occur in Africa. Children below 5years, pregnant women, and travelers with non-immune status from non-endemic countries who travel to endemic countries are among those usually at risk of infection (CDC, 2015). As part of the global war against malaria, an attempt to check the spread of malaria disease by the year 2015 during which man would have begun to attempt to significantly reduce the number of new cases– is one of the millennium development goals which were set in year 2000.

Artemisisnin is of biological importance because of its outstanding antimalarial activity (CDC 2012) and its has been reported through publications in reputable journals that it has anti-tumour potentials (Nam *et al*, 2007; Singh *et al*; 2004, Crespo-Oritz and Wei, 2012).

The number of cancer deaths is 171.2per 100,000 men and women per year (based on 2008-201 deaths in the United States (National Cancer Institute, 2015). There are several types of cancer named according to the region or organ of the body affected. Unlike malaria which manifests in fewer forms in terms of disease state (uncomplicated mild and severe malaria types, with specific types such as cerebral malaria common among children), several forms of cancer exists which are associated with specific concentrated manifestations in various parts of the body. Typical examples include:

Colon cancer, Pancrearic adenocarcinoma, Brain malignancy (Brain cancer), Prostate cancer, Cervical cancer, Ovarian cancer, Leukaemia, Breast cancer, Skin cancer, Lung cancer, CNS cancer, among others (National Cancer Institute, 2015). Among these several cancer types, the globally leading causes of death by cancer appear to be lung, liver, stomach, colorectal types of cancer (WHO, 2016; De Martel *et al*, 2012; World Cancer Report, 2014). Among women, it was breast, colorectal lung and cervix cancer as the leaders in terms of death toll, and it was lung prostate and colorectal among men.

The use of ACTs derived from Artemisia in form of combination therapies to successfully treat individual malaria cases, and foraging into exploits of attempts to use it for treatment of cancer on one hand, and its possible consequent impact on large scale populations can provide information that directly affect the health of millions of people globally each year, with its attendant public health significance, This goes not only for Artemsinin, but also for related analogues of Artemisinin which have come in handy for treatment of malaria and attempts for treatment of cancer.

The antimalarial properties of Artemisinin and its mode of action, success story and impact of Artemisinin on war against malaria, the shortcomings in the chemical structure of Artemisinin with regards to effectiveness as an anti-malarial, attempts at improving its shortcomings and introduction non-synthetic derivative analogues, introduction of ACTs and benefits from ACTs' based chemotherapy of malaria, active compound in *A. annua* for cancer chemotherapy, and *A. annua* Genetic Resources and its benefits for malaria and cancer treatment have been presented in this article, all in one synchronized piece.

History of use of Artemisia for malaria treatment

For over four centuries, *A. annua* has been associated with the treatment of malaria, a disease which is known to be accompanied by several symptoms of which include fever. Considering the fact that documentation of evidence that

A. annua was used to treat fever as far back as 340AD, around when the Handbook of Prescriptions for Emerging Treatment was published, it may not be unlikely therefore, that some of the treated cases of fever may have been possibly due to *Plasmodium* malaria infection. Moreso, recalling that malaria was first described in 400BC by Hippocrates. However, a publication dated to 1596 contained a description of the use of *A. annua* to treat chills and fever caused by malaria in China (McVaugh, 1984; Kaptein *et al*, 2006; Efferth 2007). At a stage in history, Artemisia annua was used to treat worm infections (Wright, 2002; Graziose *et al*, 2010). Ukoh and Ozurumba (2016) from their study, observed that intestinal parasitic infections (IPIs) (caused by worms) such as *Taenia, Strongyloides*, Hookworm, *Schistosoma*- to a higher extent in terms of prevalence, and to a lesser extent- *Trichuris, Cryptosporidium and Dicrocoelium dendriticum* were the ones found to be most prevalent in a certain population in North eastern Nigeria; with the first group requiring more public health attention than the second group at the period of the study (Ukoh and Ozurumba, 2016).

Currently, the active compound of *A. annua* has been used to treat malaria in well over hundreds of thousands of people in China and Vietnam and has now extended to the global level in the area of its usage as an antimalarial-be it in form of monotherapies or in form of combined therapies called artemisinin combined therapy-ACT (Klayman 1993; WHO, 2012).

A plant of *Artemisia annua* is now known to yield 0.3–0.5% Artemisinin (Woerdenbag *et al*, 1984; Delabays *et al*, 1993; WHO, 2006). High level semi-synthetic production the potent antimalarial Artemisinin was invented and described by Paddon *et al* (2013), providing a biosynthetic route to production of artemisinic acid using a dehydrogenase and a 2nd cytochrome that facilitated efficient biosynthesis.

Chemical Structure and properties of Artemisinin (Qinghaosu)

Artemisinin is an aromatic compound with a molecular mass of 282,332g/mol and possess a 3D structure (PUBCHEM, 2016). It was originally introduced for the treatment of resistant *Plasmodium falciparum* malaria and has been reportedly used to treat *vivax* malaria. Artemisinin is a naturally occurring endoperoxide sesquiterpene lactone, forms colourless orthorhombic crystals that are soluble in alcohol and in ethyl acetate (Meshnik *et al*, 1996; Crespo *et al*, 2007). It is a quadricycle, possessing a basic structure of 4 rings. One of these four rings has a peroxide linkage as part of the ring. Also, it is an endoperoxidase, containing a peroxide linkage of two oxygen (O-O) between 2 points on one of the rings. A sensitive endoperoxide bridge is shielded by a Ring system (WHO, 2006).

