Chapter 27

Modulation oOf tThe Host-Parasite Redox Metabolism tTo Potentiate Antimalarial Drug Efficiency

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Abstract

Artemisinin-based combination therapy (ACT) is nowadays the most effective treatment for *P. falciparum* malaria: artemisinin is the most active drug able to rapidly kill all erythrocyte stages of the malaria parasite. However, due to its short half-life, it requires the association with other long-acting drugs. Even if the exact mechanism of action of most antimalarial drugs is still unknown, many of these compounds are able to interact directly or indirectly with the redox metabolism of the parasite and-/-or the host, enhancing the effectiveness of the antimalarial therapy. This review focuses on many natural compounds, isolated mainly from plants, and used as traditional antimalarial treatments, known to possess a potent antimalarial activity (IC50 lower than 1 ug/mL). These compounds belong to some specific chemical family, mainly alkaloids, terpenoids, quassinoids, limonoids, and polyphenols, sharing some common chemical features. These natural molecules could offer new possibilities of combination therapies development as antimalarials when associated with artemisinin.

Keywords

Antimalarial drugs

Artemisinin-based combination therapy

Natural antimalarial compounds

Host-parasite redox metabolism;

27.1. Introduction

27.1.1. Current Antimalarial Therapy

The natural antimalarial product artemisinin and its semi-synthetic derivatives represent the front-line treatment of *P. falciparum* malaria, as they are the most active antimalarials available, rapidly killing all blood stages of the malaria parasite. Artemisinins contain an endoperoxide bridge which plays a key role in the antimalarial activity with a mode of action starting from radical transient species initiated by the cleavage of this bridge. Few other natural compounds with such a peroxide bridge are known. On the other hand, the oxygen-oxygen bridge, being chemically unstable, determines a very short plasma half-life, constituting a major limiting factor to the use of artemisinin as a single drug [1]. To solve this problem, artemisinin was ~~early~~ used early on in combination with partner drugs characterized by much longer half-life. Artemisinin-based combination therapy (ACT) is the most effective treatment for *P. falciparum* malaria. Artemisinin derivatives such as: dihydroartemisinin, artesunate, and artemether, are combined with a partner drug such as~~including~~ lumefantrine, mefloquine, amodiaquine, and piperaquine. Since the introduction of artemisinin-combination therapies (ACTs), the overall number of malaria cases displayed a marked decline, but, since the last few years, the rate of decline has stalled or even reversed in some regions [2].

The reasons of the recent increase of the number of malaria cases ~~is~~ are plausibly multi-factorial, including: insufficient investments for treatment and prevention, insecticide resistance, and antimalarial drug resistance. The relative role of each factor is undefined. In the Greater Mekong s~~S~~ub-region, artemisinin resistance raised concern and ~~it~~ is currently defined as "partial artemisinin resistance" in patients showing a delayed parasite clearance following treatment with an ACT. Notably, in the same region, resistance to the partner drugs is present. To rule out between artemisinin and partner drugs resistance in the development, treatment failure is obviously very difficult. Currently, no evidence of artemisinin resistance has been observed in African countries accounting for about 90% of malaria cases and deaths worldwide.

27.2. Interactions oOf Antimalarial Drugs wWith Host-Parasite Redox Homeostasis

27.2.1. Antimalarial Drugs Showing Redox Activity

Although the precise mechanism of action of most of the antimalarial drugs is still unknown, most of the antimalarial drugs have the potential of interacting directly or ~~un~~in~~-~~ directly with redox metabolism of the parasite and/or of the host.

A direct redox effect exerted by some antimalarial drugs on the host cells is clearly evidenced as hemolysis (oxidative damage and rapid destruction of erythrocytes leading to variable degrees of anemia) in G6PD-~~-~~deficient individuals. Powerful antimalarial drugs such as primaquine, methylene blue, and sulf~~ph~~onamides cause acute and severe h~~a~~emolytic anemia in G6PD-~~-~~deficient subjects [3, 4]. In addition, popular antimalarial drugs and their combinations such as halofantrine, quinine, chloroquine, and chlorproguanil-dapsone have been associated with~~to~~ variable degrees of h~~a~~emolytic anemia, generation of ROS, and depletion of erythrocyte GSH [5, 6]. Artemisinin and its derivatives also cause delayed hemolysis. The central role of the endoperoxide bridge of artemisinin and the generation of free radicals following its cleavage has been clearly established. Artemisinin activation needs iron provided by the host cells, resulting in the rapid generation of free radicals and the formation of heme-artemisinin adducts. To explain its high activity (IC50 ≈ 2 nM), specific molecular targets are expected to play a role in its mechanism of action.

