EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 6
315-321
Year: 2024

A COMPENDIUM OF RECENT PHYTOCHEMICAL ANTIMALARIALS ISOLATED FROM MEDICINAL PLANTS

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Article Received on 26/04/2024 **Article Revised on 17/05/2024** **Article Accepted on 07/06/2024**

ABSTRACT
Malaria is a major parasitic disease in many tropical and subtropical regions of Africa and some parts of the world. It is responsible for more than 1 million deaths each year in Africa. The rapid spread of resistance encourages the search for new active compounds. Nature and particularly plants used in traditional medicine are a potential source of new antimalarial drugs as they contain molecules with great variety of potency and pharmacological activities. A large number of antimalarial compounds with different structures have been isolated from medicinal plants and can play important roles in the development of new antimalarial drugs. Ethnopharmacological approaches appear to be a promising way to find plant metabolites that could be used as templates for designing new derivatives with improved properties. This review covers twenty five phytochemically based anti-plasmodial/antimalarial agents isolated recently and sourced from medicinal plants which are used in the treatment of malaria in Africa and other parts of the world. Their activity against malaria parasites in vitro and in vivo (using experimentally infected mice) ranges from promising and excellent to moderate antiplasmodial activities. Macluraxanthone, volkensiflavone, pinocembrin, dehydrotylophorine, dehydroantofine, tylophoridicine, (—) – milonine, stephanine, crebanine, O-methylbulbocapnine, cheilanthifoline, simplicifolianine, palmatine, pseudopalmatine, 2-hydroxyatherosperminine and kuercitin which possessed interesting, promising, excellent and very significant antimalarial properties among the reported isolated phytyconstituents may present an array of potential lead compounds towards development of novel antimalarial drugs. The search for new drugs from medicinal plants is important due to the emergence and widespread of chloroquine-resistant and multiple drug-resistant malaria parasites with artemisinin-based combination therapy (ACT) which hitherto requires the development of new antimalarials. The use of plants as antimalarials may be a springboard for new phytotherapies that could be affordable and accessible in treating malaria, especially among the less privileged people living in endemic areas of the tropics that are vulnerable and at risk of this devastating disease. It is recommended that in-vivo antiplasmodial activities of compounds 1-6 and 13-25 and in-vivo cytotoxicty activities of compounds 1–16, 20, 22, 24 and 25 which have not been carried out should investigated further in other to substantiate their anti-malarial property and safety in treating malaria infections in orthodox medicine.

KEYWORDS: Antimalarials, Phytochemicals, Medicinal plants and Malaria.

INTRODUCTION
Malaria, a parasitic disease caused by *Plasmodium* species and transmitted by anopheles mosquitoes, remain one of the most common infectious diseases with high mortality and morbidity, especially in the sub-Saharan Africa, Asia and Latin America. According to WHO estimation, 216 million new malaria cases and 445,000 deaths have occurred worldwide in 2016. Of all, more than 90% were recorded in sub-Saharan Africa, the remaining occurring in South-East Asia and South America (WHO, 2017). Morbidity and mortality due to malaria have fallen in recent years with the advent of artemisinin-based combination therapy (ACT) and widespread use of impregnated bed nets. However, ACT treatment failures have been reported in some countries (Holmgren *et al.*, 2007) justifying the search for new antimalarial drugs.

The world's poorest people are the most affected with malaria and many of them get treatment from traditional medicines because they are readily available and cheap compared to conventional medicine. Some local

communities perceive traditional medicine as more effective than conventional medicine and Traditional Medical Practitioners (TMPs) use herbal remedies for treatment of malaria in Uganda and in other parts of the world (Adia *et al.,* 2001) A remarkable feature about malaria therapy is that the two herbal treatments which include cinchona bark and qinghao leaves were used to treat malaria effectively for hundreds of years even prior to our basic understanding of malaria. With advances in analytical techniques, the active antimalarial molecules which are quinine in the bark of cinchona trees and artemsinin in the leaves of qinghao (*Artemisia annua*) were identified and used as the magic bullets against malaria (Singh *et al.,* 2015). Chemotherapeutic prophylactics sourced from plant species are the core of malaria treatment (Fabricant *et al.,* 2001). Over 1200 plant species are reportedly used for the treatment of malaria and fevers worldwide, and are potentially important sources of new anti-malarial treatments (Willox *et al.,* 2004). This review gives a critical account of isolated phytochemicals from medicinal plants possessing reasonable levels of antimalarial or antiplasmodial activity and reported from 2010 – 2023.

