# A review on the role of artemisia in the malarial disease

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***Abstract*- The antimalarial energetic compounds in Artemisia annua encompass artemisinin, flavonoids, and aromatic oils. Artemisinin is the primary antimalarial compound in A. annua, it is used inside the formula of artemisinin-primarily based blended remedies used to treat malaria. Artemisinin is largely received from A. annua plant however the content material in its miles is very low and it's manufacturing commercially isn't value powerful worldwide.**

**Flavonoids have a synergistic impact with artemisinin against malaria and are in part accountable for the prophylactic effect of A. annua herbal tea. critical oils from A. annua are effective mosquito repellents. Most tries had been made to try to raise artemisinin content material. However, few or none has tried to grow the flavonoids and aromatic oils. This newsletter offers an evaluation of various efforts which have been done to increase those antimalarial compounds. [1]**

***Key words:*** **Artemisia, Artemisia annua, Artemisinin, Malaria, Endoperoxide bridge.**

## 1.INTRODUCTION:

A World Health Organization survey reported that about 80% of the world's population relies on non-conventional medicines, especially herbal sources, for their primary health care citation, 2003). Medicinal herbs are a local heritage with global significance. The world is blessed with a richwealth of medicinal herbs. Due to the global trend to improve the "quality of life", there is considerable evidence of an increase in the demand for medicinal plants. Using plants to treat various human and animal ailments is a practice as old as human life itself.[2]

The genus Artemisia is one in every one of the most important and maximum extensively distributed genera of the own family Asteraceae (Compositae). It is a heterogenous genus, consisting of over 500 diverse species dispersed specifically inside the temperate zones of Europe, Asia and North the us. These species are perennial, biennial and annual herbs or small shrubs.

Global malaria report (2020) predicted 229 million cases of malaria in 87 international locations reportedly endemic for malaria. Twenty-nine international locations of the African place were predicted for ninety-five% of overall malaria instances which have been suggested globally. In 2019, India most effective accounted for six. three million instances of malaria. Globally, the full malaria-related deaths were anticipated to be round 409,000 inside the year 2019. India crowned the list with 84% of total deaths reported because of malaria inside the WHO Southeast Asia area (WHO, 2020).[3]

After the failure of chloroquine and sulfadoxine-pyrimethamine-primarily based capsules because of the acquired resistance in malaria-causing pathogen (Plasmodium parasite), Artemisinin-based totally aggregate cures (ACTs) are the first line of remedy in opposition to malaria as endorsed by way of the world fitness employer. Artemisinin is a sesquiterpene class secondary metabolite, produced by means of Artemisia annua. the global requirement of ACTs is growing because of the sizable gap in demand and deliver chain. The extraction of artemisinin from evidently cultivated vegetation is the primary supply and considered secure for human health. The development of cultivars with advanced ordinary artemisinin content material and the use of various techniques is the foremost goal of plant scientists all over the world.[4]

## 2.ARTEMISIA DRUG PROFILE: -

**2.1. Synonyms: -** Mugwort, wormwood, sagebrush is a plant of Daisy antonica and worm seeds.

**2.2. Biological sources: -**

Artemisia consist of unexpanded flower-head obtained from the plant Artemisia annua, Artemisiae apiaceae, Artemisia lancea, Artemisia brevifolia, Artemisia maritima, **Family: -Asteraceae**

**2.3. Geographical source: -**

Artemisia plant is found in the Kurran valley region of Pakistan, Turkey, and Himalayas, and in the states of Punjab, Uttar Pradesh and Haryana.

**2.4. Macroscopic Features**: - **A) Colour: -** Flowers are yellow in colour, while the other parts are whitish grey.

**B) Odour: -** Aromatic and sweet.

**C) Taste: -** Bitter and comphoraceous. It contains yellowish or brownish, oval- shaped flower- heads. The flowers are fertile in presence of tubular corolla and short cylindrical tube and narrow limb. It lacks calyx.[5]

**2.Phytochemistry: -**

An exhaustive literature survey on phytochemical reports of the genus Artemisia exhibits that the Artemisia species comprise in particular terpenoids, flavonoids, coumarins, caffeoylquinic acids, sterols and acetylenes. among numerous species of Artemisia, A. absinthium, A. afra, A. annua, A. maritima and A. scoparia (Waldst et package) are mainly wealthy in terpenoidsTable 1 summarises the phytoconstituents of various species of Artemisia, and Figure 1 represents the chemical structures of the most commonly occurring major volatile compounds.

