GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

# A review of new strategies to combat malaria resistance: The essential oils approach

Amarachukwu Ukamaka Onwuzuligbo [1, *], Chukwunonso Chukwudike Onwuzuligbo [2] and Emmanuel Maduabuchi Uronnachi [1]

[1] *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.*

[2] *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Chukwuemeka Odumegwu Ojukwu University, Igbariam, Anambra State, Nigeria.*

GSC Biological and Pharmaceutical Sciences, 2024, 28(02), 073–083

Publication history: Received on 24 June 2024; revised on 31 July 2024; accepted on 03 August 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.28.2.0286

## Abstract

Essential oils have been a subject of interest to pharmaceutical researchers for over a century but very recently has evoked much more interests due to their widely reported advantages. One of the advantages of essential oils is the ability to resist and reverse resistance. Malaria is a serious health concern globally with almost half of the world population at risk. Although several investments have been made in antimalarial drugs research and development, malaria continues to pose as a global threat. This is attributable to the high propensity of malaria parasites to develop resistance to the various treatment options. It has however, become important to seek for alternative or new strategies for treating malaria without the risks of malaria resistance. This research is aimed towards reviewing the potentials of harnessing the advantages of essential oils in the treatment of malaria and combating malaria resistance. The various novel drug delivery systems for formulating essentials into dosage forms were also reviewed. It is the view of the authors that the use of essential oils in the treatment of malaria and combating of malaria resistance hold great promises and potentials and therefore recommend that essential oils with scientifically proven antimalarial activity should be formulated as either a nanoemulsion, liposome, NLC, or SLN. This will in addition to protecting the essential oils from rapid degradation, improve their efficacy and effectiveness.

**Keywords:** Essential oil; Malaria; Resistance; Novel drug delivery systems

## 1. Introduction

### 1.1. General overview of Malaria

Malaria is a haematoprotozoan tropical disease resulting from an infection by apicomplexan parasites of the genus Plasmodium. The disease is a serious global health problem with nearly half of the world population at risk, over 200 million cases and greater than 400,000 deaths in 2018 alone [1]. Over 90% of malaria deaths occur in the WHO-defined African region, mostly in children less than five years old [1]. Since the dawn of the new millennium in the early 2000s, substantial progress has been made in malaria control. For example, between 2010 and 2018, the incidence rates of malaria have declined by ~19% globally [1]. By 2018, 49 countries had reported less than 10,000 cases up from 40 in 2010 while 27 countries reported fewer than 100 local cases as compared to 17 in 2010 [1]. More importantly, between 2000-2016 the number of countries with endemic malaria has dropped from 106 to 86 while annual mortality rates have declined by over 60% [2]. However, despite these remarkable feats, the disease continues to have a significant impact on people's health and daily livelihoods. This is being recently worsened by the failure of effective control efforts like the emergence of resistance to frontline antimalarial drugs, resistance to insecticides used in vector control and the absence of effective vaccines soon [2,3,4]. More worryingly and the likely consequence of these threats, a global stall in

* Corresponding author: Amarachukwu Ukamaka Onwuzuligbo

malaria control has been recently reported with an observed increase in malaria cases from 2014 to 2016 which has remained at similar levels through to 2018.

### 1.2. Causative agents

Plasmodium has been identified as the parasite that causes malaria. These parasites are spread to humans through the bites of malaria vectors; infected Anopheles female mosquitoes. Four (4) species of Plasmodium parasite infects humans, namely; *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae,* and *Plasmodium ovale. P. falciparum* and *P. ovale* are the most common whereas *P. falciparum* is the deadliest.