PHYTOCHEMICALS BASED ANTI-PLASMODIAL/ANTIMALARIAL AGENTS

Phytochemicals are the non-nutritional bioactive compounds found in various parts of plants. In plants, these compounds perform vital functions particularly protection from predators and harsh environmental conditions. These compounds are also important in pharmaceutical and medicinal field due to their anti-plasmodial and other biological properties (Guevara, 2000). Plants contain a number of bioactive phytochemical compounds which includes phenols, polyphenols, phenolic acids, flavonoids, flavone glycosides, anthocyanins, carotenoids, terpenes/terpenoids, alkaloids, steroids, luteins, tannins, saponins, volatile oils amongst others (Guevara, 2000) which have been isolated, characterized and investigated for their biological activities and pharmaceutical functions.

Azebaze *et al.,* (2015) isolated macluraxanthone **(compound 1)** and volkensiflavone **(compound 2)** from *Allanblackia floridabunda*. After 24 hours of contact with the malaria parasites**,** volkensiflavone (IC_{50}: 0.99 µg/mL) and macluraxanthone (IC_{50}: 0.46 µg/mL) displayed the best activity on the F_{32} strain while chloroquine (IC_{50}:0.036 µg/mL) was used as reference antimalarial drug. With FcM29 *Plasmodium falciparum* strain, volkensiflavone with IC_{50}: 0.93 µg/mL and macluraxanthone with IC_{50}: 0.33 µg/mL are strongly active compounds, but the macluraxanthone was more active than the reference (chloroquine: IC_{50}: 0.57 µg/mL). After 72 hours of contact with the parasitemia, macluraxanthone with IC_{50} value of 0.36µg/mL exhibited extremely high activity on the F_{32} strain and with FcM_{29} strain, it was more active (IC_{50}: 0.27 µg/mL). Macluraxanthone was allowed to have contact with the parasites from 24 hours to 72 hours and there was increased activity of 0.1 µg/mL with the F_{32} strain and 0.06 µg/mL with FcM_{29} strain. In contrast, for volkensiflavone, there was a decrease in activity of 0.19 µg/mL with the F_{32} strain and 0.02 µg/mL with FcM_{29} strain when the incubation period was increased from 24 hours to 72 hours in order to have more contact with parasites.

Gadetskaya *et al.,* (2015) obtained myricetin **(compound 3)** from aerial parts of *Limonium caspium* revealed potent antimalarial activity against both resistant (W2) and sensitive (D6) strains of *Plasmodium falciparum* with IC_{50} values of 1.82 and 1.51 µg/mL, respectively. Kaempferol 3-O-α-L-(2″,3″- di-E-p-coumaroyl) rhamnoside **(compound 4)** *and* Kaempferol 3-O-α-L-(2″-Ep-coumaroyl-3″-Z-p- coumaroyl) rhamnoside **(compound 5)** were extracted by Cai *et al.,* (2016) from the leaves of *Platanus occidentalis L.* which exhibited anti-plasmodial activities of IC_{50} values 0.6±0.2/7±1µM and 2.0±0.6/4.1±0.5µM against HB_3/NHP_{133} strains of *Plasmodium falciparum* respectively. Samson *et al.,* (2017) isolated 6 – prenylapigenin **(compound 6)** from *Cannabisativa L*. which was found to disclose IC_{50} value of 6.7 µM and 4.8µM against D_6 and W_2 strains of *Plasmodium falciparum* respectively.