**Figure 1**. Chemical structures of the commonly occurring major volatile components of Artemisia species.[6]

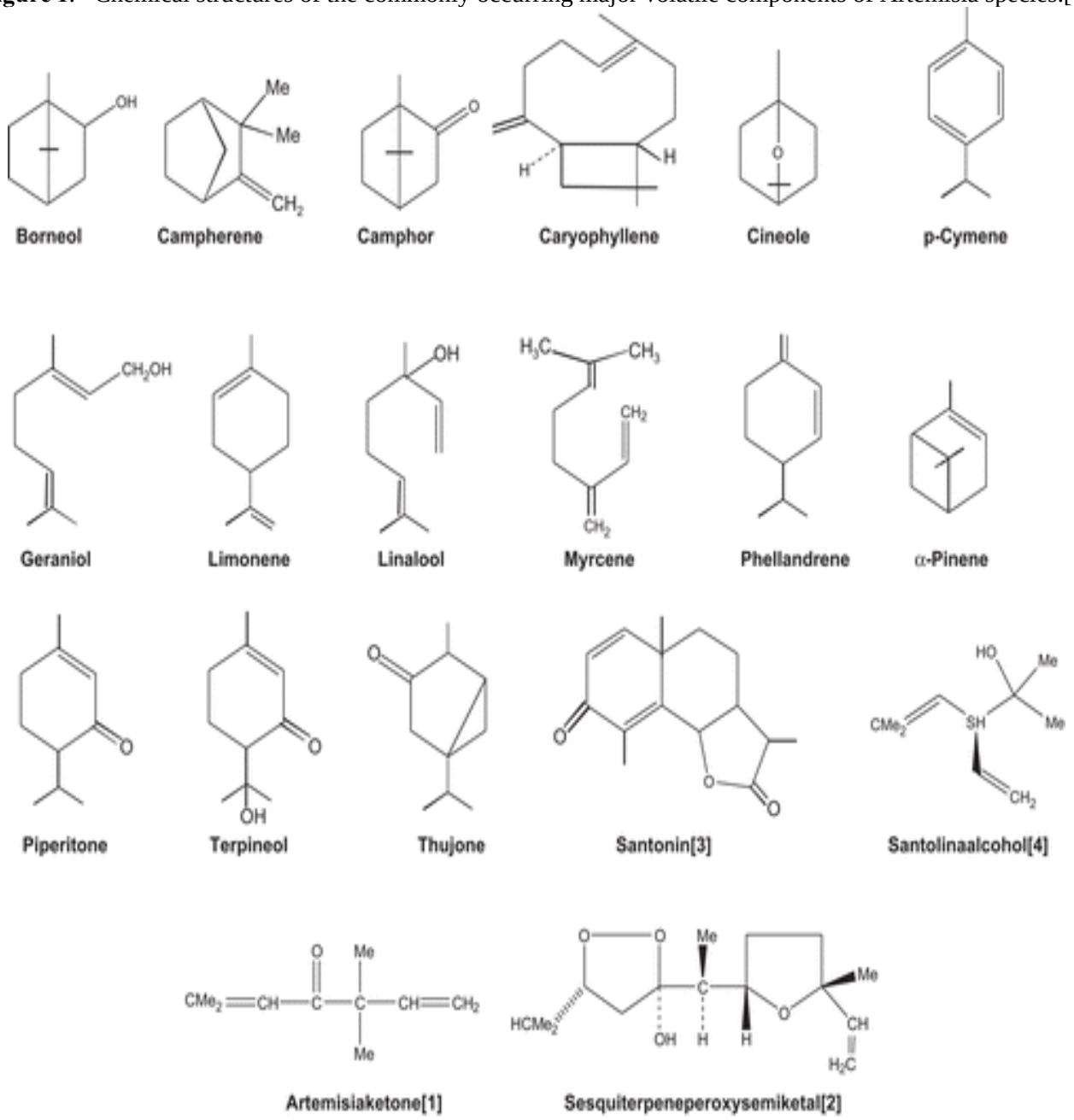


**Table No.: -1 Represents the species of Artemisia along with phytoconstituents.**

| Species | Phytoconstituents |
|---|---|
| **1). A. absinthium** | **Essential oil c**ontaining (Z)-thujone, (E)-thujone, myrcene, trans-sabinyl acetate, chrysanthenyl acetate, β-pinene, sabinene, 1,8-cineole, artemisia ketone [1], linalool, hydrocarbon monoterpenes 5), sesquiterpene lactones; polyphenolic compounds, flavonoid, tannins. |
| **2). A. abrotanum** | **Volatile oil** containing 1,8-cineole, linalool, davanone, thujone **flavonols, tannins**, caffeic acid, **coumarins**. |
| ***3)A. afra*** | **Volatile** and **non-volatile** secondary metabolites such as **monoterpenoids**, **sesquiterpenes; glaucoides, guaianolides**; **flavonoids** |
| ***4)A. annua*** | **Volatile oil** containing cineole, α-pinene, camphene, borneol, camphor, germacrene-D, hydroxyl amino iso artemisia ketone sesquiterpene **lactones** artemisinin, artemisinic acid, arteannuin B, artemisinin derivatives artesunate, trioxanes, artemether artemisinin G and arteether **phenolic compounds**, **flavones** |
| ***5)A. arborescens*** | **Terpenes** thujone, borneol, thujol; **flavonols, fatty acids** |
| ***6)A. asiatica*** | **Volatile oil, flavone**, alkaloids, artemisolide |
| ***7)A. capillari*** | **Volatile oil** containing **β**-pinene, camphor, 1,8-cineole, **β**-caryophylleneborneol flavonoids |
| ***8)A. campestriss*** | **Volatile oil** containing α- and **β**-pinene, 1,8-cineole, 1-thujone, thujyl alcohol, geraniol, flavonoids |
| ***9)A. douglasiana*** | **Monoterpenes** such as cineole, camphor, linalool, iso thujone, thujone **Sesquiterpene lactones** such as vulgarin and psilostachyin. |