27.2.2. Antimalarial Drugs Causing tThe Accumulation oOf Free Heme TThrough tThe Inhibition oOf Hemozoin Synthesis

Many antimalarial drugs including chloroquine, lumefantrine, mefloquine, amodiaquine, and piperaquine~~,~~ show the capability to inhibit heme polymerization ~~in~~to form hemozoin, an inert crystal, in a specialized digestive vacuole of *P. falciparum* [7, 8]. Heme detoxification and its polymerization constitute a central step of the parasite metabolism, and its inhibition leads to parasite death. On the other hand, free iron released during h~~a~~emoglobin digestion~~,~~ and heme constitute a powerful source of free radicals needing to be neutralized ~~both~~ by both parasite and erythrocyte enzymes [9, 10]. Although the chemical and metabolic interactions occurring between artemisinin derivatives and heme polymerization inhibitory drugs are scarcely understood, it is interesting~~ly~~ to notice that the drugs that inhibit h~~a~~emoglobin metabolism are the best candidates to be utilized in

combination with artemisinin in ACTs [11] suggesting a combined mechanism of action [12, 13].

27.3. Response of the Host Cell tTo Redox Changes Exerted bBy Parasite Growth aAnd/oOr Antimalarial Drugs

Redox metabolism of the parasitized erythrocyte depends on the equilibrium between the antioxidant defencesdefenses of both erythrocyte and parasite and, on the free radicals produced by the parasite and by the erythrocyte [14]. Iron plays a central role in free radical production in the parasite through hemoglobinaemoglobin digestion and in the parasitized erythrocyte which accumulates large amounts of denatured hemoglobinaemoglobin generated by the oxidative stress exerted by the parasite [15, 16]. As an evidence of this unstable equilibrium, a large number of mutations have been selected by malaria such as G6PD deficiency (defect of production of NADPH), sickle cell anemia, thalassemias, HbC, HbE, and many other hemoglobinaemoglobin disorders triggering oxidative stress through haemoglobin denaturation and plausibly amplifying the redox stress exerted by the intracellular parasite. More than 500 million people living in malaria endemic areas are affected by one or more of those mutations conferring variable levels of protection to severe malaria [17, 18].

It has been demonstrated that mild oxidative stress exerted by malaria parasite activates a specific redox signalling pathway in the host erythrocyte inducing the Tyr phosphorylation of some membrane proteins [19] which, in turn, appear to be essential for the remodelling of the parasitized erythrocyte membrane needed to activate new functions essential for the parasite growth such as import of nutrients and insertion of parasite proteins binding to endothelium [20]. The activation of Syk kinase, constituting a key element of such pathway, has been directly implicated both in the egress of merozoites and in the infection of new erythrocytes occurring after the 48--hours life cycle of the parasite. A new class of drugs has been developed to interfere with this pathway revealing good antiplasmodial efficacy [21].

Targeting the redox metabolism of *P. falciparum* by antimalarial drugs is believed to create an overload of oxidative stress leading to parasite death [22]. Anyway, much more complex mechanism of action appears to be involved in the interactions occurring between parasite and host cell metabolism and in the interference exerted by a large number of redox active antimalarial drugs (Fig. 27.1).

Fig. 27.1 Redox homeostasis perturbation between host and parasite

27.4. Natural Antimalarial Compounds

In addition to artemisinin, a large number of natural compounds present in plants, are known to possess a potent antimalarial activity. In some cases, their clinical efficiency and activity have been demonstrated by their use as traditional antimalarial treatments.

A comprehensive list of plant compounds with antimalarial activity, quantified as in vitro IC50, is reported in Table 27.1. Only the compounds, whose IC50 is lower than 1 ug/mL, have been selected.

It shall be noticed that most of these compounds belong to the families of alkaloids, in particular, indole and naphthoisoquinoline alkaloids, with few exceptions including sequipertenessequiterpenes, quassinoids, limonoids, and a polyphenolic compound (ellagic acid).

