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DISCOVERY, BIOLOGICAL ACTIVITIES AND REPURPOSING OF ARTEMISININS: A NARRATIVE REVIEW

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ABSTRACT

Malaria is an infectious disease caused in the human species by *Plasmodium* parasites. There are five parasite species that cause malaria in humans, and two of these species, *Plasmodium falciparum* and *Plasmodium vivax*, cause the majority of malaria cases and deaths. The WHO World Malaria Report 2021 reported nearly 241 million malaria cases in 2020 from 85 malaria-endemic countries. The discovery of artemisinin (ART) by Professor Tu Youyou and her team as a traditional medicine to conquer life-threatening diseases worldwide has saved millions of lives over the years. Professor Tu Youyou was rewarded with the Nobel Prize in Physiology or Medicine 2015 "for her discoveries concerning a novel therapy against Malaria". These traditional medicines for malaria have continuously gained a reputation as an alternate drug, for their high efficacy against malaria parasites and safety profile. There has been an increased prevalence of antimalarial resistance to standard drugs such as chloroquine, quinine, proguanil, pyrimethamine, etc. Thus, artemisinin-based combination therapy (ACT) is currently recommended by the World Health Organisation (WHO) and used as a first-line malaria therapy in endemic countries to treat uncomplicated *falciparum* malaria. Artemisinins are highly effective with rapid clearance of the parasites and minimal side effects. Presently, six ACTs are recommended by the WHO for treating malaria cases globally. Artemisinin-derived drugs have revolutionized malaria treatment and infused a newer emphasis on folklore and traditional remedies that can be used to derive novel phytochemicals or design chemical compounds with clinical significance. This article focuses on the pleiotropic activities shown by the traditional medicine artemisinin against various pathogens or disease conditions.

Keywords: Artemisinin, Malaria, Repurposing Drugs, *Plasmodium, Artemisia annua*

INTRODUCTION

Background

Malaria is a deadly tropical disease caused by *Plasmodium* parasites, which are transferred to humans through infected female Anopheles mosquito bites. Five parasite species cause malaria in humans: *P. vivax* and *P. falciparum* are found to cause severe illness and death (https://www.who.int/news-room/fact-sheets/detail/malaria). The World Health Organisation's (WHO's) world malaria report 2021 confirmed that approximately 241 million malaria cases were reported in 2020 in 85 malaria endemic countries (including the territory of French Guiana), increase from 227 million malaria cases in 2019 (**WHO, 2021**). The WHO South-East Asia's regional report of WHO mentioned that 2% of the global malaria cases were from India, and 83% of malaria cases in this region were reported from India. In 2016, Sri Lanka was certified as a malaria free country, which continues to maintain its status till date. World Malaria Day, an international observance, is celebrated every year on 25th April and in 2022, it was marked under the theme "Harness innovation to reduce the malaria disease burden and save lives" (**WMD, 2022**).

Artemisinin is a sesquiterpene lactone peroxide, which was extracted from the leaves of the shrub *Artemisia annua* (qinghao). Artemisinins (ART) offer a new class of the most potential antimalarials available till date, with a high potential to destroy all asexual stages of *P. falciparum* and widely used for treating multidrug-resistant malaria. Although most of the antimalarials contain a heterocyclic ring structure containing nitrogen, artemisinin lacks it. (Figure 1). Artemisinin has low water solubility, which limits its bioavailability. Therefore, a successful chemical modification converts it into half ester of succinic acid to produce the drug of choice, artesunate (Figure 2) (**Rosenthal, 2008**). In comparison to other standard antimalarial drugs, artemisinin was reported with less toxic effects; thus, it augments its therapeutic effect against diseased cells. Some derivatives of artemisinin are used widely: the water-soluble hemi-succinate derivative, *i.e.*, artesunate, the oil soluble methyl ether and ethyl ether derivatives, *i.e.* artemether and arteether, and dihydroartemisinin (DHA) (Figure 2). Artemisinin and its derivatives are mostly safe and tolerated well. The 2015 Nobel Prize in Medicine or Physiology was awarded to Professor Youyou Tu, which rekindled international attention on artemisinin and the discovery of modern-day medicines from the extracts of natural products and traditional sciences in an affordable way. Artemisinins have received increased consideration for other potential pharmaceutical effects, such as antiviral, anti-inflammatory, antifungal, antiparasitic, and anticancer properties, in preclinical and clinical studies. Drug repurposing of artemisinins has shown new inhibitory and therapeutic pathways for a boundless diversity of human diseases, thus giving us hope for greater accessibility and affordability globally. With its high potency and low toxicity, the use of artemisinin-based combination therapies will help to reduce drug-resistant parasites and may eventually help to eradicate malaria across the globe. This review summarizes the information on ART-based drugs and their repurposing in other pathologies with the hope of exploring possible priority areas for future drug development programs.

From *Artemisia annua* L. to Artemisinins: The Discovery and Development of Artemisinins as Antimalarial Agents

Artemisia annua L. is an annual aromatic herb, which belongs to the Asteraceae family (Figure 1). It may reach up to 2 meters or more in height. The plant is erect, single stemmed with alternate branches. The stem is green when young, becames violet-brown at maturity, is ribbed and may or may not be covered with fine hairs. The leaves are alternate, pubescent, aromatic, deeply dissected and 2.5 to 5 cm in length (**WAC, 2023**). The plant is native to China, where it grows naturally in northern parts of Chahar and Suiyan provinces (**Ferreira *et al.*, 2005**). However, it was also found to occur naturally in temperate zones of south-eastern Europe and western Asia. It was brought to western and southern Europe, North and South America, Australia, India, Russia, Iran and several other countries of the world at the end of 19th century (**Ekiert *et al.*, 2021**).

A. annua L. has been used for treating fevers of Malaria and chills in China for more than a thousand years. Pharmacological studies of the leaf extract of *A. annua* showed a wide range of biological activities such as antiprotozoal, antifungal, antibacterial, anti-inflammatory, antioxidant, immunosuppressive, analgesic, nephroprotective and anticancer activities. *A. annua* is also used in cosmetics applications, dyes, and as an important ingredient of vermouths (**Ekiert *et al.*, 2021**).