### 1.3. Life cycle of *P. falciparum*

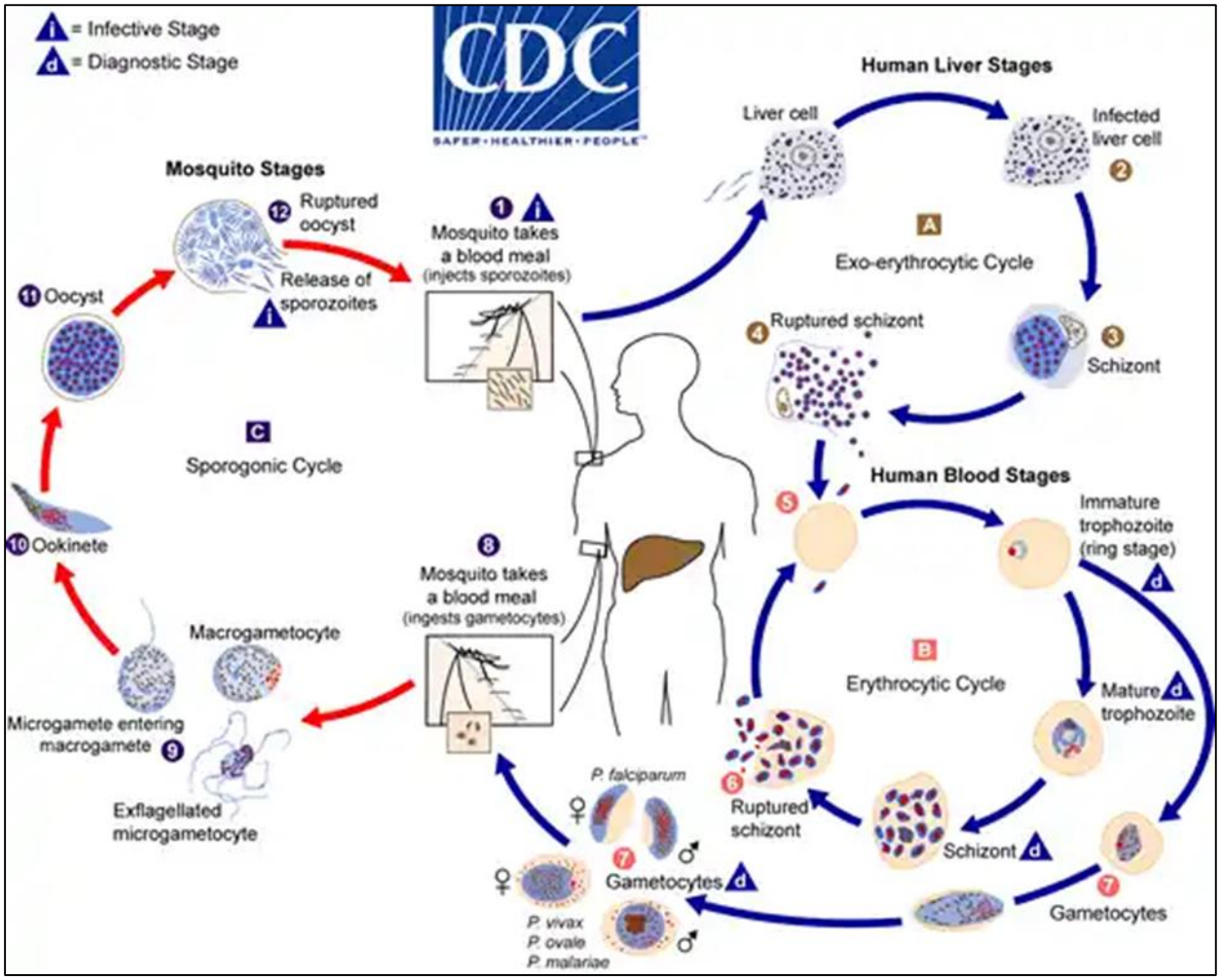


**Figure 1** The Life cycle of *P. falciparum* [5] (available at http://www.cdc.gov/malariaworldwide/impact.)

The life cycle of the malaria parasite *P. falciparum* comprises two (2) hosts; humans and mosquitoes, and three (3) distinctive stages; human liver stage (exo-erythrocytic cycle), human blood stage (erythrocytic cycle), and mosquito stage (sporogonic cycle). The exo-erythrocytic cycle commences during the blood meal during which malaria-infected female anopheles mosquito inoculates into the human host the sporozoites. The sporozoites on entry into the human host infect the human liver cells, where they mature into schizonts which rupture and release merozoites. The released merozoites then infect the human red blood cells. This marks the beginning of the erythrocytic cycle. In the red blood cells, the parasite multiples asexually, some of the merozoites develop into ring-stage trophozoites while some mature into schizonts. The schizonts rupture and release more merozoites while some of the trophozoites differentiate into gametocytes. During a blood meal, the *Anopheles* mosquito ingests the male gametocytes (microgametocytes) and the female gametocytes (macrogametocytes) and this marks the beginning of the sporogonic cycle. Inside the mosquito's gut, the macrogametocytes are penetrated by the microgametocytes giving rise to the zygotes. The zygotes develop into the ookinetes by becoming motile and elongated. The ookinetes permeates the mid-gut walls of the mosquito where they further develop into the oocysts. The oocysts then grow, rupture and release the sporozoites which migrate to the

salivary glands of the mosquito. During a blood meal, the sporozoites are inoculated into a new human host and this continues the malaria life cycle [5].

### 1.4. Common classes of drugs used in Malaria treatment and their mechanisms of action

The table 1 shows the different classes of drugs used in the treatment of malaria and their various mechanisms of action.