Furthermore, Bezu *et al.,* (2015) extracted embelin **(compound 7)** from the fruit of *Embelia schrimperi* and it was reported to be show 54.8% parasite suppression rate at 400mg/kg/day against *Plasmodium berghei* (Pb) in their *in -vivo* anti-malarial evaluation of embelin and its semi-synthetic aromatic amine derivatives. Compound embelin indicated good antiplasmodial activity. Alebachew *et al.,* (2021) isolated knipholone **(compound 8)** from the hydroalcoholic extract of rhizomes of *Kniphofia foliosa* and the compound was discovered to show percentage parasite elimination rate of 55.14% at 100mg/kg/day and 60.2% at 200mg/kg/day against *Plasmodium berghei* (Pb) in an in *–vivo* animal experiment using albino rats. Knipholone **(compound 8)** disclosed very good anti-plasmodial activity (against *Plasmodium berghei)* in-vivo. Aloinoside **(compound 9)** was reported to be isolated from *Aloe macrocarpa* leaf latex by Tewabe *et al.,* (2018) and evaluated for anti-plasmodial/anti-malarial activity and it was found out to suppress the parasitemia by 100% at 400 mg/kg oral dose in *P. berghei* infected mice, and its LD50 was above 2000 mg/kg. Abdissa *et al.,* (2017) obtained aloesaponarin **(compound 10)** from the root of *Aloe pulcherrima* during their phytochemical investigation of *Aloe pulcherrima* roots and evaluation for its antibacterial and antiplasmodial activities. It was discovered that compound aloesaponarin exhibited anti-plasmodial activity against *Plasmodium berghei* and D_6 strains/species of *Plasmodium* with IC_{50} value of 7.8µM indicating good activity. Melaku *et al.,* (2017) isolated pinocembrin **(compound 11)** from the leaves of *Dodonaea angustifolia* and bio-assayed for its anti-malarial activity against *Plasmodium berghei* and it was

observed that pinocembrin disclosed an excellent antiplasmodial/antimalarial activity (*in-vivo*) with percentage inhibition of parasitemia of 77.03% and 81% at 20mg/kg/day and 40mg/kg/day respectively.

Teka *et al.*, (2016) succeeded in extracting 7-hydroxyaloin **(compound 12)** from *Aloe pulcherrima* leaf latex in their study titled "Anti-malarial activity of the chemical constituents of the leaf latex of *Aloe pulcherrima",* which was bioassayed against *Plasmodium berghei* in infected mice and found out to exhibit good antiplasmodial activity by eliminating the parasites by 56.2% at 200mg/kg/day. Kubo *et al.*, (2016) obtained three phenanthroindolizidine alkaloids: dehydrotylophorine **(compound 13)**, dehydroantofine **(compound 14)** and tylophoridicine **(compound 15)** from chloroform fraction of the active extract of methanol of *Ficus septic* which exhibited anti-plasmodial activity of IC_{50} values of 0.42 µM, 0.028 µM and 0.058 µM against 3D7 *Plasmodium* strain respectively with low cytotoxicity. Zahari et al., (2014) investigated antiplasmodial and antioxidant isoquinoline alkaloids from *Dehaasia longipedicellata* and extracted (—) – milonine **(compound 16)** which is a morphinanedienone alkaloid from the bark