Leaves of *A. annua* L. contain two types of trichomes, namely glandular secretory trichomes (GSTs) and T-shaped nonsecretory trichomes (TSTs) which are sites for the accumulation of different secondary metabolites like sesquiterpenodis, monoterpenes, essential oils and artemisinin (**Shi *et al.*, 2018**). T-shaped nonsecretory trichomes (TSTs) are five celled and filamentous, while the glandular secretory trichomes (GSTs) are ten celled biseriate structures with five cells on each sector. Artemisinin is mainly produced and accumulated in glandular secretory trichomes (GSTs) which contain two basal cells, two stalk cells, four subapical cells, and two apical cells (**Olsson, *et al.*, 2009**).

The discovery of artemisinin with its high potency and low toxicity has been documented as the "best hope for the treatment of malaria" by WHO. In 1955, the first Global Malaria Eradication Programme (GMEP) was initiated by WHO for global efforts to control and eliminate malaria. During the Vietnam war, North Vietnam requested China to assist for fighting malaria disease, which caused a large number of casualties among its soldiers. The single celled *Plasmodium* parasites with decreased sensitivity and increased resistance to chloroquine was making the malaria epidemic control problematic in the 1950s. On 23rd May 1967, Chinese Chairman Mao Zedong launched a national project called 'Project 523' to search for new antimalarial medicines and found a cure for chloroquine-resistant malaria (**Shi *et al.*, 2022**). In 1969, Dr. Youyou Tu, who was working as a young scientist at the Institute of Chinese Materia Medica of the China Academy of Chinese Medical Sciences, was selected as the key research person and principal investigator of 'Project 523' (https://www.nobelprize.org/womenwhochangedscience/stories/tu-youyou).

Hundreds of scientists were working in 'Project 523' with an aim to identify different herbs/plants with medicinal properties and antimalarial activities. After comprehensive studies on the inhibition of *A. annua* extract against monkey malaria and rodent malaria, Tu's team isolated the active ingredient from the extract of *A. annua* plant. Professor Tu and her team carried out the initial clinical trial in humans in August 1972 using *Artemisia* extract. Tu and two colleagues tested the compound on themselves before testing it on twenty-one patients (including 11 cases of *P. vivax*, 9 cases of *P. falciparum*, and 1 case of a mixed infection) in the Hainan Province of China (**Tu, 2011; Su *et al.*, 2015**). All the patients recovered quickly after doses and many showed absences of parasites in their blood smear. On November 8, 1972, this antimalarial drug was named '*Qinghaosu*' or Artemisinin (Figure 1). It has the chemical formula $C_{15}H_{22}O_5$ and contains three fused rings with a peroxide bridge (C-O-O-C). Professor Tu and her research team also established 'dihydroartemisinin', which was found to be a highly active artemisinin derivative.

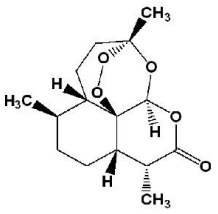

Figure 1 *Artemisia annua* L. is an aromatic herb, which grows annually and belongs to the Asteraceae family and source of Artemisinins (Qinghaosu) (Photo Credit: Dr. Vidhi Chaudhary, Daulat Ram College, University of Delhi; Photo taken at Central Institute of Medicinal and Aromatic Plants (CIMAP), Lucknow, India, Coordinates: 26.8948° N, 80.9824° E).

Phytochemical and Pharmacological properties of Artemisinin and its derivatives

Artemisinins are familiar for their potent antimalarial biological activity (Figure 2). These natural products have been found to be active against *P. falciparum* malaria and drug-resistant strains (**Krishna *et al.*, 2008**). These compounds come under the classification of sesquiterpene lactones, and their antimalarial activity is associated with the endoperoxide trioxane moiety present in these molecules. Artemisinin-based combination therapy (ACT) has emerged as the frontline of action for uncomplicated *P. falciparum* malaria, which comprises the co-administration of an artemisinin derivative along with longer acting partner drug (**Penissi *et al.*, 2006**). WHO has endorsed ACT as a major treatment for malaria disease caused by *P. falciparum*. In this study, young ring forms of malarial parasites were targeted and the process of development into mature pathogenic stages was stopped (**Nosten *et al.*, 2007**). Alternately, these natural products might interfere with hemoglobin digestion in the parasite food vacuole or might attack the mitochondria present in the cells of the parasite.

Artemisinin and its derivatives interfere with the inhibition of heme polymerization and the plasmodial hemoglobin catabolic pathway. The *in vitro* experiments showed the inhibition of digestive vacuole proteolytic activity of the malarial parasite by ART. *Ex vivo* experiments also showed that accumulation of hemoglobin occurred in the parasites when treated with artemisinin, which suggested possible inhibition of hemoglobin degradation. It was reported as a potent inhibitor of heme polymerization activity, which is mediated by *P. yoelii* lysates as well as *P. falciparum* histidine-rich protein II (**Penissi *et al.*, 2006**). The antimalarial effect of *A. japonica, A. maritima, A. nilagirica* extracts is also studied by researchers (**Valecha *et al.*, 1994**). The results showed extended time of survival for the treated mice in comparison to controlled mice (dose range of 640-320 mg/kg subcutaneously). Authors reported that aerial parts of *A. japonica* in lower doses caused prolonged mean survival time.

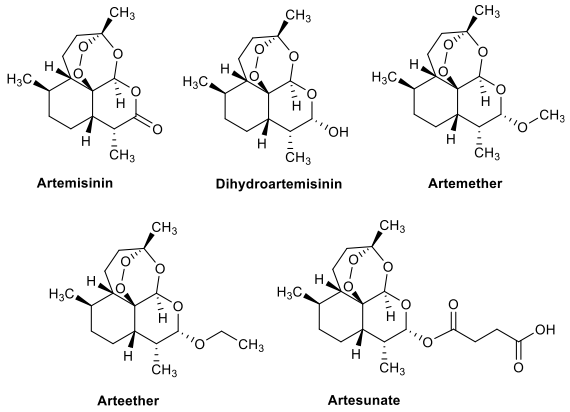

Figure 2 Artemisinin and its various derivatives.