Antimalarial properties of Artemisinin and mode of action

Artmisinin exerts its properties as an anti-malarial compound through a pharmacophoric peroxide bond in a unique 1,2,4– trioxane heterocycle. The peroxide bridge or bond in Artemisinin is critical for its chemotherapeutic anti-malarial activity (Crepo *et al*, 2007).

A secondary ozonide contains the endoperoxide bridge that is critical and vital for the antimalarial action of Artemisinin. This endoperoxide bridge is unstable and stability was improved upon by the emergence of some developed synthetic and semi-synthetic analogues to Artemisinin.

Several years back, it was hypothesized that Artemisinin reacts with a chemical compound that is found at high concentrations on the surface of *Plasmodium* parasite. This chemical compound has high concentrations of Iron. The reaction between the chemical compound and Artemisinin then lead to a cascade of other reactions that eventually lead to killing of the parasite.

Following this malaria parasite Iron and Artemisinin reaction, some other chemical reactions occur which spawn charged atoms called “free-radicals”. These free radicals then attack the parasite cell membrane through a lytic process that dismembers the parasite’s cell membrane and lead to the killing of this unicellular protozoan *Plasmodium* parasite (Harrill, 2001).

This hypothesis may not be an unlikely event, as certain insights by Ozurumba in his previous researches, some of which have partly published. One of them revealed that a compound in the form of Iron (III) Haem accumulates in the *Plasmodium* parasite in an event involving Haemoglobin digestion in the parasite (Ozurumba, 2012).

Shortcomings in Chemical structure with regards to effectiveness as an anti-malarial

Though Artemisinin has shown lots of promise as an effective anti-malarial, being successfully engaged against uncomplicated malaria, clears all gametocyte stages of the parasite from the mammalian system, worked in cerebral malaria cases in children-helping to revive the children and recover; certain features in the chemical structure of Artemisinin have been found to be some of its few areas of shortcomings in its efficacy as an anti-malarial.

Artemsinin is poorly soluble in water, while the endoperoxide bridge appears to be unstable as this sensitive peroxide bridge is shielded by a Ring System (WHO/TDR, 2004, WHO, 2006). Also, the bio-availability of Artemisinin based antimalarials is a shortcoming in Artemisinin malaria therapy.

Artemisinin has a short half-life which also manifests in its other form that is used in Artemisinin combination therapy, as one of the factors that tend to cause some of the few related drug resistance problems by *Plasmodium,* recorded for Artemisinin based therapies, be it mono or combined therapies. Its short half-life and bio-availability defects are problems related to its bio-pharmaceutical profile.

Attempts at improving shortcomings and non-synthetic derivative analogues

Though some non-synthetic derivatives of Artemisinin have been developed, and are produced by pharmaceutical companies in form of Artesunate, Artemether and few others, attempts are being made to improve on the shortcomings in Artemisinin by developing semi-synthetic and synthetic analogues of Artemisinin (WHO/TDR, 2004) geared towards solving or reducing the defects and challenges related to availability of the anti-malarial, water solubility, stability and cost. Many of these efforts have received support and funding from the WHO and MMV. One of such synthetic analogues include: OZ227.

The synthetic analogue OZ227 that was developed by a scientist based in the United States- at the period of its initial development, this compound had an improved solubility in water and was more stable than Artemisinin (Crespo *et al*, 2007). However, OZ227 was not entirely devoid of defects. For instance, though it was more water soluble than Artemisinin, it was still regarded as having poor solubility in water, based on standard yardsticks for determining water solubility (WHO/TDR, 2004). In addition, oral administration of 0Z227 showed that it was not very reactive via this route for treatment.

Success stories and impact of Artemisinin on war against malaria

As at 2010, scientists believed that no other natural non-synthetic chemical compound with its unique endo-peroxide bridge is known. This scenario would remain the same unless another natural compound with such anti-malarial property is discovered. However, each anti-malarial of completely different basic chemical structure tend to have different inherent antimalarial mode of action and properties.

Traditionally in China, Artemisia (Qing Hao), has been used for reducing fevers, inflammation, headache and treat malaria. Artemisia has been reportedly used on over 1million patients in China and Vietnam to treat cases of malaria (Graziose *et al*, 2010).

Apart from oral and intravenous routes of administration of Artemisinin based drugs from which successes have been recorded, anti-malarial suppositories derived from *A. annua* have been developed, which are injected rectally. This has been engaged in remote areas in endemic countries as emergency lines of initial treatment before the patient reaches the hospital for follow-up treatment. Artemisinin has been used to successfully treat *falciparum* and *vivax* malaria. *A. annua* has been widely used in the tropics for both prevention and treatment of malaria. Its active compound Artemisinin has been found to treat malaria and relatively free of side effects. The use of Artemisinin by itself is a monotherapy. Artemisinin was introduced for the treatment of resistant *Plasmodium* malaria. Artemisinin based monotherapy involving use of its non-synthetic derivatives such as Artemether, Artemotil, Artesunate, Artenmal and sodium Artesunate have recorded various levels of efficacy against *falciparum* malaria and were found to be more effective than Quinine based antimalarials such as Chloroquine and Mefloquine drug lines that were at a stage, the first line of treatment which were beginning to fail during treatment- showing drug resistance, had adverse reactions on patients such as extreme bitter taste and intense itching among others, which the introduced Artemisinin based drugs did not possess.