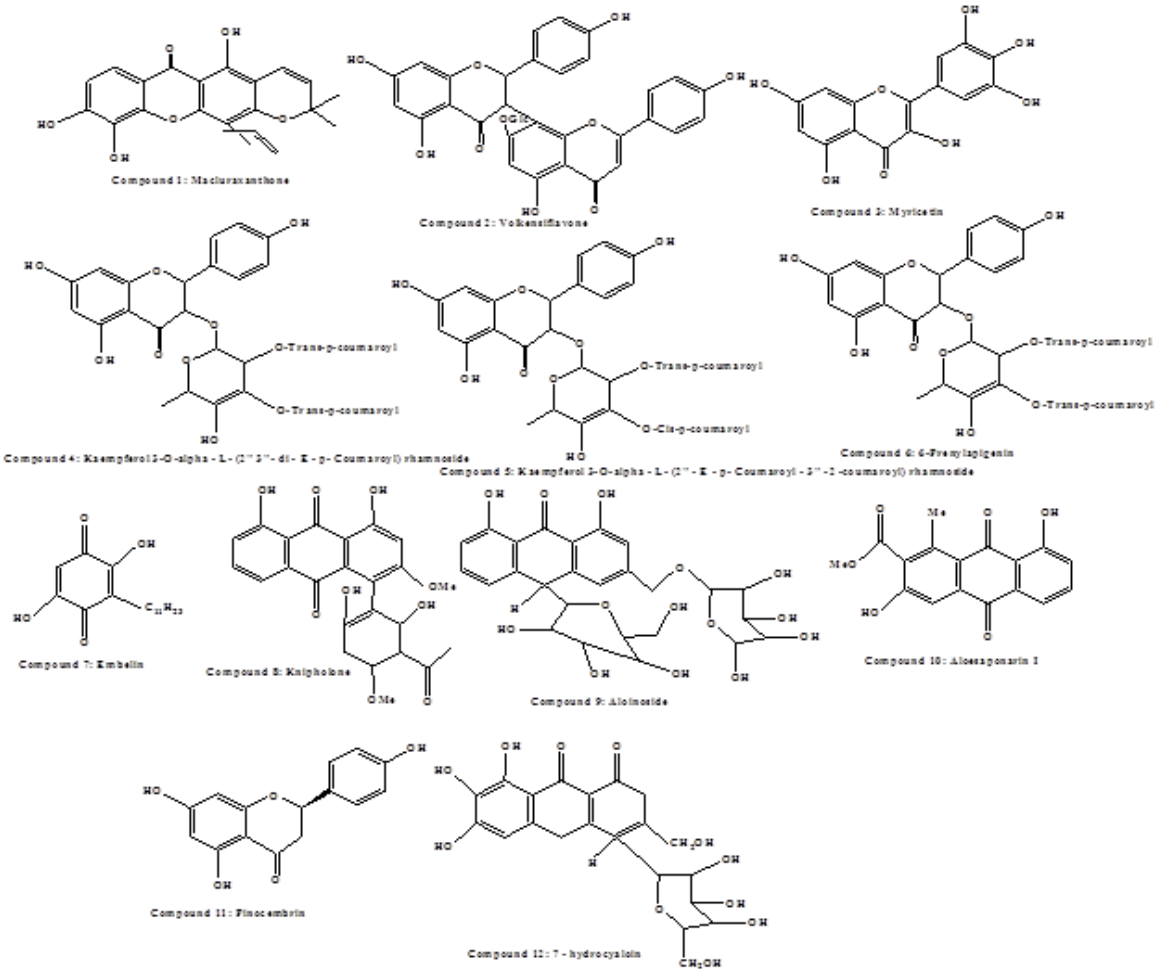

Figure 1: Chemical structures of Phytochemical Antiplasmodial/Antimalarials Isolated from Medicinal Plants.

of *Dehaasia longipedicellata* (Lauraceae). The compound was found to reveal an antimalarial activity having the IC_{50} value of 0.097µM against K1 strain of *Plasmodium falciparum* parasite. Three compounds namely, stephanine, crebanine and *O*-methylbulbocapnine **(compound 17 – 19)** which are considered to be aporphine alkaloids were isolated from *Stephania venosa* (Blume) Spreng and investigated to show antiplasmodial activity against 3D7 and W2 strains of *Plasmodium falciparum* with IC_{50} of 0.69 µM and 1.32 µM; 1.56 µM and 2.16 µM; 2.81 µM and 5.71 µM respectively. However, **compound 17**, stephanin which is found to be the most potent against 3D7 and W2 parasites amongst **compounds 17 -19** was also discovered to be the most cytotoxic to cancerous and non-cancerous cell lines. Wagchuk *et al.*, (2010) obtained c**ompound 20,** cheilanthifoline (a tetrahydroprotoberberine alkaloid) cheilanthifoline from *Corydalis calliantha* (Papaveraceae) which is a popular annual herb employed in Bhutanese traditional medicine to cure malaria. This compound, cheilanthifoline displayed antimalarial activity with IC_{50} values of 2.78µM and 3.76µM against the TM_4 and K_1 strains of *P. falciparum*.