Artemisinin derivatives are a relatively new group of compounds with potent antimalarial properties. The four main derivatives are the water-soluble hemisuccinate artesunate (AS), dihydroartemisinin (DHA), and the lipophilic methyl ethers artemether (AM) and artemotil (previously known as arteether) (**Balint, 2001; Davis *et al.*, 2005**). Some of the artemisinin derivatives are in common clinical use, namely dihydroartemisinin, artesunate and artemether. Recent clinical studies suggest that artemisinin and its derivatives have therapeutic effects on parasites (non-malaria), viruses, tumors, inflammation, skin diseases, autoimmune inflammatory diseases, and autoimmune disorders as safe and effective candidates (**Huang *et al.*, 2023; Long *et al.*, 2024; Liu *et al.*, 2020**). Hence, exploring the potential of these ART derivatives can lead to significant improvements in future research directions (Figure 3) and may prevent the spread of multidrug resistance.

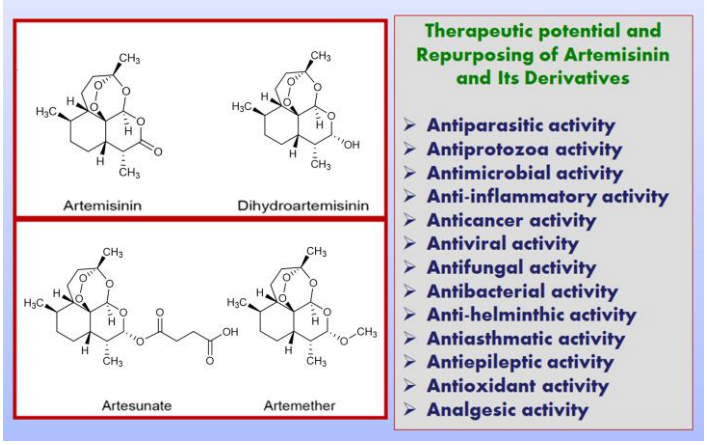

Figure 3 Recent therapeutical advances and repurposing of artemisinin and its derivatives.

The Nobel Prize in Medicine or Physiology in 2015 Awarded for Novel Therapies Against Parasitic Diseases

The Nobel Prize in Medicine or Physiology 2015 was awarded for discoveries concerning novel treatments for some of the most devastating parasitic diseases: Malaria, Lymphatic Filariasis (Elephantiasis or Lymphedema) and River Blindness (Onchocerciasis). The Nobel prize was jointly given to Dr. William C. Campbell and Dr. Satoshi Ōmura 'for their discoveries concerning a novel therapy against infections caused by roundworm parasites' along with Dr. Tu Youyou 'for her discoveries concerning a novel therapy against Malaria' (**Nobel Prize Organization, 2015**). Collectively, Dr. Ōmura's and Dr. Campbell's contributions led to the discovery of a new class of drugs with extraordinary efficacy against two major diseases caused by parasitic worms (**Callaway *et al.*, 2015**). A bioactive agent, Avermectin, purified from *Streptomyces avermitilis* cultures, was found to be effective in killing parasites. Avermectin was additionally modified to Ivermectin, which was found to be extremely effective in killing parasites in both humans and animals, including those parasites responsible for causing Lymphatic Filariasis and River Blindness. Tu was the first to show that the extracted from the plant Artemisia annua was highly effective against the malaria parasite and gave rise to a new class of antimalarial agents that rapidly kill the Plasmodium parasites,

both in infected animals and in humans (**Tu *et al.*, 1981**). The discoveries of the drugs Avermectin, Avermectin-derivative Ivermectin, and Artemisinin have transformed treatment methods for patients distressed by parasitic diseases and fundamentally changed the therapy of these parasitic diseases, primarily in the poorest regions of the world.

Artemisinin-based Combination Therapies (ACTs): The official first-line treatment for malaria

Artemisinin-based combination therapy (ACT) has been approved by the WHO as a first-line treatment for a simple kinds of *P. falciparum* malaria. ACTs have shown rapid parasite removal in contrast with any other standard anti-malarial drugs (Figure 2), reduced parasite transmission in malaria-endemic areas, and lesser levels of reinfection in patients. Artemisinin over the years has become a very powerful tool for controlling malaria, and ACTs constitute a new class of antimalarial compounds. The derivatives of artemisinin currently available in different formulations for treatment of malaria are artesunate (intravenous, rectal, oral), artemotil (intravenous), artemisinin (intravenous, rectal, oral), artelinate (oral), artemether (intravenous, oral, rectal), and dihydroartemisinin (oral). Eckstein-Ludwig et al. proposed that artemisinin specifically inhibits PfATP6, the SERCA (Sarco-Endoplasmic Reticulum Calcium ATPase) orthologue of *P. falciparum,* outside the food vacuole after activation by iron (**Eckstein-Ludwig *et al.*, 2003**).

WHO endorses ACTs for treating simple malaria instigated by *P. falciparum*. ACTs, due their protecting efficacy and safety profile, have become an integral part of global malaria control and are utilized as a first-line malaria treatment in endemic countries worldwide. WHO strongly recommends treating children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following Artemisinin-based combination therapies (ACTs) formulations: artemether plus lumefantrine; artesunate plus amodiaquine; artesunate plus mefloquine; dihydroartemisinin plus piperaquine; and artesunate plus sulfadoxine-pyrimethamine (SP) (Table 1) (**WHO, 2023**). The 'WHO Guidelines for Malaria' is now available on a user-friendly and easy-to-navigate online platform (https://app.magicapp.org/#/guideline/7089) (**WHO, 2023**).