**Table 1** Classes of antimalarial drugs and respective mechanism of action

| S/N | Class of Drug | Examples | Mechanism of Action |
|---|---|---|---|
| 1 | Artemisinin and its derivatives | Artemether, Artesunate, Dihydroartemisinin. | Disrupts the malaria parasite's metabolic processes, leading to the death of the parasite. |
| 2 | Chloroquine and related compounds | Chloroquine, Hydroxychloroquine. | Inhibits the heme polymerase enzyme, preventing the detoxification of heme, which is toxic to the parasite. |
| 3 | Quinoline compounds | Mefloquine | Disrupts the parasite's ability to build essential proteins, affecting its growth and replication. |
| 4 | Antimalarial antiprotozoal agents | Atovaquone-Proguanil combination (Malarone) | Atovaquone interferes with the parasite's mitochondrial electron transport chain, while proguanil inhibits DNA synthesis. |
| 5 | Sulfadoxine-Pyrimethamine combination | Fansidar,<br>Amalar,<br>Malareich | Sulfadoxine and pyrimethamine inhibit two enzymes involved in the folate synthesis pathway, essential for the parasite's growth. |
| 6 | Antimalarial antibiotics | Doxycycline, Clindamycin | These antibiotics interfere with protein synthesis within the parasite by binding to the parasites' ribosomes. |
| 7 | Primaquine | | Kills the dormant liver stages (hypnozoites) of the parasite, which can cause relapses. |

### 1.5. Resistance patterns found in malaria treatment.

Treatment and complete eradication of malaria has consistently been challenged by the development of resistance to various treatment options by the malaria parasite. Some of these resistance patterns have been identified and efforts to reverse them are still in-process whereas some of the patterns are yet to be understood. Table 2 below shows some of the resistance patterns to antimalarial drugs.

**Table 2** Major antimalarial drugs and their resistance status in Africa [6]

| | Use | Resistance polymorphisms | Situation in Africa |
|---|---|---|---|
| **4-aminoquinolines** | | | |
| Chloroquine | Treatment of non-*Plasmodium falciparum* malaria | *Pfcr*t 76Thr primary mediator; *pfmdr1*<br>86Tyr and 1246Tyr; other SNPs in these<br>two genes contribute, mainly outside of Africa | Resistance, mediated primarily by *pfcrt* 76Thr,<br>has been widespread, but reversion to wild-type<br>(sensitive) parasites is ongoing in many areas |
| Amodiaquine | Treatment in combination with artesunate | Impacted by the same mutations as<br>chloroquine, but active against resistant parasites | Cross-resistance with chloroquine,<br>but artesunate-amodiaquine is highly efficacious |

| | | | |
|---|---|---|---|
| **Bis-quinoline** | | | |
| Piperaquine | Treatment in combination with DHA | Increased plasmepsin-2 copy number;<br>*pfcrt* SNPs | Highly effective in combination with DHA;<br>resistance polymorphisms seen in southeast Asia<br>are uncommon in Africa |
| **Arylamino alcohols** | | | |
| Quinine | Treatment, including severe malaria | SNPs in *pfmdr1*, *pfmdr6, pfcrt*, *pfmrp1*, and<br>*pfnhe1* might be associated with resistance | Parasites generally susceptible |
| Mefloquine | Treatment or prophylaxis as monotherapy or in<br>combination with artesunate | Increased *pfmdr1* copy number | Highly effective in combination with artesunate |
| Lumefantrine | Treatment in combination with artemether | Resistance not documented;<br>decreased sensitivity associated with<br>*pfcrt* and *pfmdr1* polymorphisms | Highly effective in combination with artemether |
| **Mannich base** | | | |
| Pyronaridine | Treatment in combination with artesunate | *pfcrt* 76Thr mutation associated with<br>decreased ex vivo sensitivity | Highly effective in combination with artesunate |
| **Artemisinins** | | | |
| DHA | Treatment in combination with piperaquine | K13PD mutations | Highly effective as ACT component |
| Artemether | Treatment in combination with lumefantrine | K13PD mutations | Highly effective as ACT component |
| Artesunate | Treatment in combination with amodiaquine,<br>mefloquine, or pyronaridine; severe malaria (intravenous) | K13PD mutations | Highly effective as ACT component |
| **Quinone** | | | |
| Atovaquone | Treatment and prophylaxis, both in combination with<br>proguanil | Mutations in cytochrome b,<br>particularly 268Ser, 268Cys, 268Asn | Resistance has been reported, but uncommon |
| **Folate antagonists** | | | |
| Pyrimethamine | Treatment in combination with sulfadoxine | Step-wise resistance with acquisition of<br>*pfdhfr* mutations (108Asn, 51Ile, 59Arg,<br>and 164Leu) | Widespread resistance |
| Proguanil | Treatment and prophylaxis, both in combination with | Step-wise resistance with acquisition of | Widespread resistance |

| | | | |
|---|---|---|---|
| | atovaquone | *pfdhfr* mutations (108Asn, 51Ile, 59Arg, and 164Leu) | |
| **Sulfonamide folate antagonist** | | | |
| Sulfadoxine | Treatment in combination with pyrimethamine | Step-wise resistance with acquisition of *pfdhps* mutations (primarily 437Gly, 540Glu, 581Gly) | Widespread resistance |
| **Tetracycline antibiotic** | | | |
| Doxycycline | Treatment in combination with quinine; prophylaxis | SNPs in *pfmdt* and *pftetQ* | Unclear if clinically relevant resistance is present |
| **8-aminoquinolines** | | | |
| Primaquine | Elimination of dormant stages *Plasmodium vivax* and *Plasmodium ovale*; elimination of gametocytes; prophylaxis | Resistance not documented | Little used in Africa; single-dose therapy being studied to control transmission |
| Tafenoquine | Elimination of dormant stages *P vivax* and *P ovale*; elimination of gametocytes; prophylaxis | Resistance not documented | Newly approved |

SNP=single nucleotide polymorphism. DHA=dihydroartemisinin. ACT=artemisinin-based combination therapies.