Quinine-derived antimalaria drugs such as chloroquine were used in the 1960s during the period of campaign to eradicate malaria worldwide. There had been initial success before the malaria parasites were found to be developing resistance to these quinine-derived medicines, which negatively affected the efficacy of the drug and **interrupted** the initial success.

This placed a burden and strain on the need to develop new drug application strategies to effectively treat the disease and fight back the clever evasive action mounted by the parasite against drug-potency. Thus, ACTs which were originally developed by the Chinese in form of Artemisinin based monotherapy before it was upgraded into combined therapeutic forms in the ACTs– was recommended by WHO as first line of treatment for malaria treatment in several affected tropical countries.

The demand for ACTs at a period between 2010 and 2011 was close to 100million, while this figure has been estimated to reach around 190million or more by the year 2012 (then, meeting the demand at the level it could be in 2012 seem to be the new challenge as earlier indicated) (WHO, 2011; Morris *et al*, 2014).

Evidences of resistance by *Plasmodium* to Artemisinin based monotherapy (Artemisinin and its derivatives) were observed in some endemic countries in Southeast Asia such as Cambodia (Kariko, 2015) among other countries-encouraged the need for an innovative type of treatment with Artemisinin in the form a combination therapy. Thus, a treatment paradigm shift from Artemisinin based monotherapy to Artemisinin based combination therapy (ACT) was birthed. The WHO at this stage started discouraging Artemisinin based monotherapy in favour of ACTs. ACTs have been found to be highly effective against malaria parasites that have exhibited resistance to antimalarials (CDC, 2010). Thus, ACTs appear to be one of the few options available for treating malaria.

Several combinations in the ACTs have been developed and are in use, of which includes: Artemether–Lumefantrine, Artesunate-Mefloquine, Dihydroartemisinin–piperaquine, Artesunate– Amodiaquine and Artemisunate–Pyrimethamine–Sulfadoxine.

Several other ACTs are being worked out for development. These includes:

Artesunate–Chloroproguanil–Dapsone, among others. However, Amodiaquine and Pyrimethamine-Sulphadoxine are said to be longer acting antimalarials of longer half lives. This property may make them suitable for combinations with ACTs, which is a combination of both.

Some benefits from ACTs' based chemotherapy of malaria:

These benefits includes reduced risks from its usage such as adverse effects and reduced chances of progression of infection from uncomplicated to severe form of the disease and mortality, and its relieving and curing more persons affected by the disease more than other antimalarials. Thus, ACTs have been found to limit the chances of emergence of drug resistance by malaria parasite.

Finally, areas with high intensity (high transmission rates of malaria), a combination of two longer– acting antimalarials has been suggested because in such areas, the general success rate with ACTs may be challenged by factors such as partial immunity and resolution of symptoms with incomplete dosage treatment. This is unlike the observed high success rate with ACT usage in areas of low intensity of malaria.

Some of the major reasons attributed for the emergence of anti-malarial drug resistance include:

.

Non-compliance with drug dosage regimen that are ineffective.
Slow clearance of the drug from the human system during usage.
Use of anti-malarials whose quality may have nose-dived possibly due to storage conditions.
Widespread haphazard usage of anti-malarials, among other reasons.

Overt time, the levels of resistance by the parasite to treatment courses with Artemisinin and its derivatives–based monotherapy has increased.

History of attempts or engagement of *A. annua* based compounds against cancer

In 1972, the active compound involved in treating malaria and its accompanying fever was characterized and led to the formal documentation and approval of *A. annua* to treat malaria– especially in its processed forms that incorporate its active compound called Artemisinin. Drugs such as Artemotil and Artemetherin (in monotherapies) among others have come to light in treating malaria, before they got incorporated into other therapeutic forms called Artemisinin combination therapies ACTs, a combined therapeutic form. *A. annua* against malaria has been a great discovery as it had immense impacts on malaria control via therapy. Also, *A. annua* found usage to treat parasitic infections involving worms, some microbes and fungal infections (Harrill, 2001). By and large, it may have given clues of need to attempt its usage against a disease that has also ravaged humans like malaria, which is cancer.

Cancer may be induced by either parasitic (pathogenic) or non-parasitic agents. Then, there is cancer having parasitic and non-parasitic inducers of the disease condition.

In the late 1990s, a group of researchers in Cancer Biology led by a distinguished Professor Lai in the United States of America, took a closer look at Artemisinin and its usage against malaria, examined the mechanism of action of the active compound Artemisinin against the Protozoa malaria parasite *Plasmodium*. The lead scientist's insight into the event led to his hypothesizing that the process through which Artemisinin reacts with a chemical compound Iron, noticed to accumulate at high concentrations in the *Plasmodium* parasite, leading to the eventual killing of the parasite after a series of reactions, might possibly either have a killing effect or impact on cancer cells or work as a drug against cancer disease (as a drug whose components may still be on investigation).