Table 1 ACT regimens currently available as per the WHO Guidelines for malaria, 2022

ACTs	Formulations currently available	Target doses (ranges) and recommended dosage regimen
Artemether plus lumefantrine	Two different types of tablets are available: i) Standard/dispersible tablets (20 mg artemether + 120 mg lumefantrine), ii) Standard tablets (40 mg artemether + 240 mg lumefantrine) in a fixed-dose combination formulation.	Artemether: A total dose of 5–24 mg/kg bw (body weight) and lumefantrine: 29–144 mg/ kg bw. It is recommended two times every day for 3 consecutive days (six doses in total). The first two doses need to be given 8 hours apart (preferably).
Artesunate plus amodiaquine	A combination of fixed-dose formulations in tablets is available which contained 25 + 67.5 mg, 50 + 135 mg or 100 + 270 mg of artesunate and amodiaquine, respectively.	The target doses (and ranges): 4 (2–10) mg/kg bw per day artesunate + 10 (7.5–15) mg/kg bw per day amodiaquine one time every day for three consecutive days. Recommended therapeutic dose range: 6 - 30 mg/kg bw per day artesunate + 22.5 - 45 mg/kg bw per dose amodiaquine.
Artesunate plus mefloquine	Fixed-dose formulation of paediatric tablets available: Comprises 25 mg of artesunate + 55 mg of mefloquine hydrochloride (equivalent to 50 mg mefloquine base). Adult tablets available: Comprises 100 mg artesunate + 220 mg mefloquine hydrochloride (equivalent to 200 mg mefloquine base).	The target doses (ranges): 4 (2–10) mg/kg bw per day artesunate + 8.3 (7–11) mg/kg bw per day mefloquine, given one time every day for 3 consecutive days is recommended.
Artesunate plus sulfadoxine-pyrimethamine	Blister-packed, scored tablets available: Contains 50 mg artesunate. Fixed dose combination tablets including 500 mg sulfadoxine plus 25 mg pyrimethamine. No fixed-dose combination formulations are available.	The target doses (ranges) of 4 (2–10) mg/kg bw per day artesunate administered one time every day for 3 consecutive days and a single administration of at least 25 / 1.25 (25–70 / 1.25–3.5) mg/kg bw sulfadoxine-pyrimethamine given as a single dose on the first day of treatment.

(Table Data compiled from WHO Guidelines for malaria, World Health Organization 2022; WHO/UCN/GMP/2022.01Rev.2).

Over the past few decades, emerging biological threats such as mosquito resistance to insecticides and drug resistance of *Plasmodium* parasites have developed an issue of extreme concern and an emerging problem in clinical malariology. The poor control of the utilization of rational antimalarial drugs, weak health systems and gaps in access to effective interventions are the important factors that lead to antimalarial drug resistance. **Sinha *et al.* (2014)** noted that the artemisinin resistance problem on the Cambodia-Thailand border can significantly cut the usefulness of artemisinin or currently used ACTs and affect the global malaria control strategies (**Sinha *et al.*, 2014**). Hence, there is an utmost requirement to reinforce and expand current drug-resistance observation systems and search for novel and highly efficacious partner drugs to artemisinin, to reduce dependence on current antimalarials by synthesis of artemisinin at the industrial level, which should reduce its cost.

Therapeutical Utilization and Repurposing of Artemisinin and Its Derivatives

Natural products constitute valued chemical scaffolds for pharmaceuticals and new drug discovery. The plant *Artemisia annua* species contains bioactive constituents with pleiotropic biological effects with relatively low toxicity for normal human cells. Several preclinical investigations have suggested possible anticancer effects of artemisinin and the derivatives of artemisinin, mainly through the generation of toxic-free radicals by its endoperoxide moiety. Although the exact mechanisms of action of ART derivatives to kill tumour cells are not clear. However, they cause cell cycle arrest, initiation of apoptosis, and blockage of tumour angiogenesis (**Li *et al.*, 2016**). Recently in a review by **Firestone *et al.* (2021)**, authors discussed the repurposing of quinoline and artemisinin antimalarials as therapeutic options for the treatment of SARS-CoV-2 in clinical settings. Few clinical studies have shown that the class of quinolines and artemisinins are active against SARS-CoV-2 both *in vivo* and *in vitro*. Artemisinin and its derivatives have also shown good antiviral *in vitro* and *in vivo* activity against DNA viruses of the Herpesviridae and Hepadnaviridae families, like cytomegaloviruses, human herpesvirus 6, herpes simplex viruses 1 and 2, Epstein-Barr virus and Hepatitis B virus (**Efferth, 2018**). Artemisinins also act against phylogenetically unrelated parasitic infections such as schistosomiasis. Artemisinin derivatives- artemether and artesunate- have shown useful efficacy in human studies and in models of metazoan infections, particularly *Schistosoma spp*. (**Utzinger, 2007**). The anti-inflammatory, antioxidant, and antimicrobial properties of artemisinin are also well-established (**Kim *et al.*, 2015**). Newer developments in the arena of phytomedicine and synthetic biology for drugs based on artemisinin and artemisinin's production might pave the way for newer artemisinin-based synergistic drug combinations to fight against viral infections, other protozoan and metazoan parasites, and treatment of tumours in the future.

Antiparasitic activity: Artemisinin and its derivatives obtained from *A. annua* L. were found to possess antimalarial and antischistosomal activities, whereas some of these compounds were also found to be active against parasitic protozoa (**Bisht *et al.*, 2021**). Artemisinin analogs were reported against protozoan parasites such as *Acanthamoeba castellanii*, *Babesia* spp, *Eimeria tenella*, *Cryptosporidium parvum*, *Giardia lamblia*, *Leishmania* spp, *Neospora caninum*, *Naegleria fowleri*, Trypanosoma spp and *Toxoplasma gondii*, etc. *Artemisia absinthium* was found to be an effective herb when used as an additive in livestock feeds and has proficient flavours (**Bisht *et al.*, 2021**). The essential oils extracted from *A. annua* was evaluated for antibacterial (*Staphylococcus aureus, Echerichia coli*, and *Pseudomonas aeruginosa*) and antifungal activities (*Candida albicans* and *Saccharomyces cerevisiae*). The study reported the maximum inhibitory activity of essential oils and their active ingredients against fungal microorganisms. A protozoal parasite, *Neospora canum* which infects a wide range of mammals and causes abortion in cattle was studied (**Das, 2012**). Artemisinin was found to inhibit the intracellular growth of *N. caninum* tachyzoites ($p < 0.05$) with a 0.1 µg/ml concentration. The antileishmanial activity was shown by artemisinin in both promastigotes and amastigotes with IC_{50} values of 160 and 22 µM respectively, with a high safety index (>22-fold) (**Das, 2012**).