| **10)A. dracunculus** | **Volatile oil** containing menthol, anethole, anisol, anisic acid, d-sabinene, estragole, limonene, myrcene, ocimene, α-phellandrene, anisaldehyde **β**-pinene, 1-methoxy-4-(2-Propenyl)-benzene, 1R-α-pinene<br>**coumarins**, **polyphenolic compounds**, **glucosides** |
| ***11)A. judaica*** | **Volatile components** piperitone, trans-ethyl cinnamate, Judaicin **phenolic contents** |
| ***12)A. maritima*** | **Volatile oil** containing **β**-thujone, α-thujone, α-pinene, sabinene, p-cymene, sabinol cuminaldehyde, isobutyrate, isovalerate, sesquiterpene peroxysemiketal **[2]**, 1,8-cineole, camphor, borneol, chrysanthenone<br>**sesquiterpene lactones** santonin **[3]**; **fatty acids** |

| | |
|---|---|
| ***13)A. vulgaris*** | **Terpenes** p-cymene, fenchone, α- and **β**-thujone, cineole, camphor, **β**-pinene,4-terpineol, borneol α-thujone, α-terpineol, geraniol, caryophyllene; **coumarins**, sterols, caffeoylquinic **acids** |
| ***14)A. monosperma*** | **Eudesmane sesquiterpenes, coumarins** |

**3.ARTEMISIA ANNUA**

The species Artemisia annua L (Asteraceae) is local to China. Its historic Chinese language name, QingHao, actually means "green herb." The genus Artemisia accommodates over four hundred species, a lot of which have an aromatic, bitter flavour. There are theories as to the foundation of its call. Ferreira et al. (1997) say that it is known as after the Greek goddess Artemis, meaning literally "she who heals illness," who became in reality goddess of the search of forests, and was thought to be accountable for surprising dying in ladies (Guirand, 1959). seemingly flowers of this genus, possibly Artemisia absinthium, have been used to control ache in childbirth and to induce abortions. Bruce says that Artemisia become named after Queen Artemisia of Caria (Turkey), who lived within the fourth century B.C. She turned into so aggrieved at the dying of her husband and brother, King Mausolus of Halicarnassus, that she combined his ashes with something she drank to make it taste bitter.