### 1.6. Essential oils as antimalarial agents

Several essential oils have been successfully evaluated and identified to possess antimalarial activity. These essential oils present a range of strategies that can be employed in combating the increasing cases of malaria resistance. Ashokkumar *et al.,* reviewed the pharmacological properties of *Myristica fragrans* (Houtt.) essential oil and confirmed that amongst other properties, the essential oils from *M. fragrans* possess antimalarial activity [7]. Tchoumbougnang *et al.,* investigated the essential oils of *Cymbopogon citratus* and *Ocimum gratissimum* with the conclusion that both essential oils showed significant antimalarial activities in the four-day suppressive *in vivo* test in mice [8]. Similarly, Mota *et al.,* evaluated the essential oils from *Vanillosmopsis arborea, Lippia sidoides* and *Croton zehntneri* and reported the varying degrees of antimalarial activities of the plants' essential oils [9]. The essential oil of *Rhododendron subarcticum* was investigated by Séguin *et al.* [10]

A good number of medicinal plants have been reported to possess antimalarial properties which can provide alternative treatment strategies against malaria parasites.

Ganfon *et al.,* investigated *Acanthospermum hispidum* D.C. use in malaria treatment and reported that crude acidic water extract, fractions and pure isolated compounds from *A. hispidum* show promising *in vitro* antiplasmodial activity [11]. Ethanolic extracts of *Bidens pilosa* L. (Asteraceae) was reported by Andrade-Neto *et al*., to possess activity against *P. falciparum* drug-resistant parasites *in vitro* and also in rodent malaria *in vivo* [12]. Lusakibanza *et al.,* evaluated five (5) Congolese medicinal plants; *Anisopappus chinensis, Physalis angulate, Strychnos icaja, Entandrophragma palustre* and *Melia azedarach* and concluded that *A. chinensis, P. angulate* and *S. icaja* possess very high anti-plasmodial activity *in vivo* [13]. Konziase evaluated the antimalarial potencies *in vitro* and *in vivo* of pure biflavanones from *Garcinia kola* and determined significant *in vivo* antimalarial activities in mice infected with *P. berghei* (ANKA strain) following a four-day suppressive test [14].

Extracts of *Phlomis kurdica, P. leucophracta, Scrophularia cryptophila, Morina persica,* and *Asperula nitida* subsp. *Subcapitellata* were reported by Tasdemir *et al.,* as possessing very potent antiplasmodial activity against the multi-drug resistant K1 *Plasmodium falciparum* strain [15]. Muthaura *et al.,* evaluated ten (10) Kenyan medicinal plants; *Boscia angustifolia, Schkuhria pinnat, Sphaeranthus suaveolens, Clutia abyssinica, Ocotea usambarensis, Fuerstia africana,*

*Ludwigia erecta, Pittosporum viridiflorum, Vangueria acutiloba Robyns,* and *Clerodendrum eriophyllum* with the conclusion that methanolic extracts of all ten plants have varying degrees of *in vivo* activities against chloroquine-sensitive *P. falciparum* clone and resistant clone [16]. Similarly, *in vivo* intrinsic antimalarial activities of methanolic extracts of *Maytenus undata, Flueggea virosa, Maytenus putterlickioides, Warburgia stuhlmannii,* and *Harungana madagascariensis* against chloroquine-sensitive *P. falciparum* clone and resistant clone were determined by Muthaura *et al* [17]. Antimalarial activities of several other plants such as *Croton mubango*, *Nauclea pobeguinii*, *Pyrenacantha staudtii* [18], *Eucalyptus globulus* [19], *Azadiracta indica* [20], etc. have been investigated and reported.

### 1.7. Active compounds in essential oils with antimalarial activity

A list of some active compounds that have been reported to be present in essential oils with antimalarial activity are listed in table 3.