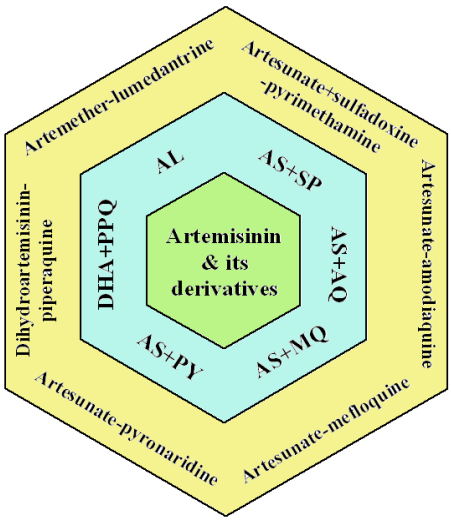

Figure 4 Artemisin-based combination therapy (ACTs) for treatment of *P. Falciparum* malaria.

Antiprotozoal activity: *In vitro* antihistomonal activities of artemisinin were evaluated on clonal cultures of *Histomonas meleagridis* and it revealed the dose-dependent reductions in the count of protozoa of six clones of *H. meleagridis* at two different concentrations, *i.e.* 5.10 and 20 mg/mL by artemisinin treatment. However, *in vivo* experiments showed the inability of artemisinin and its DCM extract, at concentrations of 100 and 2600 mg/kg (**Zyad *et al.*, 2017**), while other authors mentioned the *in vitro* activity of artemisinin against *Trichomonas vaginalis* and *Leishmania spp*. with IC_{50} values between 100 and 120 mM concentrations. However, these concentrations were found to be higher than the effective dose against the parasite of malaria having IC_{50} values in the nanomolar range (**Zyad *et al.*, 2017**).

Antimicrobial activity: The essential oil extracted from aerial parts of *Artemisia annua* consists of monoterpenes, camphor, ketones, β-caryophyllene, 1,8-cineole, and germacrene sesquiterpene hydrocarbons that showed antimicrobial properties because of these secondary metabolites. Following the disc diffusion method and Minimal Inhibitory Concentration (MIC) assay, the antimicrobial activity of these plant extracts was tested against *Staphylococcus aureus, Bacillus thuringenesis, Bacillus subtilis, E. Coli and Salmonella* (**Verma *et al.*, 2020**). Extracts of various solvents were screened for antimicrobial activity, where the methanolic extract showed the highest activity against *S. aureus*. Multidrug-resistant *Mycobacterium tuberculosis* strains, an organism that is resistant to potent TB drugs, is a threatening barrier to tuberculosis eradication programs. This has encouraged the researchers to explore novel phytochemicals such as artemisinin as a promising antitubercular agent. Researchers reported that dichloromethane (DCM) extracts from leaves of *A. afra* Jacq. ex Willd. and *A. annua* L. showed anti-mycobacterial activity higher than artemisinin (**Trifan *et al.*, 2022**). The chloroform and ethanolic extracts of artemisinin were screened for antifungal and antibacterial activities following different methodologies (EUCAST, www.eucast.org). MIC of the screened derivatives were evaluated for the wide panel of the corresponding microorganisms, which included Gram-negative bacteria such as *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Salmonella Typhimurium* ATCC14028, *Proteus mirabilis* ATCC 12453 & *Pseudomonas aeruginosa* ATCC 9027 and Gram-positive bacteria such as *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Staphylococcus aureus* ATCC 6538, *Micrococcus luteus* ATCC 10240, *Bacillus cereus* ATCC 10876, *Bacillus subtilis* ATCC 6633, *Streptococcus pneumoniae* ATCC 49619, *Streptococcus pyogenes* ATCC 19615, *Streptococcus mutans* ATCC 25175) and fungi like *Candida parapsilosis* ATCC 22019, *Candida albicans* ATCC 10231 (**Mamatova *et al.*, 2019**). **Mamatova *et al.* (2019)** described the preliminary screening of antimicrobial activity against several strains of bacteria and fungi. The assayed extracts were able to inhibit the growth of the corresponding microorganisms when treated with an MIC of 1.25 to > 20 mg/ml, depending on the solvents and strains used for the experiments. The ethanolic and chloroform extracts showed comparable biological activity where Gram-positive bacteria *Bacillus* spp., *Micrococcus luteus* and *staphylococci* (MIC = 1.25–5 mg/ml) and yeasts denoted by *Candida* spp. (MIC = 2.5–5 mg/ml), were found to be highly sensitive irrespective of the assayed extract. These two extracts showed very low biological activity against Gram-negative rods. **Sukanya *et al.* (2009)** screened the leaf extract of a few Indian medicinal plants against clinical and phytopathogenic bacteria to check their antimicrobial efficacy. Various extracts of *Artemisia parviflora* were screened against clinical bacteria such as *Escherichia coli* and *Staphylococcus aureus* and phytopathogenic bacteria such as *Xanthomonas vesicatoria* and *Ralstonia solanacearum* using the agar disc diffusion method. A zone of 2 mm of inhibition was observed by ethanolic extract of the plant against *X. vesicatoria* and *S. aureus*. However, the extracts of *A. parviflora* exhibited very low inhibition when screened against phytopathogenic and clinical bacteria.
A. annua extracts induce clearance of *P. berghei* in mice was observed, followed by the identification of the active compound artemisinin from *A. annua* (**Zyad *et al.*, 2017**). Barnes and White reported that artemisinin reduced the number of gametocytes in blood, due to their effect against the early gametocytes (Stages I to III) and sexual stages precursors (**Barnes *et al.*, 2005**). No clinical resistance was observed with the artemisinin class of antimalarial drugs, whereas these compounds were found to be efficient on multidrug-resistant *P. falciparum*. *A. annua* and artemisinin acted effectively in humans and mice against otherwise drug-resistant malaria. Mutations in genes related to multidrug resistance have altered the sensitivity of some *P. falciparum* strains towards artemisinin (**Zyad *et al.*, 2017**).