Eventual attempts by the lead scientist in the team, surprisingly recorded apoptoses of nearly all breast cancer cells while the normal breast cancer cells appeared unaffected or minimally affected. The success of his team

seem to have encouraged them to attempt using Artemisia against another type of cancer called Leukaemia. The team got some positive results.

Similar successes were recorded in the studies of the following scientists:

.Singh *et al* (2004) in which dihydroartemisinin DHA treatment was found to significantly decrease cell counts while increasing the proportion of apoptosis in cancer cells compared to controls;
.Nam *et al* (2002) observed and remarked that deoxyartemisinin trimer had greater anti-tumour effect on tumour cell lines than other commonly used chemotherapeutic drugs such as 5-FU, Cisplatin and Paclitaxel;
.Mu *et al* (2008) finding that DHA induce apoptosis of lung cancer cell line PC-14 cells with calcium and P38 playing roles in apoptosis signaling pathways;
.Zhou *et al* (2008) identifying induction of apoptosis in human leukemia cells HL60 by DHA;
.Singh *et al* (2005) which studied and noted the synergistic anti-tumour action of Artemisinin and sodium butyrate on cancer cells with artemisinin found to selectively kill cancer cells in vitro while sparing normal cells;
.Li and Hickman (2011) remarked that several studies have demonstrated that ART s and their derivatives possess anti-angiogenic activity and inhibition of cancer progression.

Ever since, the earlier mentioned team of scientists (led by Lai) appeared to have stepped up gear with experiments both in-vivo in animal models like Dog and in-vitro in diverse forms of cancer. In recent times, attempts have been made to treat skin cancer in humans using Artemisinin based drugs in form of oral and topical (rubbed on the skin) medications. Instances have been recorded and reported in some south-east Asian countries.

Worthy of note is the use of some new herb plants which have been screened and discovered to show anti-cancer properties to battle cancer; thus complimenting and joining the race in the attempts and engagement of well synthesized plant products to combat and treat of Cancer. Some of these new plant derived anti cancer agents in clinical use include Vinca alkaloids, Vinblastine VLB, and Vincristine VCR isolated from *Catharanthusroseaus G. Don* (*Apocynaceae*), extracts from *Podophyllaceae* family and Paclitaxel derived from leaves of *Taxus species* and extracts from *Archeranthes aspera* plant (Prakash *et al*, 2013).

Possibly with time, some combinations of the active anti-cancer compounds in these herb plants and plants, could be found to possess “growth advancement inhibition capacities” against raging cancer, in the multi-faceted attempts by man against the threat posed by “these strange and deranged cells that grow for the sake of growth but with no clearly constituted means of modulating the growths”.

Active compound in *A. annua* for cancer chemotherapy

In studies and investigations examining compounds derived from the *A. annua* plant for treating cancer, some monotherapeutic and combined therapeutic forms of the drug have been examined and screened for levels of potency and toxicity on the animal models, before they were attempted on humans.

Some of these drugs have included: Dihydroartemisinin, Coartem, and Dihydroartemisinin in combination with Holotransferrin to confer some properties that make Dihydroartemisinin effective, among other forms (PUBCHEM, 2016).

Tumour cells have been found to have an enhanced vulnerability to ROS damage as they exhibit lower expression of antioxidant enzymes such as superoxide dismutase, catalase and gluthatione peroxide compared to that of normal cells; while artemisinin has been linked to artemisinin cytotoxicity to factors of which include enhanced level of oxidative stress (Gorrini *et al*, 2013). It is worth noting that the preloading of cancer cells with iron or iron saturated holotransferrin (diferric transferring) has been found to cause artemisinin cytotoxicity (Gorrini *et al*, 2013) increasing the activity of artemisinin by values close to 100fold in some cell lines (Crespo-Orittz and Wei, 2012). The derivatives of artemisinin such artesunate, arteether and artemether have been found to exhibit anti-tumour activity against melanoma, breast, ovarian, prostrate, CNS and renal cancer cell lines (Nam *et al*, 2007).

By and large, the active compound in these therapeutic drug forms attempted against cancer had been Artemisinin which in Chinese is called Qinghaosu. In some forms of the drug, Artemisinin has been aided to be effective by compounds that bind on to cell-surface receptors to facilitate certain processes that enhance drug action potency of Artemisinin. For instance, cancer cells exhibit an increase in transferring receptors which have been found to be responsible for the iron uptake and regulation of intracellular concentrations (Gorrini *et al*, 2013).

Artemisinin and its derivatives are among compounds whose anti-tumour activities have been discovered through discovery efforts that focus on screening drugs that are engaged in other diseases and other plant products.

The 1st account of anti-cancer activity of artemisinin and its derivatives was presented in 1993 while Lai and Singh (1995) made their landmark contribution through their publication in which they presented the selective killing of MOLT-4 lymphoblastoid leukemic cells by artemisinin.