A. annua is so named because it's miles almost the only member of the genus with an annual cycle. It's far from a shrub, often developing over 2 m excessively. Its leaves and flora comprise artemisinin, first isolated in China in 1971; this is the constituent with the finest antimalarial interest (see table three. three). Artemisinin has been located in two other species, Artemisia apiaceae and Artemisia lancea.[7]

**3.1. General considerations**

Artemisinin or qinghaosu became isolated by way of chinese language researchers in 1972 from Artemisia annua, L. (sweet or annual wormwood), and its structure become elucidated in 1979. The plant has been utilised in conventional Chinese medicine as a remedy for chills and fevers for more than 2000 years. The drug is present inside the leaves and plant life of the plant in ~ 0.01–0.8% of dry weight. Chemically, artemisinin is a sesquiterpene trioxane lactone containing a peroxide.[9]

**Figure No.2: -** Represents the unexpanded flower-head of the species **Artemisia annua.**

**4.MALARIA**: -

Malaria is an ancient ailment having a massive social, monetary, and health burden. it's far predominantly present within the tropical international locations. Despite the fact that the sickness has been investigated for loads of years, it still remains an important public fitness hassle with 109 international locations declared as endemic to the disorder in 2008. There were 243 million malaria cases mentioned, and almost 1,000,000 deaths - more often than not of children below five years [1]. With No powerful vaccine in sight and many of the older antimalarial drugs dropping effectiveness due to the parasite evolving drug resistance, prevention (the use of mattress nets) is still the only advisory given to bothered humans.[8]

Malaria has also gained prominence nowadays considering that weather change or international warming is predicted to have surprising results on its prevalence. Both boom and fluctuation in temperature impacts the vector and parasite lifestyles cycle. This could cause decreased incidence of the disorder in some regions, at the same time as it may grow in others, hence weather change can affect malaria prevalence patterns through shifting away from decreased latitudes to regions where populations have now not evolved immunity to the disorder [2-8]

Malaria is due to the protozoan parasites of genus Plasmodium.In people it is because of Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, and Plasmodium vivax. of those, P. falciparum is the maximum not unusual reason of contamination in Africa and P. SouthEast Asia, and is accountable for ~80% of all malaria instances and ~90% of deaths [1]. India, P. vivax, has been the number one pathogen liable for malaria, even though P. falciparum instances are at the rise these days [9].The parasite requires two hosts to finish its existence cycle- the vector woman Anopheles mosquito and human.The bites/blood meals of inflamed mosquitoes are the mode of transmission of the parasite between the human hosts.Grassi and Ross found the mosquito's position inside the parasite lifestyles cycle and transmission in 1897[1], and the genomes of Anopheles mosquito and P. falciparum were sequenced in 2002 [10,11]. at some point of the meantime 105 years,

an awful lot of medical studies are undertaken and development made within the know-how of the host-parasite-vector interactions and their biology.

Antimalarial active compounds in A. annua include artemisinin, flavonoids, and aromatic oils.

Artemisinin in the form of artemisinin-based combination therapies (ACT) is recommended

for the treatment of malaria caused by resistant Plasmodium species (WHO, Citation2006).