**Table 3** Essential oil constituents with reported antimalarial activity

| S/N | Active compound in Essential Oils with antimalarial activity |
|---|---|
| 1 | α-thujene [10, 21] |
| 2 | α-pinene [10, 21] |
| 3 | Camphene [10, 21] |
| 4 | Sabinene [10, 21] |
| 5 | β-pinene [10, 21] |
| 6 | 1-octen-3-ol [10, 21] |
| 7 | Myrcene [10, 21] |
| 8 | α-phellandrene [10, 21] |
| 9 | δ-3-carene [10, 21] |
| 10 | *α*-terpinene [10, 21] |
| 11 | *p*-cymene [10, 21] |
| 12 | Limonene [10, 21] |
| 13 | β-phellandrene [10, 21] |
| 14 | (*Z*)-β-ocimene [10, 21] |
| 15 | (*E*)-β-ocimene [10, 21] |
| 16 | *γ*-terpinene [10, 21, 22] |
| 17 | Terpinolene [10, 21] |
| 18 | p-cymenene [10, 21] |
| 19 | Linalool [10, 21] |
| 20 | n-nonanal [10] |
| 21 | 1,3,8-p-menthatriene [10] |
| 22 | dehydro sabina ketone [10] |
| 23 | cis-p-menth-2-en-1-ol [10] |
| 24 | trans-pinocarveol [10, 21] |
| 25 | trans-p-menth-2-en-1-ol [10] |
| 26 | Camphor [10, 21] |
| 27 | Pinocarvone [10, 21] |

| | |
|---|---|
| 28 | Borneol [10, 21] |
| 29 | terpinen-4-ol [10, 21] |
| 30 | thuj-3-en-10-al [10] |
| 31 | Cryptone [10] |
| 32 | Myrtenal [10] |
| 33 | α-terpineol [10, 21] |
| 34 | *p*-cymen-8-ol [10, 21] |
| 35 | Estragol [10] |
| 36 | Myrtenol [10, 21] |
| 37 | Ascaridole [10] |
| 38 | cis-piperitone [10] |
| 39 | carvenone oxide [10] |
| 40 | Phellandral [10] |
| 41 | bornyl acetate [10, 21] |
| 42 | *p*-cymen-7-ol [10] |
| 43 | Thymol [10, 21] |
| 44 | Carvacrol [10, 21, 22] |
| 45 | Isoascaridole [10] |
| 46 | *p*-mentha-1,4-dien-7-ol [10] |
| 47 | citronellyl acetate [10] |
| 48 | geranyl acetate [10, 21] |
| 49 | Aromadendrene [10] |
| 50 | (*E*)-*β*-farnesene [10] |
| 51 | caryophyllene oxide [10] |
| 52 | 14-hydroxy-(*Z*)-caryophyllene [10] |
| 53 | Germacrone [10] |
| 54 | *E*- and *Z*-(±)-Nerolidol [22] |
| 55 | Linalyl acetate [21, 22] |
| 56 | (−)-Pulegone [22] |
| 57 | isobutyl isobutyrate [21] |
| 58 | 1,8-cineole [21] |
| 59 | *β*-thujone [21] |
| 60 | 1-octen-3-yl acetate [21] |
| 61 | α-fenchol [21] |
| 62 | α-thujone [21] |
| 63 | methyl chavicol [21] |
| 64 | lavandulyl acetate [21] |
| 65 | myrtenyl acetate [21] |

| | |
|---|---|
| 66 | citronellyl acetate [21] |
| 67 | neryl acetate [21] |
| 68 | methyl eugenol [21] |
| 69 | *β*-caryophyllene [21] |
| 70 | α-humulene [21] |
| 71 | β-famesene [21] |
| 72 | germacrene D [21] |
| 73 | γ-cadinene [21] |
| 74 | δ-cadinene [21] |
| 75 | Ledol [21] |
| 76 | benzyl benzoate [21] |

### 1.8. Advantages of essential oils in malaria treatment and combating resistance

The advantages of essential oils in malaria treatment and combating antimalaria resistance are attributed to the wide variety of chemical compositions of essential oils with individualized characteristics and activities. The lifecycle of malaria-causative organisms is comprised of several developmental and maturation stages. Use of essential oils with antimalarial properties has the advantage of multifactorial mechanisms of action by having each or some of the chemical constituents acting at different points of the parasites' transmission, development, and/or infective stages. Papulwar *et al.,* investigated the insecticidal property of *Cymbopogon winterianus* (Lemon grass) essential oil with the key findings that *C. winterianus* essential oil causes deformations in different stages of insect development, repellence, and deterrence. This insecticidal property of *C. winterianus* essential oil can be beneficial in the treatment of malaria by either repelling or killing mosquitoes, the malaria vector [23]. Other attributable advantages of essential oils include low toxicity, high availability, synergistic effects, etc [23].