Moving from the petri-dishes, test tubes and laminar flow hood in-vitro chamber to the real life cases on the field and in the clinic, it was reported in the Dec 15th 2004 that artesunate and artemisinin were successfully used to treat grafted human tumors in laboratory animals; while the German scientist Efferth and his team demonstrated the anti-tumour activity of artemisinin and some of its derivatives against leukemia and colon cancer and what the group called 'modest anti-cancer activity against melanoma, ovarian, breast, prostrate and renal cancer. In a follow-up by the same Efferth's research team, their attempt to treat two melanoma patients with ART artesunate after chemotherapy had failed, resulted in one of the patients going on to live for 24months and the 2nd patient for 47months as at 2007 which went beyond the median survival of 2-5months using other chemotherapy (Chang, 2012).

A report by WRAIR Silver Spring, USA, published online in 2013 by "In Tech Open", presented the use of artemisinin and its derivatives as angiogenesis inhibitors to treat cancer.

A. annua Genetic Resources: genetic map and benefits for malaria and cancer treatment

In the light of the foregoing, it seems imperative to have a genetic resource for the plant herb *A. annua*, considering its varied uses in natural medicine and modern synthesized medicinal drugs, alongside its numerous non-medicinal uses. In developing a genetic resource for *A. annua*, it has incorporated intensive study and observations to complete and produce the first genetic map for the plant.

Some of the prominent research teams who have made valuable contributions to the genetic resources of *A. annua* include those at the University of York, Mediplant in Switzerland, CPOBA – UNICAMP in Brazil and CIMAP Luknow which has a vital presence in India.

The first genetic map of *A annua* provided information on the loci for Artemisinin, the active compound in *A. annua* engaged against malaria disease and being investigated for its potency and possible engagement against cancer (Nordquist; 2010; Graham *et al*, 2010).

CONCLUSION

The journey on the war against malaria, using the antimalarial Artemisinin derived directly either from the herb plant *Artemisia annua* or from synthetically produced forms of this drug, has been interesting and challenging. This took the form of the emerged ACTs, developed by scientists to overcome the drug resistance challenge to Artemisinin and its analogues, posed by *Plasmodium* parasites. Several analogues of Artemisinin have since emerged, all contributing to the same global fight back against malaria. The exploitation of some of the attributes in mode of action of Artemisinin to clear malaria parasites by oncologists and drug development experts to target the killing of cancer cells has been tough and challenging with some levels of successes but yet to get to the level of synchronizing the various results into the 1st real potent *Artemisia annua* or Artemisinin compound involving drug against cancer. Like attempts with use scientifically synthesized *Artemisia annua* derived chemical compounds against cancer, there are a myriad of other herb plants being investigated through use of some observed active compounds in these herb plants, for potency against cancer, with some of them also showing some levels of successes. By and large, the impactful public health implications of the success of ACTs incorporating Artmisinin and its analogues in contributing to the reduction of the burden of malaria on humans, appears obvious; with that of its impact on cancer burden still speculative at present.

ACKNOWLEDGEMENTS:

Ozurumba appreciates Prof Walter G. Land- a Transplantation, Immunology& Oncology expert; & Prof Claude P. Muller (Molecular Immunologist-Luxembourg) for inspiration and trainings. Also, he expresses gratitude to School of Public Health, College of Health Sciences of Walden University, MN, USA. Ukoh and John-Bull are grateful to friends in Uyo, Bauchi and Benin who motivated them on their studies.

CONTRIBUTION OF AUTHORS:

The idea in this work and the manuscript was developed by Ozurumba L.N.; Mr Ukoh V. was MSc Medical Parasitology student at Univ of Uyo Nigeria when this manuscript was developed while David J. is currently Msc Biology (Parasitology) student at ATBU Bauchi, Nigeria – these two other co-authors made their good contributions in the area of gathering other related literature information.

REFERENCES

American Cancer Society (2014). Cancer Facts and Figures. Explore Cancer Facts and Statistics. www.cancer.org. Retrieved 8th February, 2016.

American Cancer Society (2016). Facts on Cancer, learn about cancer. Retrieved on 8th Februaray, 2016.

American Society of Clinical Oncology (2015). Cancer information. www.cancer.net. Retrieved 8th February, 2016.

Brooks G.F., Butel J.S., Morse S.A., 2004. Jawetz, Melnick and Aldelberg's Medical Microbiology. 23rd Edition. McGraw Hill Publishing Incorporated. 818pp.

Campbell NA, Reece J.B., Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V., Jackson R.B., 2008. Biology. 8th Edition. Pearson-Benjamin Publishing Incorporated. 1267pp.

Bui T.T.T., Minh T.V., Lim B.P. and Keng C.L. (2011). Effects of environmental factors on growth and Artemisinin content of Artemisia annua L. Trop Life Sci Res; Vol 22(2): 37- 43.

CDC (2011). *Plasmodium falciparum* parasites and Artemisinin: Description of chemical composition and properties of Artemisinin. www.cdc.org.

CDC (2012). Global Health. Divsion of Parasititic Diseases and Malaria. Malaria Facts. Page last updated September 19th, 2012. Retrieved 27th March, 2016.

CDC (2015). Malaria Facts. www..cdc.gov/malaria/about malaria. Retrieved 14th November 2015.