Flavonoids have been reported to have a synergistic effect with artemisinin against malaria and are believed to be responsible for the prophylactic effect of Artemisia annua herbal teas against malaria. Finally, the aromatic oil of A. annua is a mosquito repellent. In general, the amount of the above antimalarial compounds varies from one region to another. [11-12]

**5.CHARACTERISTICS OF MALARIA: -**

**5.1. Existence cycle and morphology: -**

When the infected anopheline mosquito takes a blood meal, sporozoites are inoculated into the bloodstream. Within an hour sporozoites input hepatocytes and begin to divide into exoerythrocytic merozoites (tissue schizogony). For P. vivax and P. ovale, dormant bureaucracy known as hypnozoites typically remain quiescent within the liver until a later time; P. falciparum does not now produce hypnozoites. once merozoites go away the liver, they invade erythrocytes and grow to be early trophozoites, which are ring formed vacuolated and uninucleated. As soon as the parasite begins to divide, the trophozoites are called schizonts, inclusive of many daughter merozoites (blood schizogony). sooner or later, the infected erythrocytes are lysed by the merozoites, which subsequently invade different erythrocytes, starting a brand-new cycle of schizogony. The period of every cycle in P. falciparum is about 48 hours. In nonimmune people, the contamination is amplified about 20-fold each cycle. After numerous cycles, some of the merozoites expand into gametocytes, the sexual stage of malaria, which cause no signs, but are infective for mosquitoes [13] Life cycle of the malaria parasite P. falciparum is shown by below figure no: -3