Anti-inflammatory activity: Artemisinin and scopoletin, two major natural ingredients of *A. annua*, have been reported to possess anti-inflammatory effects. The crude extracts of twigs and leaves of *A. annua* inhibited the generation of NO in macrophages and showed noteworthy inhibitory activity against TNF-α and PGE2 production by activated neutrophils (**Verma *et al.*, 2020**). Artemisinin was capable of inhibiting interleukin 6 (IL-6) release and the plant extracts containing artemisinin derivatives demonstrated anti-inflammatory activities. The highest inhibitory activity was shown by the acetone extract on the release of the proinflammatory cytokine, lipopolysaccharide-induced nitric oxide and prostaglandin E2 (**Yu, 2012**). Dihydroartemisinin, an artemisinin derivate, was found to inhibit lipopolysaccharide-stimulated TNF- production, IL-6, and the release of nitric oxide from the murine macrophage-like RAW264.7 cell line in mice when the concentration range was 12.5–100 μM. Dihydroartemisinin was found to inhibit macrophage's release of inflammatory factors (TNF-α and IL-6) and inflammatory mediator nitric oxide, by reducing nitric oxide synthase (iNOS) protein. Moreover, artemisinin in combination with dihydroartemisinin exhibited an anti-inflammatory effect (**Yu, 2012**). **Yang *et al.* (2009)** screened alcoholic extracts of the plant to check their inhibitory activity for nitric oxide (NO) synthesis in lipopolysaccharide (LPS) activated macrophages. Murine macrophage RAW 264.7 cells with LPS, a perfect model for screening of drug followed by subsequent assessment of potential inhibitors against NO and iNOS production was utilized. The ethanolic aerial parts extract of *A. japonica* showed 45.61% and 89.61% of nitric oxide inhibition and cell viability, respectively (**Yang *et al.*, 2009**). This result showed the possibility of an anti-inflammatory effect through NO pathway inhibition, and it was assumed that the suppression of the NO pathway could influence the inhibition of phagocytosis and immunomodulation.

Anticancer activity: Artemisinin could be utilized for the prevention and treatment of cancer, as it showed both *in vivo* and *in vitro* anti-cancer/antitumor activity against a wide range of cancerous cells. It is considered a safer drug due to its well-known pharmacokinetics and pharmacodynamics effects and low toxic effects on normal cells. The endoperoxide group present in artemisinins was found to be essential for their antimalarial and anticancer activities (**Bisht *et al.*, 2021; Verma *et al.*, 2020**). Artemisinin derivatives activate the intrinsic or the cytochrome C-mediated pathway for apoptosis, which causes induce programmed cell death of cancer cells (**Isani *et al.*, 2019**). However, main mechanism for the anti-cancer activity was found to be the production of free radicals generated from the reaction between artemisinin and molecular iron. Artemisinin and aqua-ethanolic extract of *A. annua* showed a high level of toxicity in *Canine Osteosarcoma* cell line, whereas artesunate showed inhibition of proliferation of cells. When artesunate was mixed with captopril, it showed synergistic action against tumorous cells (**Gordanian *et al.*, 2014**). Artemisia has been found to produce anti-angiogenic actions in tumor cell lines, and the methanolic extract of *A. absinthium* inhibited the growth of MDA-MB-231 and MCF-7 cells at different concentrations at a dose of 20 g/ml and 25 g/ml over three days caused 50% suppression in MDAMB-231 and MCF-7 cells, respectively with control (**Bisht *et al.*, 2021**). It was also found that a few extracts of artemisia diversities showed an eminent effect on ER-positive T47D cells along with prohibitory or stimulatory effect on cell dissemination. When extracts of artemisia spp. were applied at concentrations over 100 mM for 72 h, it prohibited the distribution of cells exceptionally. All these plant extracts signified nearly the same anti-cancer activity in HS578T cells when treated following a dose and time-dependent pattern. However, the growth of T47D cells was less at lower concentrations, and it prevented the growth of T47D cells at higher concentrations (> 100 mg/ml for 72 h) (**Nobel Prize Organization, 2015**). Root, stem, leaf, and flower extracts of *A. absinthium*, *A. fragrans*, *A. incana*, *A. spicigera* and *A. vulgaris* were tested against breast cancer cell line (MCF7) at concentrations (62.5, 125, 250, 500 μg/ml), following 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Leaf, stem, flower, and root extracts of *A. vulgaris* and *A. absinthium* done with methanol extraction showed anticancer activity, whereas the floral part extract displayed high cytotoxicity on MCF7 cells (IC_{50} of 221.5 > 500 μg/ml). The cytotoxic consequence of *A. incana*, *A. absinthium* and *A. vulgaris*, against MCF7 was found to be 10–40% higher in comparison to HEK293 cells. *A. fragrans* and *A. spicigera* did not show any cytotoxic effects on both cell lines, but *A. vulgaris* and *A. absinthium* demonstrated new anticancer compound (**Gordanian *et al.*, 2014**).

Identification of 130 different constituents obtained from *A. monosperma* essential oil while some of these compounds have shown high biological activities. It was envisioned that the alkylating ability of artemisinin was because of the presence of endoperoxide linkage in artemisinin which would react with iron and the heme group. Artemisinin can induce apoptosis, slow cell proliferation, and arrest the cell cycle, while its accumulation inside lysosomes and mitochondria was assumed to play a role in cell death.