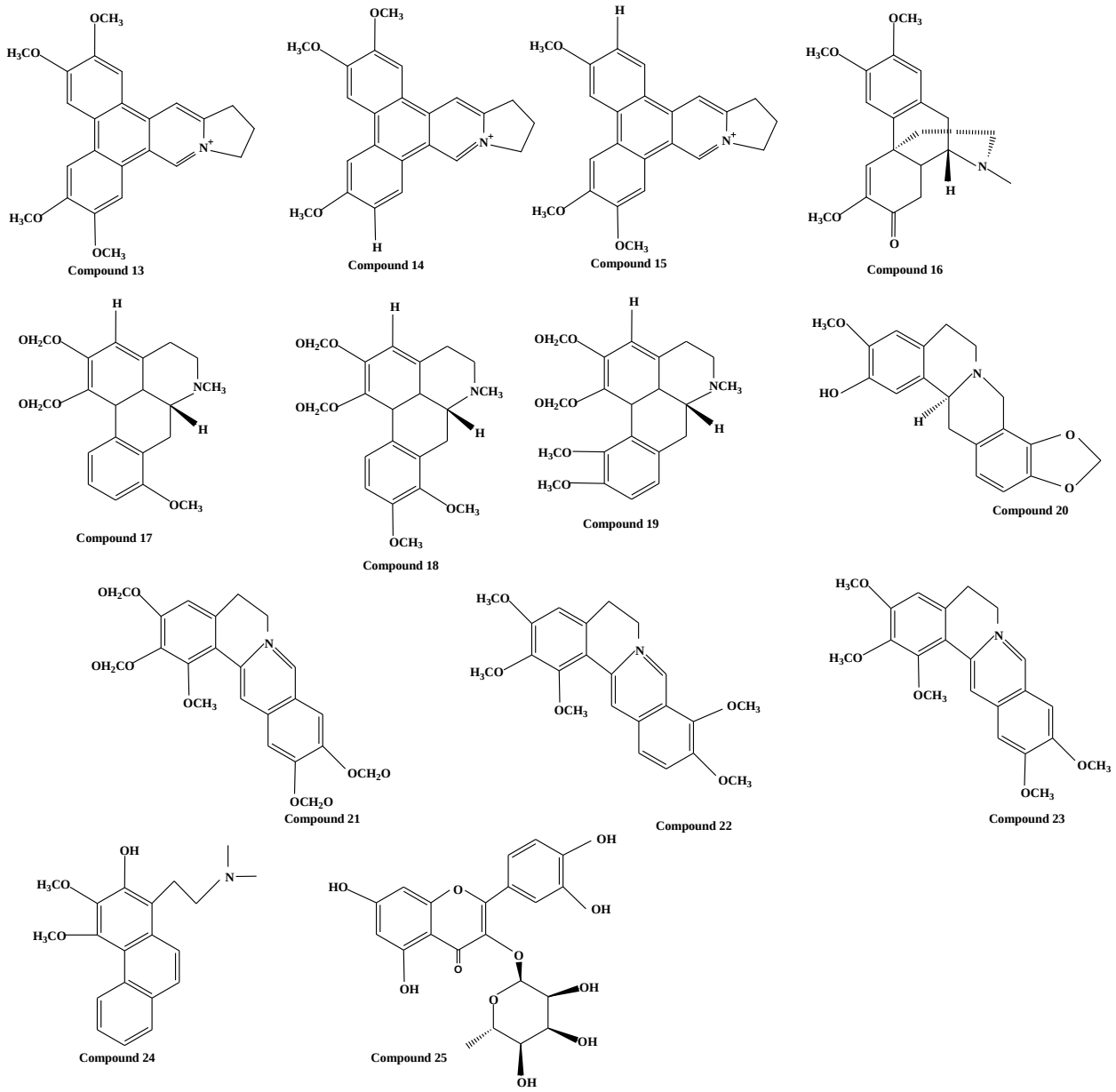

Figure 1: Chemical structures of Phytochemical Antiplasmodial/Antimalarials Isolated from Medicinal Plants (Continuation).