### 1.9. Formulation strategies for oral delivery of essential oils

Despite the versatility of essential oils and their associated advantages, they are still prone to a couple of limitations such as high volatility, hydrophobicity, instability and certain degrees of toxicity [24, 25]. Several formulation strategies have been recommended by researchers as a means of overcoming these challenges or limitations. These strategies involve formulating the essential oils into various novel drug delivery systems namely; nano and microemulsions, solid lipid nanoparticles (SLN), liposomes, nanostructured lipid carriers (NLC), nano-capsules and soft gelatin capsules. Terpenes extracted from *Melaleuca alternifolia* was nanoencapsulated by Donsi *et al.,* and demonstrated that the nanoencapsulated terpenes had higher antimicrobial activity compared with the unencapsulated mixture [26]. Sugumar *et al.,* formulated nanoemulsions of *Eucalyptus* essential oil which showed greater antimicrobial activity in comparison with pure *Eucalyptus* essential oil [27]. Clove essential oil-loaded nanoemulsions demonstrated better activity in wound healing than the pure Clove essential oil [28]. Essential oils have equally been formulated as liposomes by different researchers with reported greater activities than the pure essential oils administered as such [29-41].

## 2. Conclusion

It is the view of the authors that the use of essential oils in the treatment of malaria and combating of malaria resistance hold great promises and potentials; these essential oils when discovered to possess antimalarial activities should be strategically formulated either as a nanoemulsion, liposome, NLC, or SLN. This will in addition to protecting the essential oils from rapid degradation, improve their efficacy and effectiveness.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest is to be disclosed.

## References


[1] WHO. Malaria. World Malaria Report, World Health Organization, Geneva, Switerzaland. 2019

[2] Feachem, R. G. A., Chen, I., Akbari, O., Bertozzi-Villa, A., Bhatt, S., Binka, F., Boni, M. F., Buckee, C., Dieleman, J., Dondorp, A., Eapen, A., Sekhri Feachem, N., Filler, S., Gething, P., Gosling, R., Haakenstad, A., Harvard, K., Hatefi, A., Jamison, D., Jones, K. E., Karema, C., Kamwi, R. N., Lal, A., Larson, E., Lees, M., Lobo, N. F., Micah, A. E., Moonen, B., Newby, G., Ning, X., Pate, M., Quinones, M., Roh, M., Rolfe, B., Shanks, D., Singh, B., Staley, K., Tulloch, J., Wegbreit, J., Woo, H. J., Mpanju-Shumbusho, W. Malaria eradication within a generation: ambitious, achievable, and necessary. Lancet, 2019; 394, 10561112.

[3] Cui, L., Mharakurwa, S., Ndiaye, D., Rathod, P. K., Rosenthal, P. J. Antimalarial drug resistance: literature review and activities and findings of the ICEMR network. The American journal of tropical medicine and hygiene, 2015; 93, 5768.

[4] Hemingway, J., Ranson, H., Magill, A., Kolaczinski, J., Fornadel, C., Gimnig, J., Coetzee, M., Simard, F., Roch, D. K., Hinzoumbe, C. K., Pickett, J., Schellenberg, D., Gething, P., Hoppé, M. and Hamon, N. Averting a malaria disaster: will insecticide resistance derail malaria control? Lancet (London, England), 2016; 387, 1785-1788.

[5] Center for Disease Control and Prevention (CDC, 2012). Impact of Malaria World wide CDC 24/7 http://www.cdc.gov/malariaworldwide/impact. Accessed 21/05/2024..

[6] Conrad, M. D., & Rosenthal, P. J. (2019). Antimalarial drug resistance in Africa: the calm before the storm? The Lancet Infectious Diseases. doi:10.1016/s1473-3099(19)30261-0

[7] Ashokkumar K, Simal-Gandara J, Murugan M, Dhanya MK, Pandian A. Nutmeg (Myristica fragrans Houtt.) essential oil: A review on its composition, biological, and pharmacological activities. Phytother Res. 36(7), 2022: 2839-2851. doi: 10.1002/ptr.7491.

[8] Tchoumbougnang F, Zollo PH, Dagne E, Mekonnen Y. In vivo antimalarial activity of essential oils from Cymbopogon citratus and Ocimum gratissimum on mice infected with Plasmodium berghei. Planta Med.71(1), 2005:20-3. doi: 10.1055/s-2005-837745.

[9] Mota ML, Lobo LT, Costa JM, Costa LS, Rocha HA, Rocha e Silva LF, Pohlit AM, Neto VF. In vitro and in vivo antimalarial activity of essential oils and chemical components from three medicinal plants found in northeastern Brazil. Planta Med. 78(7),2012:658-64. doi: 10.1055/s-0031-1298333.

[10] Séguin JC, Gagnon D, Bélanger S, Richard D, Fernandez X, Boudreau S, Voyer N. Chemical Composition and Antiplasmodial activity of the essential oil of Rhododendron subarcticum leaves from Nunavik, Québec, Canada. ACS Omega; 8 (19) 2023: 16729-16737. doi: 10.1021/acsomega.3c00235.

[11] Ganfon H, Bero J, Tchinda AT, Gbaguidi F, Gbenou J, Moudachirou M, Frédérich M, Quetin-Leclercq J. Antiparasitic activities of two sesquiterpenic lactones isolated from Acanthospermum hispidum D.C. J Ethnopharmacol. 7, 2012;141(1):411-7. doi: 10.1016/j.jep.2012.03.002.