The effectivity of artemisinin was studied under *in vitro* conditions at different concentrations, which showed that artemisinin blocked the colony formation and growth of human hepatocellular carcinoma cells through the apoptosis pathway (**Deng *et al.*, 2013**). Artemisinin inhibited the growth and cell viability of human ovarian carcinoma cell lines, whereas it showed a differential effect on cancer cells and lysis on the murine mastocytoma cancer cell line (P815) and on Kidney adeno-carcinoma cell line of hamsters (**Tilaoui *et al.*, 2014**). However, artemisinin has shown pharmacokinetic limitations such as low solubility in water or oil and poor bioavailability (**Zyad *et al.*, 2017**). So, semisynthetic derivatives of this molecule were developed by synthetic organic chemists to overcome these limitations. Semisynthetic derivatives such as dihydroartemisinin and artesunate exerted *in vitro* anticancer activity against various cancer cell lines. Artemisinin showed lower activity in breast cancer cells (MCF-7), and the activity in these cells was assumed to be due to estrogen receptors-attributed (ERα and ERβ) which were involved in cell proliferation. Lessened sensitivity was observed in metastatic nasopharyngeal carcinoma cell lines (CNE-2 and CNE-1) and artemisinin seemed to be related to the over-expression of polycomb complex protein BMI-1 (**Zyad *et al.*, 2017**).

Artemisinin was described to show higher cytotoxicity against cancer in comparison to normal healthy cells, as normal cells have a significantly lower amount of free iron than cancer cells (**Tilaoui *et al.*, 2014**). On the other hand, the artemisinin derivative artesunate showed cytotoxicity on isogenic *Saccharomyces Cerevisiae* and the anticancer activity of artesunate, arteether, and artemether was found to be associated with the basal mRNA expression (**Efferth *et al.*, 2002**). Under *in vitro* conditions, human breast cancer cells, molt-4-lymphoblastoid cells and a human leukemia cell line were more susceptible to the cytotoxic effects of artemisinin. The LD_{50} value for Molt-4 cells was found to be approximately 100 times less in comparison to lymphocytes. Experimental results confirmed that artemisinin was more toxic towards human breast cancer cells than to normal cells (**Zyad *et al.*, 2017**). The cytotoxic effect of artemisinin for the above mentioned cells was enhanced when transferrin was added. When holotransferrin was tagged to artemisinin, it increased the specificity of artemisinin for killing cancer cells. Like artemisinin, dihydroartemisinin with a holotransferrin tag was found to be highly potent in killing Molt-4 cells. The cytotoxicity data showed that the tagged compound was a highly potent and specific killer of Molt-4 cells (**Zyad *et al.*, 2017**).

Molecular level studies on the mechanism of artemisinin towards anticancer activity were performed on the cancer cell line HL-60, which depicted that swift generation of reactive oxygen species was associated with cell death following apoptosis when the cells were treated with artemisinin. Endoplasmic reticulum stress and calcium metabolism were also found to be associated with the anticancer activity of artemisinins and endoplasmic reticulum was identified as a possible location for artemisinin action. The induction of apoptosis effects by artemisinin and cell cycle arrest at G0/G1 cell cycle transition phase was described by researchers (**Zyad *et al.*, 2017**).

Antiviral activity: The 50% aqueous ethanolic whole plant extract of *Artemisia parviflora* Roxb. was tested for anti-viral effects against Ranikhet disease virus and Vaccinia virus, where it showed antiviral activity against the Vaccinia virus (**Dhar *et al.*, 1973**). A mixture of *Saururus chinensis* and *A. japonica* extract was found to be an effective agent and the white spot syndrome virus of arthropods was also treated and prevented. Artemisinin and its analogue artesunate showed antiviral activities against human cytomegalovirus, herpes simplex virus 1, Epstein-Barr virus, human herpes virus 6A, hepatitis B and C virus and HIV-1 virus (**Efferth *et al.*, 2008**). It was able to reduce the replication process of Hepatitis B and C viruses at low micromolar concentrations, human immunodeficiency virus−1, human herpesviruses, and bovine viral diarrhea (**Zyad *et al.*, 2017**). However, artemisinin was found to be futile against the human influenza virus A and herpesvirus 6A. Its derivative, artesunate had shown anti-herpes viral potency. **Birku *et al.* (2002)** reported that HIV-infected patients showed a late clearance of *P. falciparum* parasite when compared with the non-HIV infected patients. However, artemisinin had shown a synergistic antiviral effect as an adjuvant treatment, which did not affect host cells. The inhibitory effect of artemisinin on cytomegalovirus replicon replication showed a dose dependent way in 2 HCV sub-genomic replicon constructs at lower concentrations without affecting Huh 5–2 host cells (**Paeshuyse *et al.*, 2006**). An iron donor hemin inhibited cytomegalovirus replicon reproduction by stopping the polymerase of the virus. So, it was assumed that the hemin combination and artemisinin might possess a synergetic antiviral activity (**Zyad *et al.*, 2017**). Initial studies indicate that artemisinin and related compounds have positive effects in combating viral infections such as Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV-2) infection or COVID-19 related symptoms (**Farmanpour-Kalalagh *et al.*, 2022**). As reported by **Farmanpour-Kalalagh *et al.* (2022)**, a total of 16 trials with *Artemisia* spp. extract, artemisinin derivatives, and ACTs have been registered at the US National Library of Medicine (https://clinicaltrials.gov/) database, and three clinical trials in the database of the Chinese Clinical Trial Registry (ChiCTR) (https://www.chictr.org.cn/) for anti-SARS-CoV-2 activity. Even WHO-supervised clinical research work on the possible inhibitory activity of artemisinins to fight COVID-19 are in progress.

Antifungal activity: The essential oil extracted from *A. parviflora* showed antifungal properties against *Sporotrichum species*, *Candida albicans*, and *Cryptococcus* (**Mehrotra *et al.*, 1993**). Artemisinin exhibited reasonable antifungal activity against *Alternaria solani*, *Aspergillus flavus*, and *Fusarium oxysporum* (**Algamal *et al.*, 2013**). Similar antifungal results were shown on *Candida albicans* and *Cryptoccocus neoformans.* Artemisinin also demonstrated a fungicidal activity against phytopathogenic fungi *Rhizoctonia solani*, *Aspergillus solani*, *Aspergillus flavus*, and *Fusarium oxysporum*. *In vitro* antifungal property was shown by artemisinin against *Pneumocystis carinii* (**Zyad *et al.*, 2017**).