Also, Wagchuk *et al.*, (2013) engaged in the extraction and purification of the aerial components of *Meconopsis simplicifolia* which afforded simplicifolianine (**compound 21**) which is a protoberberine-type benzylisoquioline exhibited relatively strong antiplasmodial activity against the TM4 and K1CB1 strains of *P. falciparum* with IC_{50} values of 0.78 µM and 1.29µM respectively with low or negligible cytotoxicity to Vero and human oral carcinoma (KB) cells. Baghidikian *et al.*, (2013) extracted palmatine and pseudopalmatine (**compounds 22-23**) from the *Stephania rotunda* (an antimalarial plant used in orthodox medicine in Cambodia) which are classified as protoberberine-type benzylisoquinoline alkaloids were found to eliminate W2 strain of *Plasmodium falciparum (in-vitro)* with IC_{50} values of 3.0µM and 2.8µM respectively. **Compound 23** was discovered not to be cytotoxic against K562S cells. The reported antiplasmodial IC_{50} data of **compounds 22-23** corroborate the utilization of *Stephania rotunda* for the treatment of malaria disease by traditional medicine practitioners in Cambodia. Nasrullahi *et al.*, (2013) extracted 2-hydroxyatherosperminine **(compound 24)** which is a phenanthrene alkaloid from the *Cryptocarya nigra* (Lauraceae) dichloromethane bark extract and was discovered to be active against the *Plasmodium falciparum* K1 strain with IC_{50} value of 0.75µM. Zofou *et al.*, (2013) undertook a research tagged "New antimalarial hits from Dacryodes edulis (Burseraceae) in which kuercitin **(compound 25)** was isolated and it indicated antiplasmodial activity with IC_{50} values of 5.96µg/ml ± 0.51 and 2.26 µg/ml ± 0.28 against $3D_7$ and Dd_2 respectively.

DISCUSSION

In considering the criteria for interpretation of *in vitro* antiplasmodial activity of a compound as "good", "moderate", "low" or "inactive", earlier studies by Basco and co-workers (1994) have adopted the following criteria: IC_{50}< 10µgmL^{-1},as good activity; IC_{50} of 10-50µgmL^{-1} as moderate activity; IC_{50} of 50-100µgmL^{-1} as low activity; and IC_{50}> 100µgmL^{-1} as inactive. On the other hand, Muriithi and collaborators (2002) have expressed their IC_{50} values in µM and considered as inactive compounds showing IC_{50} > 100 µM; of low activity, those with 60 µM ≤ IC_{50} < 100 µM; of moderate activity, those displaying 20 µM ≤ IC_{50} < 60 µM; of good activity, those with 1 µM ≤ IC_{50} < 20 µM and of very good activity, those with IC_{50} of < 1 µM. In the same vein, for in *vitro* investigations, antiplasmodial activity of extracts/compounds was rated very good if the IC_{50} was less than 5µg/ml (IC_{50} < 5 µg/ml), good if the IC_{50} was greater than 5µg/ml and less than 10 µg/ml, (good: 5 µg/ml ≤ IC_{50} < 10 µg/ml), moderate if the IC_{50} was 10µg/ml ≤ IC_{50} < 20 µg/ml and 20µg/ml ≤ IC_{50} < 30 µg/ml and IC_{50} values greater 30 µg/ml and above is deemed to be in active (Deharo *et al.*, 2001). For in *vivo* investigations, an extract/compound's anti-malarial activity is deemed very good if it suppresses malarial parasites by ≥ 50% at 100 mg/kg body weight/day, good if it suppresses malarial parasites by ≥ 50% at 250 mg/kg body weight/day, and moderate if it suppresses the parasites by ≥ 50% at 500 mg/kg body weight/day and ≥ 50% at > 500 mg/kg body weight/day for in vivo studies, were considered inactive.(Deharo *et al.*, 2001). Another system of *in vitro* antiplasmodial activity which regarded an extract to be very active if IC_{50} value is less than 5 µg/mL, active if IC_{50} value is greater than 5 µg/mL but less than 50 µg/mL, weakly active if IC_{50} value is greater than 50 but less than 100 µg/mL and inactive if IC_{50} value is greater than 100 µg/mL (Rasoanaivo *et al.*, 1992).