Chang C-J, Hung M.C (2012). The role of EZH2 in tumor progression. British Journal of Cancer, 106: 243-247.

Chang R., (2011). Antimalarial artesunate's potential against cancer. In Artemisinin for Cancer care, Weeks B.S (Ed). Article by Chang Raymond MD. FACS, Feb 4th, 2011. Posted April 12, 2012. www.weeksmd.com. Retrieved 24th March, 2016.

Codd A., Teuscher F., Kyle D.E., Cheng Q., Gatton M.L. (2011). Artemisinin induced parasite dormancy: a plausible mechanism for treatment failure. Malaria Journal, 10:56. doi: 10.1186/1475-2875-10-56.

Crespo M.D., Avery T.D., Hannsen E., Fox E., Robinson T.U., Valente P., Taylor D.K., Tilley L. (2007). Artemisinin and a series of novel endoperoxide antimalarials exert early effects on digestive vacuole morphorlogy. Am Soc for Microbiology: Antimicrobial agents and chemotherapy. Jan; 52(1): 98-109. Published online on Oct 15. doi: 10.1128/AAC.00609-07. www.asm.org.

Crespo-Oritz MP and Wei MQ. (2012). Anti-tumour activity of Artemisinin and its derivatives: From a well known Antimalarial agent to a potential anticancer drug. Journal of Biomedicine and Biotechnology Vol. 2012. Article ID: 247597, 18pages. Doi: 10.1155/2012/247597.

Croft S.L., Duparc S., Arbe-Barnes S.J., Craft J.C., Shin C., Fleckenstein L., Borghini–Fuhrer I., Rim H. (2012). Review of pyronaridine anti-malarial properties and product characteristics. Malaria Journal; 11: 270.

Dalrymple D. (2006). Artemisia, agriculture and malaria in Africa: the interplay of tradition, science and policy. Roll back malaria porgramme. www.rollbackmalaria.org/doc. retrieved 26th january, 2016.

De Martel C., Ferlay J., Franceschi S., et al (2012). Global burden of Cancer attributable to infections in 2008: a review and synthetic analysis. The Lancet Oncology; 13: 607 -612.

Delabays, N., Benakis, A., Collet, G.,(1993). Selection and breeding for high artemisinin (qinghaosu) yielding strain of *Artemisia annua*. Acta Horton., 330:203-206.

Efferth T. (2006). Molecular pharmacology and pharmacogenomics of artemisinin and its derivatives in cancer cells. Current Drug Targets.Apr; 7(4): 407-21.

Efferth T. (2007). *Wimlmar Schwabe Award 2006*: Antiplasmodial and antitumour activity of artemisinin-from bench to bedside. Review article. Planta Med. Apr; 73(4): 299-309. Epub 2007 March 12.

Elyse S.B., Yang J., Kematsubara K.M., Carvaja R.D. (2016). Clinical management of Uveal and Conjuctival Melanoma. Oncology 30(1): 29-43. Oncology online at Cancer Network.

EU Genetic Resources (2011). Conservation, characterization, collection and utilization of genetic resources in agriculture (EC for Agriculture and Rural Development). 2006 – 2011. The 17 EU actions for genetic resources. www.ec.europa.eu/agriculture/geneticresources/actions/index_en,html. Retrieved November 2011.

Enwonwu C.O, Afolabi B.M., Salako L.O., Idigbe E.O., Bashirelahi N. (2000). Increased plasma levels of histidine and histamine in *falciparum* malaria relevance to severity of infection. Journal of Neural Transmission. Nov, Vol. 107, (11): 1273-1287.

Ferreira J.F.S., Simon J.E. and Janick J. (1995a). Developmental studies of *Artemisia annua*: Flowering and artemisinin production under greenhouse and field conditions. Planta medica 61:167-170.

Firestone G.L. and Sundar S.N. (2009). Anti cancer activities of atemisinin and its bioactive derivatives. Expert Rev Mol Med; Oct 30:11:e32. Review.

Gorroni C., Harriis I.S. and Mak T.W. (2013). Modulation of oxidative stress as an anticancer strategy. Nature Review Drug Discovery 12: 931-947.

Graham I.A., Basser K., Blumer S., Branigan C.A., Czechowski T., Elias L. (2010). The Genetic Map of *Artemisia annua L*. Identifies Loci affecting yield of the Artemisial Drug Artemisnin. Science Jan,: 328 – 331.doi: 10.1126/science.1182612.

Gray, A. (1959). Asteraceae Artemisia tridentate. Nutt. F. parishii. Beetle Rhodora 61: 83.

Graziose R., Lila M.A., Raskin I. (2010). Merging Chinese traditional medicine with modern Drug Discovery Technologies to find Novel Drugs and Functional Foods. Curr Drug Discov Technol. Mar; 7(1): 2-12.

Guenova M., Balatzenko G. [Ed] (2015). Leukaemias, updates and new insights. Published by In Tech Nov 2015, 362pp.

Harrill R. (2001). Ancient Chinese folk remedy may hold key to non-toxic cancer treatment. University of Washington Newsletter Archive.26th No, 2001. Retrieved 10th November, 2015.

Hartwell L.H. and Karstan M.B., (1994). Cell Cycle Control and Cancer. Science. 16th December, Vol 266: 1821-1827.