Antibacterial activity: *A. annua* L. has shown antimicrobial effects against a variety of pathogens, which included *Escherichia coli (E. coli)*, *Enterococcus hirae*, *Enterococcus faecali*, *Candida krusei*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Staphylococcus aureus*. Acetone, ethanol, and methanol extracts of *A. annua* L. were effective against *Fusobacterium nucleatum* subsp. animalis, *Fusobacterium nucleatum* subsp. polymorphum, *Aggregatibacter actinomycetemcomitans*, and *Prevotella intermedia* (**Kim *et al.*, 2015**). Bacterial phytopathologic studies described that artemisinin was effective against *Erwinia carotovoravar* and *Agrobacterium tumefaciens* (**Dhingra *et al.*, 2000**). However, no antibacterial effect of artemisinin was shown by disk diffusion antibiogram assays against *Salmonella typhimurium*, *Salmonella gallinarum* and *Salmonella enteritidis*. Some authors reported that artemisinin showed antibacterial effect on different strains of *Salmonella* spp. and on *E. coli* and *Proteus vulgaris* (**Zyad *et al.*, 2017**).

Anti-helminthic activity: Artemisinin was found to be the key compound of *A. annua* extracts, which was accountable for the anthelmintic activity. This metabolite had interference with parasite transport proteins, which disrupted the parasite's mitochondrial function, inhibition of angiogenesis and modulation of host immune functions (**Golenser *et al.*, 2006**). *A. annua* extracts were also used for pest control activity. When these plant extracts were fed to *Eurygaster integriceps*, it decreased the functional activity of α- and β-glucosidases, lipase, α-amylase, and protease enzymes. It reduced the kinetics of the reaction between the enzyme and substrate, where the affinity between the enzyme and substrate decreased, followed by the interference with the breakdown of enzyme-substrate complex. Artemisinin drugs were also found to be effective against *Leishmania, Eimeria (coccidia), Fasciola, Giardia, Trypanosoma, Babesia, Trichostrongylus,* and *Haemonchus* (**Verma *et al.*, 2020**).

Antiasthmatic and Antiepileptic activity: The chloroform extract from *A. annua* plant showed relaxing effect in the smooth muscles following the combination of Ca^{2+} antagonist and anticholinergic mechanisms where calcium influx was inhibited by voltage dependent current of calcium. The high K^+-induced contraction was also inhibited in a dose-dependent way on mouse tracheal rings (**Huang *et al.*, 2017**). The anticonvulsant and anxiolytic activities of *A. vulgaris* were screened following the elevated plus-maze test and Marble-Burying test (EPMMBT) where 2 mg/kg of diazepam was used as standard drug. Antiseizure activity was shown by the methanolic extract of the plant, whereas the ethanol extract of the genus artemisia such as *A. capillaris* Herba (AC) has displayed anticonvulsant action (**Almeida *et al.*, 2013**).

Antioxidant activity: The methanolic extract of *A. vulgaris* was tested for antioxidant properties using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging and reducing power properties (**Thangjam *et al.*, 2020**). The antioxidant property of this extract was studied to find its capability for scavenging free radicals and this extract scavenged DPPH radicals with high efficiency, which might be attributed to its ability to donate hydrogen. The antioxidant activity of this methanolic extract along with ascorbic acid (as standard) was checked at diverse concentrations, which showed DPPH radical scavenging property was concentration dependent. The methanolic extract showed a percentage inhibition in the range of 12.23–68.06% whereas that of ascorbic acid was 14.37–93.53%, implying that the inhibition percentage increased along with an increase in concentration. The plant extract was also examined by reducing power assay. It was found that at 700 nm the absorbance was increased along with the concentration of the methanolic extract due to the reduction of ferric ions into ferrous ions (**Thangjam *et al.*, 2020**).

Analgesic activity: The peripheral analgesic activity of the methanolic extract was estimated by the acetic acid (AcOH) persuaded writhing test in mice. The selected dose of the extract were 200 and 400 mg/kg b. wt., which showed a higher inhibition effect in comparison to indomethacin, a standard drug (**Thangjam *et al.*, 2020**). These doses inhibited the writhing response by 8.60% and 32.03%, respectively whereas indomethacin at a 10 mg/kg b. wt. dose exhibited 56.87%

inhibition, in accordance with tail immersion test methods. The analgesic activity of the higher dose (400 mg/kg b. wt.) of the methanolic extract was reasonable in comparison with the activity of indomethacin. However, the lower dose at 200 mg/kg b. wt. showed the least activity, which implied that the period and intensity of the analgesic effect exerted by the methanolic extract were dose-dependent (**Thangjam *et al.*, 2020**).

CONCLUSION

Artemisinin has emerged as a truly remarkable secondary metabolite and is the cornerstone of so-called plant-based pharmaceutical drugs and novel combination therapies developed for one of the world's oldest and most important disease-malaria. Artemisinins are resolutely recognized in combination therapies to cure drug-resistant malaria. Over the decades, due to the total dependance on artemisinin in every country in the world, the WHO has been worried about the emergence of drug resistance against this wonder drug. Some reports suggested a decrease in sensitivity to this drug in South-East Asia mainly due to the widespread use of artemisinin monotherapy, substandard and counterfeit drugs, and lack of proper routine surveillance of malaria (**Rehwagen, 2006; WHO, 2011**). In 2007, WHO Member States adopted World Health Assembly resolution WHA60.18 and urged the regulatory authorities in malaria-endemic countries for a progressive removal/withdrawal of artemisinin-based oral monotherapies from all pharmacies and health clinics around the world (**WHO, 2011**). It further asked them to endorse access to quality assured ACTs. More recently, Artemisinins have also shown potent inhibitory activities against other pathogenic apicomplexan parasites, metazoan parasites, tumour cell lines, and some DNA viruses thus showing their growing importance in the field of medicine (**Krishna *et al.*, 2008**). The search for therapeutic herbs (as published in the 'herbal compendia' called *ben cao*) and the isolation of active components from *A. annua* is an example of how ancient herbal remedies can lead to the discovery of an affordable drug for the deprived parts of malaria endemic world. The modern-day pharmacologists have largely ignored the other active components in *artemisia*, the cinchona bark, or other herbal extracts, which may have clinical potential, curative power, and therapeutic effect. Thus, nature may have many more secrets and undiscovered traditional remedies, which are yet to be revealed.

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