In this survey, the existing criteria have been modified in order to establish the following criteria adopted for interpreting IC_{50} values/percentage elimination, suppression or inhibition rate of malaria parasitamae (parasites) for *in - vitro* and *in - vivo* antiplasmodial investigations respectively which were reported for the twenty five antimalarial compounds in this review:

IC_{50} < 1µgmL^{-1} as excellent activity; 1 µgmL^{-1} ≤ IC_{50} < 10 µgmL^{-1} as having very good activity; 10 µgmL^{-1} ≤ IC_{50} < 20 µgmL^{-1} as showing good activity; 20 µgmL^{-1} ≤ IC_{50} < 100 µgmL^{-1} as exhibiting moderate activity; 100 µgmL^{-1} ≤ IC_{50} < 200 µgmL$^{-1}C_{50}$ as exhibiting low activity and IC_{50} ≥ 200µgmL^{-1} as inactive while IC_{50} value of < 1 µM displays an excellent activity; those with 1 µM ≤ IC_{50} < 10 µM discloses very good activity; 10 µM ≤ IC_{50} < 20 µM as revealing good activity; 20 µM ≤ IC_{50} < 100 µM as moderate activity; 100 µM ≤ IC_{50} < 150 µM IC_{50} as indicating low activity and IC_{50} >150 µM is considered to be as inactive. For *in vivo* antiplasmodial activity (malaria parasites suppression expressed in percentage), the antimalatrial activity of an extract is regarded as excellent (extremely good) if the percentage inhibition is ≥ 50% at < 100 mg/kg body weight/day; very good if the elimination is ≥ 50% at 100 ≤ mg/kg body weight/day > 250; good if the suppression is ≥ 50% at 250 ≤ mg/kg body weight/day > 400; moderate if the percentage of parasite elimination is ≥ 50% at 400 ≤ mg/kg body weight/day > 500; low activity if the suppression is ≥ 50% at 500 ≤ mg/kg body weight/day > 600 and inactive if the percentage inhibition is ≥ 50% at ≥ 600 mg/kg body weight/day.

Anti-plasmodial (in-*vitro*) activities of compounds **1-6** (macluraxanthone, volkensiflavone, myricetin, kaempferol 3-O-α-L-(2″,3″- di-E-p-coumaroyl) rhamnoside, kaempferol 3-O-α-L-(2″-E-p-coumaroyl-3″-Z-p- coumaroyl) rhamnoside and 6 – prenylapigenin were investigated against various strains of *Plasmodium falciparum*. Macluraxanthone demonstrated best, most significant and promising anti-plasmodial activity with IC_{50} value of 0.36 - 0.46µg/ml (Azebaze *et al.*, 2015) perhaps due to its unique chemical structure, followed by volkensiflavone (IC_{50}: 0.93 - 0.99 µg/mL) both exhibiting excellent activity, myricetin (IC_{50} values of 1.82 and 1.51 µg/mL indicating very good activity), kaempferol 3-O-α-L-(2″,3″- di-E-p-coumaroyl) rhamnoside (IC_{50} values of 0.6±0.2 (excellent activity) and 7±1µM (very good or strong activity against different strains of *P. falcparum*), kaempferol 3-O-α-L-(2″-E-p-coumaroyl-3″-Z-p- coumaroyl) rhamnoside (IC_{50} values of 2.0±0.6/4.1±0.5µM and 6 – prenylapigenin (IC_{50} value of 6.7 and 4.8µM) also revealed a very good anti-plasmodial activity (Gadetskaya *et al.*, 2015; Cai *et al.*, 2016 and Samson *et al.*, 2017).