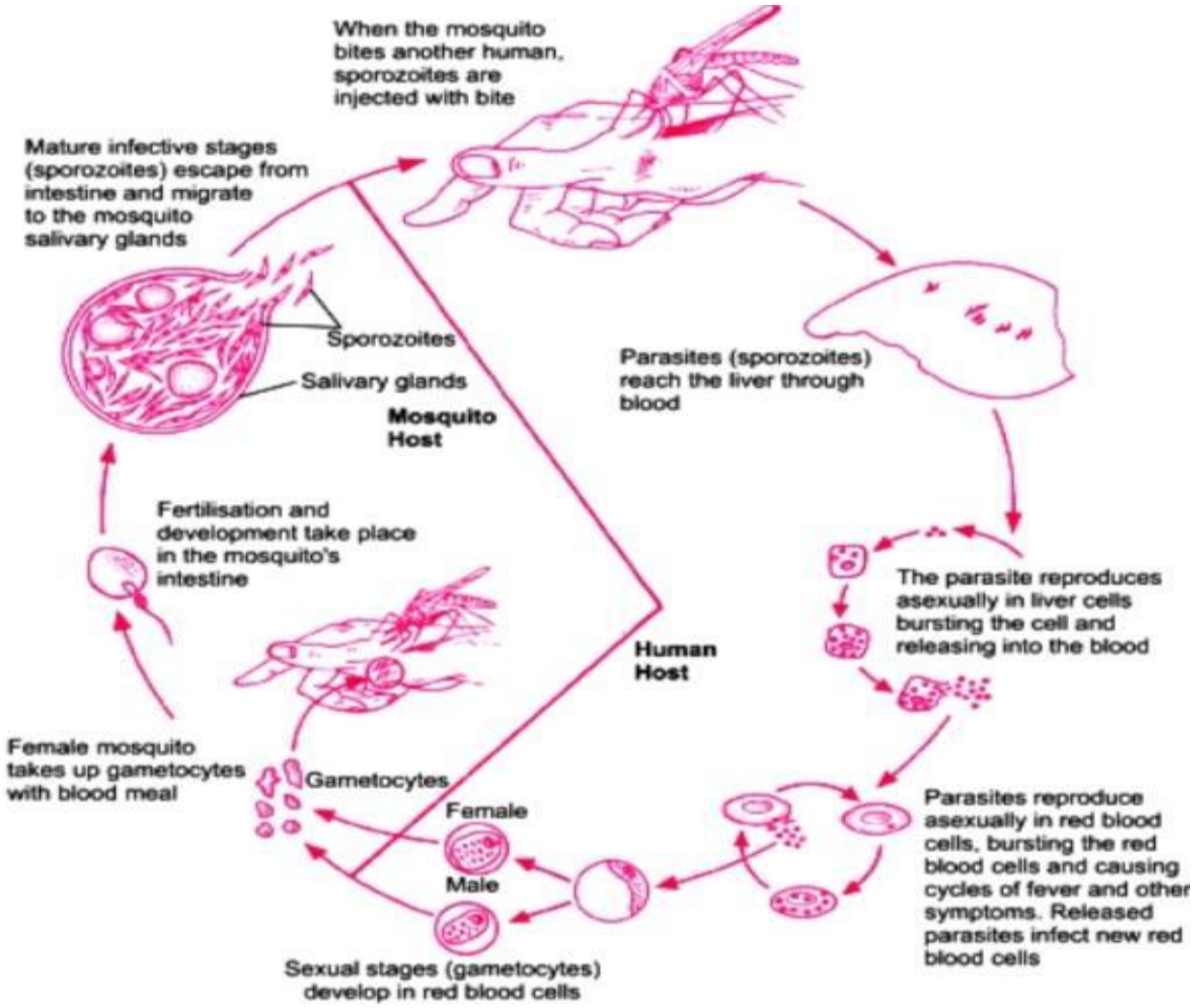


**Figure no. 3: -Life cycle of malaria parasite.**

**6.SYMPTOMS:**

The buildup and sequestration of parasite-infected RBCs in numerous organs along with the coronary heart, brain, lung, kidney, subcutaneous tissues and placenta is a function function of infection with P. falciparum. Sequestration is an end result of the interaction among parasite-derived proteins, that are present at the floor of inflamed RBCs, and some of host molecules expressed at the floor of uninfected RBCs, endothelial cells and in some instances placental cells [14]]

In unique manifestations of malaria, some receptors for parasite adhesion were implicated, along with hyaluronic acid and chondroitin sulphate A (CSA) in placental infections and intercellular adhesion molecule 1 (ICAM-1) in cerebral malaria [8,13,21]. Malaria signs can increase as quickly as 6–eight days after being bitten by means of an inflamed mosquito, or as overdue as several months after departure from a malarious area. Human beings inflamed with malaria parasites typically revel in fever, shivering, cough, breathing distress, pain in the joints, headache, watery diarrhoea, vomiting and convulsions [15]. Extreme malaria is normally complex and numerous key pathogenic techniques such as jaundice, kidney failure and extreme anaemia can integrate to motive critical and often deadly sickness [16].

There are no existence-threatening complications in most cases of malaria, however what triggers the transition from a straightforward to a critical infection isn't properly understood [17]. Malaria is mainly dangerous to pregnant ladies and small children and in endemic countries it is an essential determinant of perinatal mortality [18]. Parasite sequestration in the placenta is a key characteristic of contamination through P. falciparum during pregnancy and is associated with excessive destructive consequences for each mother and child, which include untimely transport, low birthweight and multiplied mortality in the newborn [19]. PfEMP1, a ligand for CSA, is a chief target of antibodies associated with protecting immunity and P. falciparum isolates that sequester inside the placenta ordinarily bind CSA [20]. After repeated exposure to malaria at some stage in pregnancy, women in areas of endemicity slowly expand immunity; therefore, multigravid women are comparatively less prone to pregnancy-related malaria than primigravid girls.

**7.DIAGNOSIS:**

Malaria is diagnosed using a mixture of medical observations, case history and diagnostic tests, basically microscopic exams of blood [21]. Ideally, blood ought to be amassed when the affected person's temperature is rising, as that is when the best quantity of parasites is probably to be discovered. Thick blood films are utilised in habitual diagnosis and as few as one parasite in step with 2 hundred μL blood can be detected. Fast diagnostic 'dipstick' assessments, which facilitate the detection of malaria antigens in a finger-prick of blood in a couple of minutes, are easy to perform and do not require trained personnel or a special system [22]. but they are distinctly high priced and despite the fact that P. falciparum can be recognized, P. ovale, P. malariae and P. vivax cannot be prominent from one another the usage of this approach. three consecutive days of assessments that don't suggest the presence of the parasite can rule out malaria. [22-23]