Hollyman S. [WHO]. (2015). 10 Facts on Malaria. www.who.int/features on malaria. Retrieved 14th February, 2016.

Hungle Q, Vries P.J, Giao P.T, Nam N.V, Binh T.Q, Chong M.T, Quoc N.T, Thanh T.N, Hung L.N, Kager P.A (2002). Control of malaria: a successful experience from viet Nam. Bull world Health Organ 80:660-666. National Center for Biotechnology Information, U.S. National Library of Medicine 8600 Rockville Pike, Bethesda MD, 20894 USA

Hung L.Q, de Vries P.J, Giao P.T, Nam N.V., Binh T.O., Chong N.T., Quoc T.A., Thanh T.N., Hung L.N. and Kager P.A. (2002) Control of malaria: a successful experience from Vietnam. Bull World Health Organ (WHO); 80: 660-666.

Kaptein S.J, Efferth T., Leis M., Rechter S., Auerochs S., Kalmer M, Bruggeman C.A., Vink C., Stamminger T. and Marshall M. (2006). The antimalaria drug artesunate inhibits replication of cytomegalovirus in vitro and vivo. Antiviral Res. 69(2): 60-9. Epub 2005 Nov 21.

Kaptein S.J., Efferth T., Leis M., Rechter S., Auerochs S., Kalmer M., Bruggeman C.A., Vink C., Stamminger T., Marschall M. (2006). The anti-malaria drug artesunate inhibits replication of cytomegalovirus in vitro and vivo. Antiviral. Res. 2006:69:60-9.

Kariko D. (2015). *Plasmodium falciparum* and Artemisinin combination therapies. WWARN Explorer, Jan, 2015 Issue.

Kindermans J., Pilloy J., Olliaro P.,and Gomes M. (2007). Ensuring sustained ACT production and reliable Artemisinin supply. Malaria Journal. 6: 125-130.

Klayman, D.L(1993). *Artemisia annua*: from weed to respectable antimalarial plant. In: Kinghorn, A. D. and Balandrin, M.F. (Eds), Human medicinal agents from plants, pp. 242-255.

Lai H. and Singh N.P. (1995). Selective cancer cell cytotoxicity from exposure to dihydro atemisinin and holo transferring. Cancer lett.91:41-46.

Li Q. and Hickman M. (2011). Toxicokinetic and toxicodynamic (TK/TD) Evaluation to determine and predict the neurotoxicity of atemisinin. Toxicology. Jan 11; 279(1-3): 1-9.279:1-9.

LSM (2016). Malaria Control Program, Lagos State ministry of health. www.lagosstaeministryofhealth. com/programme_info.php. Retrieved 11th March, 2016.

Mader S.S., 2008. Biology. 7th Edition. McGraw Hill Publishing Incorporated. 939pp.

Mcvaugh, R. (1984) Flora Novo-Galiciana: A Descriptive Account of the Vascular Plants of Western Mexico Vol. 12. Anderson, W.R., Ed., University of Michigun Press, Ann Arbor.

Meshnik S.R., Taylor T.E., Kamchonwongpaisan S. (1996). Artemisinin and antimicrobial endoperoxidases from herbal remedy to targeted chemotherapy. Microbiol Rev. June, 60(2): 301-315.

Morris A., Ward A., Moonen B., Sabot O. and Cohen J. (2014). Health Policy and Planning. Oxford Univ Press-LSHTM Joint publication. March 14, 2014.

Mu D., Zhang W., Chu D., Jin F. (2008). The role of calcium p38 MAPK in dihydroartemisinin-induced apoptosis of lung cancer PC-14 cells. Cancer Chemotherapy and Phamarcology. Apr, 61(14):639-45.

Nam W., Tak J., Rhu J.K., Jung ., Yook J.I., Kim H.J., Cha I.H.(2007). Effects of atemisinin and its derivatives on growth inhibition and apoptosis of oral cancer cell. Head neck. Apr, 29(4).335-40.

National Cancer Institute (2015). Cancer statistics in the United States. www.cancer.org.

Nordquist, C. (2010). First Genetic Map of *Artemisia annua* provides Malaria Treatment hope.

Ozurumba L.N. (2011). Prevalence and risk factors associated with malaria transmission in rural and urban populations in Ibadan, Nigeria. Int. Jnal of Applied. Bio. Resrch. Vol. 3(2): 58 – 73. www.ijabr.com.

OZURUMBA, L.N. (2012). A tentative flow chart for the breakdown of haemoglobin by *Plasmodium*, haemozoin formation, potential therapeutic targets and effect of chemotherapy {A review}. Adamawa State University Jnal of Scientific Research ADSUJSR; Vol. 2 (1): 115 -122. www.adsu.edu.ng. ISSN: 2251-0702.

Ozurumba L.N. (2015)**.** Apical membrane antigen-1 of malaria parasite (PF83/AMA1). Efficacy as a Malaria Vaccine, Uncertainties and Attempts at Improving Efficacy. Lambert Academic Publishing. Saabrucken, Germany. ISBN-13:978-3-659-25368-3, 52pp. https://www.lap-publishing.com, www.amazon.ca: Biology and Life Sciences on Kindle.