In-vivo anti-plasmodial activities of **compounds 7-12** (embelin, knipholone, aloinoside, aloesaponarin, pinocembrin and 7-hydroxyaloin) which involved being bioassayed or evaluated against *Plasmodium berghei* in infected mice were successfully carried out. Pinocembrin **(compound 11)** exhibited excellent anti-plasmodial activity with 77.03% malarial parasites inhibition at 20mg/kg/day and 81% at 40mg/kg/day (Melaku *et al.*, 2017), followed by knipholone (**compound 8**) which disclosed very good anti-malarial activity 55.14% parasitemae elimnation at 100mg/kg/day and 60.2% at 200mg/kg/day suppression, aloesaponarin **(compound 10**) possessing IC_{50} of 7.8 µM (good activity against Plasmodium species D7 (*Plasmodium falciparum strain*) and *Plasmodium berghei* and 7-hydroxylalion (**compound 12**) with 56.2% parasites inhibition at 200mg/kg/day disclosing very good activity. Aloinside **(compound 9)** with 100% malarial parasites inhibition at 400mg/kg/day and embelin (**compound 7**) which revealed 54.8% elimination of malaria parasites at 400mg/kg/day both demonstrating moderate anti-plasmodial activity (Deharo *et al.*, 2001; Bezu *et al.*, 2015; Alebachew *et al.*, 2021; Tewabe *et al.*, 2018; Abdissa *et al.*, 2017 and Teka *et al.*, 2016). Furthermore, **compounds 13, 14,15,16,17, 21**(0.78 µM against TM4

strain of *P. falciparum*) and compound **24** illustrated excellent antimalarial activity while compounds 18,19, 20, 21(1.29 µM against $K1C_{B1}$ strain of *P. falciparum*) **22, 23** and **25** showed very good antiplasmodial activity.

However, embelin disclosed the lowest percentage antimaiarial suppression activity (in – *vivo*) amongst compounds **7-12**. In any form of anti-plasmodial investigation, the most active extract, fraction or anti-plasmodial compound or bioactive phytochemical is the one which inhibited, eliminated or suppressed all or most of the malaria parasites at the lowest concentration with zero, negligible or minimal cytotoxicity. The hydroxyl groups in the chemical structures of the reported phytochemicals might be responsible for their anti-plasmodial/anti-malarial activities which could be improved via appropriate structural modifications or their employment in synergy with either already existing synthetic antimalarials or isolated antiplasmodial compound(s) with negligible or zero cytotoxicity belonging to any class of organic compounds.

CONCLUSION

In this survey, an attempt has been made to review twenty five phytochemical antimalarials based compounds isolated from medicinal plants which have been investigated for their anti-plasmodial/antimalarial property. Isolated phytons such as macluraxanthone, volkensiflavone, pinocembrin, dehydrotylophorine, dehydroantofine, tylophoridicine, (—) – milonine, stephanine, crebanine, *O*-methylbulbocapnine, cheilanthifoline, simplicifolianine, palmatine, pseudopalmatine, 2-hydroxyatherosperminine and kuercitin which possessed interesting, promising, excellent and very significant antimalarial properties among the reported phytyconstituents may present an array of potential lead compounds towards development of novel antimalarial drugs. It is recommended that *in-vivo* antiplasmodial activities of compounds **1 - 6** and **13 -25** and i*n-vivo* cytotoxicty activities of compounds **1 – 16, 20, 22, 24** and **25** which have not been carried out should be investigated to further substantiate their anti-malarial property and safety in treating malaria infections in orthodox medicine.

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