[12] Andrade-Neto VF, Brandão MG, Oliveira FQ, Casali VW, Njaine B, Zalis MG, Oliveira LA, Krettli AU. Antimalarial activity of Bidens pilosa L. (Asteraceae) ethanol extracts from wild plants collected in various localities or plants cultivated in humus soil. Phytother Res. 8, 2004: 634-9. doi: 10.1002/ptr.1510.

[13] Lusakibanza M, Mesia G, Tona G, Karemere S, Lukuka A, Tits M, Angenot L, Frédérich M. In vitro and in vivo antimalarial and cytotoxic activity of five plants used in congolese traditional medicine. J Ethnopharmacol. 16, 2010;129(3):398-402. doi: 10.1016/j.jep.2010.04.007.

[14] Konziase B. Protective activity of biflavanones from Garcinia kola against Plasmodium infection. J Ethnopharmacol. 22, 2015; 172:214-8. doi: 10.1016/j.jep.2015.06.038.

[15] Tasdemir D, Brun R, Perozzo R, Dönmez AA. Evaluation of antiprotozoal and plasmodial enoyl-ACP reductase inhibition potential of turkish medicinal plants. Phytother Res. (2) 2005: 162-6. doi: 10.1002/ptr.1648.

[16] Muthaura CN, Rukunga GM, Chhabra SC, Omar SA, Guantai AN, Gathirwa JW, Tolo FM, Mwitari PG, Keter LK, Kirira PG, Kimani CW, Mungai GM, Njagi EN. Antimalarial activity of some plants traditionally used in Meru district of Kenya. Phytother Res. (9) 2007: 860-7. doi: 10.1002/ptr.2170.

[17] Muthaura CN, Rukunga GM, Chhabra SC, Omar SA, Guantai AN, Gathirwa JW, Tolo FM, Mwitari PG, Keter LK, Kirira PG, Kimani CW, Mungai GM, Njagi EN. Antimalarial activity of some plants traditionally used in treatment of malaria in Kwale district of Kenya. J Ethnopharmacol;112(3) 2007: 545-51. doi: 10.1016/j.jep.2007.04.018.

[18] Mesia GK, Tona GL, Penge O, Lusakibanza M, Nanga TM, Cimanga RK, Apers S, Van Miert S, Totte J, Pieters L, Vlietinck AJ. Antimalarial activities and toxicities of three plants used as traditional remedies for malaria in the Democratic Republic of Congo: Croton mubango, Nauclea pobeguinii and Pyrenacantha staudtii. Ann Trop Med Parasitol.; 99(4) 2005:345-57. doi: 10.1179/136485905X36325.

[19] Ayalew M, Bekele A. Evaluation of the Antimalarial Activity of Crude Extract of Eucalyptus globulus Labill. Leaf against Plasmodium berghei in Mice. Evid Based Complement Alternat Med. 20; 2021: 7068999. doi: 10.1155/2021/7068999.

[20] Afolabi OJ, Simon-Oke IA, Oladokun OI. Antiplasmodial Activity of Ethanolic Extract of Neem Leaf (Azadirachta indica) in Albino Mice infected with Plasmodium berghei. Int Arch Clin Pharmacol (7) 2021: 024. doi.org/10.23937/2572-3987.1510024

[21] Milhau G., Valentin A., Benoit F., Mallié M., Bastide J.M., Pélissier Y., Bessière J.M. In vitro antimalarial activity of eight essential oils. J. Essent. Oil Res., 9 (1997), pp. 329-333

[22] Van Zyl R.L., Seatlholo S.T., Viljoen A.M. Pharmacological interactions of essential oil constituents on the in vitro growth of Plasmodium falciparum. South African Journal of Botany. 76(4) 2010: 662-667.

[23] Papulwar PP, Rathod B, Dattagonde NR. Studies on insecticidal properties of citronella grass (lemon grass) essential oils against gram pod borer (Helicoverpa armigera). Int Journal of Chemistry 2018; 2(2):44-46

[24] Cimino, C.; Maurel, O.M.; Musumeci, T.; Bonaccorso, A.; Drago,F.; Souto, E.M.B.; Pignatello, R.; Carbone, C. Essential Oils: Pharmaceutical Applications and Encapsulation Strategies into Lipid-Based Delivery Systems. Pharmaceutics 2021, 13, 327.

[25] Sultana R, Mohanto S, Bhunia A, Biswas A, Akhtar MS, Mishra V, Modi D, Aljabali AA, Tambuwala M, Faiyazuddin M. Current Progress and Emerging Role of Essential Oils in Drug Delivery Therapeutics. Curr Drug Deliv. 2024 Feb 22. doi: 10.2174/0115672018287719240214075810.