Ukoh, V. and Ozurumba, L. (2016). Comparative prevalence of intestinal parasitic infections (IPIs) in stool samples of patients attending UMTH Maiduguri between 2006 and 2007; its community health burden and proactive counter measures implications. Biores Comm. **2**(2), 276-280.

Paddon C.J., Westfall P.J., Pitera D.J., Benjamin K., Fisher K., McPhee D., Leavell M.D., Tai A., Main A., Eng D., Polichuk D.R., Teoh K.H., Reed D.W., Trenor T. et al. (2013) . High level semi-synthetic production of potent antimalarial artemisinin. Nature; 496: 528-532 April 2013 doi 10.1038/nature12051.

Prakesh O., Kumar A., Kumar P., Ajeet S.D. (2013). Anticancer potential of plants and natural products. A review. Am Jnl of Pharmacological Scs AJPS Vol. 1(6): 104 – 115.

PubChem (2016).Compund summary for Artemisinin CID 452191, NIH NLM NCBI. PubMed Chemistry Open Database. www.pubmed.ncbi.nlm.nih.gov. Retrieved 12th February, 2016.

Rowden J.R., 2010. Skin Cancer Therapy and Artemisinin. Medical Practitioner in Vietnam.

Shen-Miller J., Mudgett M.B., Schopf J.W., Clarke S. and Berger R. (1995). Exceptional seed longevity and robust growth: Ancient sacred lotus from China. Amr. Jnl of Botany.

Singh N.P. and Lai H.C. (2004). Artemisinin induces apoptosis in human cancer cells. Anticancer Res. July-Aug 24(4): 2277-80.

Singh N.P. and Lai H.C., (2005). Synergistic cytotoxicity of Artemisinin and Sodium butyrate on human cancer cells. Anticancer Res. Nov- Dec 25(6B): 4325-31.

Skvarla, J. J and D.A Larson. (1965). An electron microscopy study of pollen morphology in the compositae with special reference to the Ambrosiinae. Grana Polinol. 6:210-104.

University of Utah Med Lab (2016). Neoplasia. Univ of Utah Web Path. www.library.med.utah.edu/ NEOPL102html. Retrieved 16th February, 2016.

Vannice K.S., Brown G.V., Akamoria B.D., Moorthy V.S., (2012). Malaria Vaccine Advisory Committee MALVAC 2012 Scientific forum: accelerating development of a second-generation malaria vaccine. Meeting Report. Malaria Journal. 11:372. doi:10.1186/1475-2875-11-372.

WHO (2004). TDR News. October 2004: 6-7.www.who.int.tdr.

WHO (2004). TDRNews. October 2004: 6-7. www.who.int.tdr.

WHO (2006). Announcement. Washington DC/Geneva. May 2006. Description of chemical composition and mode of action of Artemisinin. www.who.int. Retrieved 10th January, 2016.

WHO (2006). World Health Organization Announcement. WHO Washington DC/ Geneva. May 2006.

WHO (2010). Malaria facts and figures. Information on global malaria eradication? www.who.int. Retrieved 10th January, 2016.

WHO (2011). Diagnostic testing and treatment of malaria. WHO/WMR 2011, Chapter Six.

WHO (2014). World Cancer Report. Edited by: Bernard W. Stewart and Christopher P. Wild. An IARC Publication, distributed by WHO Press.

WHO (2016). Facts sheets on Cancer. www.who.int. Retrieved 10th January, 2016.

WHO (2012). WHO facts sheet. No.94, April 2012. www.who.int. Retrieved 10th January, 2016.

WHO, 2004. TDR News. October 2004: Pages 6-7.

Van-Tyne D., Park D.J., Schaffner S.F., Neafsey D.E., Angelino E., Cortese J.F. (2011). Identification and functional validation of the novel antimalarial resistance locus PF10_0355 in *Plasmodium falciparum*. PLos Genetics 7(4): e1001383., doi: 10.1371/journal.pgen.1001383.

Woerdenbag, H. J, N. Pras, N.G Chan, B. T. Bang, R. Bos, W. Van Uden, P. Van Y.,N.V.Boi, S. Batterman, and C.B. Lugt. (1994). Artemisinin, related sesquiterpenes, and essential oil in Artemisia annua during a vegetation period in Vietnam. Planta Med; 60: 272-275.

Wright C.W. (Ed) (2002). Artemisia in Book series. Medicinal and Aromatic Plants–Industrial profiles. Published by Taylor and Francis. ISBN 0 – 415-27212-12.

Zhou H.J., Wang Z, Li A.(2008). Didroartemisinin induces apoptosis in human leukemia cells HL60 via down-regulation of transferrin receptor expression. Anti Cancer Drugs. 19(3): 247-255.

Cite this Article: Ozurumba LN, David J and Ukoh V (2015). *Artemisia annua* (Qing Hao): Solved and Adaptively Met the Drug Resistance Challenge by *Plasmodium* Malaria Parasite. It's other Chemotherapeutic attempt against Cancer; and Overall Implications on Public Health. Greener Journal of Biomedical and Health Sciences, 2(1):001-011, http://doi.org/10.15580/GJBHS.2016.1.101816180