**8.TREATMENT:**

Malaria is a curable ailment if treated thoroughly and directly. Quinine from the bark of the Andean Cinchona tree became the first extensively used antimalarial remedy and was discovered lengthy earlier than the causes of malaria were recognized. However, the parasite can unexpectedly expand resistance to commonplace antimalarial capsules. in lots of components of the arena P. falciparum has turn out to be immune to Fansidar and chloroquine, which might be the 2 maxima usually used and most cheap antimalarial pills [24,25]. to triumph over this trouble and to prolong the useful existence of present-day drugs, combination therapy is being increasingly more employed. **Artemisinin**, that's received from the plant **Artemisia annua,** is an **extremely powerful antimalarial**, and this drug, or its derivatives together with artesunate or artemether, are being utilised in in particular pairwise combinations with several other tablets along with Fansidar [26] and mefloquine [27], the latter a crucial and nevertheless surprisingly efficacious drug against which resistance, specially in southeast Asia is, but, of growing difficulty. [26-27]

**9.MECHANISM OF ACTION OF ARTEMISIA ON THE MALARIAL PARASITE:**

**Artemisinin** is the chemical constituent which is present in the **Artemisia.** Artemisinin is an extraordinarily active molecule containing endoperoxide bridge (bridge becoming a member of oxygen atoms), which is unstable and fast to react and release its strength.

Received from the molecule are semi-synthetic derivatives, namely,dihydroartemisinin, artemether,artesunate and artemether which aren't notably more efficient than artemisinin, and are pretty rapidly useless compared to artemisinin.Artemisinin is powerful on early trophozoïte stages of malaria and this movement prevents evolution to later degrees, during which there may be adherences of the parasite to the vascular endothelium.A trophozoite is the lively, motile feeding level of a sporozoan parasite. The penetration of artemisinin into the

frame stops the maturation of schizonts. A schizont is a malaria parasite which has matured and consists of many merozoites. Merozoite is a parasite degree that infects red blood cells. Artemisinin produces a better gametocytocidal effect than preferred antimalarial drugs and this decreases the chance of transmission from human to mosquitoes. This gametocytocidal effect is very crucial as gametocytes may additionally latently persist inside the blood.[28]

Golenser et al. (2006) proposed mechanisms of movement of A. annua. The particular mechanisms include interference with the protein metabolism of the parasite and interference with the mitochondrial activity of the parasite. other mechanisms are no longer precise. Eckstein-Ludwig et al. (2003) proposed their mechanism concerning the inhibition of the Ca++ ATPase.Ca++ATPase, is an important enzyme for the synthesis of mobile membrane proteins gift within the parasite to ensure the preservation of calcium ions awareness. The action entails the binding of artemisinin to the enzyme while leaving the peroxide bridge exposed. This permits the bridge to be open as iron draws the electron of oxygen to prompt oxygen atoms attracting the hydrogen ions. This binding generates carbon-targeted radicals which leads to inactivation of the Ca++-ATPase and sooner or later demise of the parasite.[29]

Both sexual and asexual stages of Plasmodium falciparum need mitochondrial activity for respiratory chain. The ion contained in the mitochondria in the mitochondria activates

artemisinin. The iron contained within the mitochondria activates artemisinin. The oxygen atoms reactively interfere with the parasite's electron delivery chain, leading to the depolarization of the mitochondrial membrane. This motion prevents the biosynthesis of pyrimidine which causes the dying of the parasite similar to the movement of the inactivated Ca++-ATPase.

One essential function of artemisinin when activated is its capacity to inhibit irritation alongside the aggression of the parasite because it adheres to the vascular endothelium in the capillaries. The efficacy of artemisinin is on edema and haemorrhages because of inflammation.[30]

**10.CONCLUSION:**

This review reveals how the Artemisia used to treat the malarial disease. The herbal plant Artemisia having an **Artemisia annua** species which contains the **sesquiterpene lactones artemisinin**, chemical constituent which contains the **endoperoxide bridge** shows the **antimalarial properties. They are the only reliable treatment for highly drug**

**resistant malaria [28]**. This review also reveals the brief information about the Malaria and This gives the knowledge not only about the symptoms, Diagnosis, Treatment of Malaria but also the details about malarial parasite, Life cycle of Malarial parasite **Plasmodium Falciparum.** Also, if artemisinin group of drugs have to be used alone for complete parasitological cure (without recrudescence) longer duration of treatment is required for which caution should be exercised since possibility of subclinical neurotoxicity cannot be ruled out19. [24-26]

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The authors have no conflict of interest to declare.

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