[26] Donsi, F.; Annunziata, M.; Sessa, M.; Ferrari, G. Nanoencapsulation of essential oils to enhance their antimicrobial activity in foods. LWT Food Sci. Technol. 2011, 44, 1908–1914.

[27] Sugumar, S.; Ghosh, V.; Nirmala, M.J.; Mukherjee, A.; Chandrasekaran, N. Ultrasonic emulsification of eucalyptus oil nanoemulsion: Antibacterial activity against Staphylococcus aureus and wound healing activity in Wistar rats. Ultrason. Sonochem. 2014, 21, 1044–1049.

[28] Alam, P.; Ansari, M.J.; Anwer, M.K.; Raish, M.; Kamal, Y.K.T.; Shakeel, F. Wound healing effects of nanoemulsion containing clove essential oil. Artif. Cell Nanomed. B 2017, 45, 591–597.

[29] Valenti, D.; De Logu, A.; Loy, G.; Sinico, C.; Bonsignore, L.; Cottiglia, F.; Garau, D.; Fadda, A.M. Liposome-incorporated Santolina insularis essential oil: Preparation, characterization and in vitro antiviral activity. J. Liposome Res. 2001, 11, 73–90.

[30] Sinico, C.; De Logu, A.; Lai, F.; Valenti, D.; Manconi, M.; Loy, G.; Bonsignore, L.; Fadda, A.M. Liposomal incorporation of Artemisia arborescens L. essential oil and in vitro antiviral activity. Eur. J. Pharm. Biopharm. 2005, 59, 161–168.

[31] Liolios, C.C.; Gortzi, O.; Lalas, S.; Tsaknis, J.; Chinou, I. Liposomal incorporation of carvacrol and thymol isolated from the essential oil of Origanum dictamnus L. and in vitro antimicrobial activity. Food Chem. 2009, 112, 77–83.

[32] Khosravi-Darani, K.; Khoosfi, M.E.; Hosseini, H. Encapsulation of Zataria multiflora Boiss. Essential Oil in Liposome: Antibacterial Activity against E-Coli O157:H7 in Broth Media and Minced Beef. J. Food Saf. 2016, 36, 515–523.

[33] Dorman, H.J.D.; Peltoketo, A.; Hiltunen, R.; Tikkanen, M.J. Characterisation of the antioxidant properties of de-odourised aqueous extracts from selected Lamiaceae herbs. Food Chem. 2003, 83, 255–262.

[34] Sebaaly, C.; Jraij, A.; Fessi, H.; Charcosset, C.; Greige-Gerges, H. Preparation and characterization of clove essential oil-loaded liposomes. Food Chem. 2015, 178, 52–62.

[35] Sebaaly, C.; Greige-Gerges, H.; Agusti, G.; Fessi, H.; Charcosset, C. Large-scale preparation of clove essential oil and eugenol-loaded liposomes using a membrane contactor and a pilot plant. J. Liposome Res. 2016, 26, 126–138.

[36] Sebaaly, C.; Charcosset, C.; Stainmesse, S.; Fessi, H.; Greige-Gerges, H. Clove essential oil-in-cyclodextrin-in-liposomes in the aqueous and lyophilized states: From laboratory to large scale using a membrane contactor. Carbohydr. Polym. 2016, 138, 75–85.

[37] Najafi, M.N.; Arianmehr, A.; Sani, A.M. Preparation of Barije (Ferula gummosa) Essential Oil-Loaded Liposomes and Evaluation of Physical and Antibacterial Effect on Escherichia coli O157:H7. J. Food Prot. 2020, 83, 511–517.

[38] Palmas, L.; Aroffu, M.; Petretto, G.L.; Escribano-Ferrer, E.; Diez-Sales, O.; Usach, I.; Peris, J.E.; Marongiu, F.; Ghavam, M.; Fais, S.; et al. Entrapment of Citrus limon var. pompia Essential Oil or Pure Citral in Liposomes Tailored as Mouthwash for the Treatment of Oral Cavity Diseases. Pharmaceuticals 2020, 13, 216.

[39] Hammoud, Z.; Gharib, R.; Fourmentin, S.; Elaissari, A.; Greige-Gerges, H. Drug-in-hydroxypropyl-beta-cyclodextrin-in-lipoid S100/cholesterol liposomes: Effect of the characteristics of essential oil components on their encapsulation and release. Int. J. Pharm. 2020, 579.

[40] Hammoud, Z.; Gharib, R.; Fourmentin, S.; Elaissari, A.; Greige-Gerges, H. New findings on the incorporation of essential oil components into liposomes composed of lipoid S100 and cholesterol. Int. J. Pharm. 2019, 561, 161–170.

[41] Lin, L.; Zhu, Y.L.; Thangaraj, B.; Abdel-Samie, M.A.S.; Cui, H.Y. Improving the stability of thyme essential oil solid liposome by using beta-cyclodextrin as a cryoprotectant. Carbohydr. Polym. 2018, 188, 243–251.