27.4.1. Alkaloids

Alkaloids are one of the most important antimalarial compound classes known from ancient time. Quinine, which represents the first antimalarial natural drug used, belongs to this group. It is a quinidine alkaloid isolated from the bark of *Cinchona succirubra* and it has been used for more than three centuries for the treatment of malaria [23]. Numerous studies reported in literature described the significant antimalarial activity of over 100 natural alkaloids, which have been considered more potent than chloroquine [24]. Some of the active reported alkaloids can be also grouped according to their structural chemical classes. In particular, indole alkaloids which from a chemical point of view contain an important indole group in their structure and derive from the amino acid tryptophan, represent one of the largest class of alkaloids grouping together many antimalarial compounds [25]. The naphthoisoquinoline alkaloids represent as well potential antimalarial compounds. These compounds are secondary metabolites naturally present mainly in some plants of the Ancistrocladaceae and Dioncophyllaceae families. Structurally, they are chiral molecules characterized by the presence of C,-C and C-,N bonds typical of the naphthalene and isoquinoline structures contained in them. In addition to the antimalarial activity, these alkaloids have shown many biological activities including anti-leishmanial, anti-trypanosomal, fungicidal, insecticidal, and larvicidal [26].

27.4.2. Sesquiterpenes

An important medicinal plant used from ancient time because of its content in antimalarial artemisinins is the *Artemisia annua*, an herb used in Chinese traditional medicine. As already mentioned, artemisinin-combination therapies (ACTs) are nowadays the standard treatment in the world against *P. falciparum* [1,~~;~~ 27]. Chemically, artemisinin belongs to sesquiterpenes, namely, terpenes characterized by three isoprene units ($C_{15}H_{24}$), which represent a very important class of secondary metabolites obtained from plants. In addition to artemisinin, several other sesquiterpene compounds have shown a potentially antimalarial activity [25]. Structurally, as already mentioned, artemisinin presents a characteristic endoperoxidic group which is considered responsible for its activity. However, the other sesquiterpene compounds reported in Table 27.1, do not contain the typical peroxide group of artemisinin. Interestingly, this chemical group is found in another antimalarial compound, named Plakortin, recently isolated from a tropical sponge instead of from plants. It is a polyketide endoperoxide isolated from the sponge *Plakortis simplex*, and it has shown antiparasitic activity against *P. falciparum*. It has been shown that the activity of this compound also depends on the functionality of the peroxide [28].

27.4.3. Quassinoids

Quassinoids are related to terpenes group too. They are a class of degraded triterpenes, and most of them are characterized by a C-20 and δ-lactone skeleton [22]. Concerning the quassinoids, in particular, three compounds have reported significant antimalarial ~~-malarial~~ activity with very low IC50 values as a result of our free research: Ailanthone and 6-alpha-t~~T~~igloyloxychaparrinone isolated from *Ailanthus altissima* and s~~S~~imalikalactone D obtained from the roots of *Simabaorinocensis*. The presence of the ester function seems to be important for in vitro antiplasmodial activity of these compounds [29].

27.4.4. Limonoids

Limonoids present a similar structure to q~~Q~~uassinoids. These compounds, classed as tetranortriterpenes, present different variations of the furanolactone core structure. *Meliaceae*, *Cucurbitaceae*, and *Rutaceae* are the plant families richer of these phytochemical compounds, some of which have demonstrated different biological properties such as antimalarial activity [23].

27.4.5. Polyphenolic Compounds

As regards the polyphenolic compounds, only the ellagic acid (EA) has shown a very interesting IC50 value. This is an antioxidant molecule which chemically belongs to the hydrolysable tannins class, known for its antimalarial activity. EA is derived~~s~~ from the hydrolysis of ellagitannins (ETs). ETs are hydroly~~z~~sed, chemically by acids or bases or enzymatically, into hexahydroxy diphenic acid, which spontaneously tends to EA [30]. EA explains its antiplasmodial activity by interfering with h~~a~~emoglobin metabolism and, in particular, inhibiting the β-h~~a~~ematin formation [31]. For these reasons, ellagic acid could be a potential candidate to be utilized in combination with artemisinin in ACTs.

Table 27.1 Summary of antimalarial ~~malarial~~ natural compounds selected for their activity "in vitro" (IC50 < 1 ug/mL)

IUPAC name	Chemical s~~S~~tructure	Chemical group	Botanical source	Anti-m~~M~~alarial activity	IC50 (µg/ strai
(2S,3R,12bS)-3-ethenyl-2-[[(1S)-2-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-9-ol		Indole a~~A~~lkaloids	*Strychnos usambarensis*	In vitro [32]	0.48 20) 0.16
2,16,19,20-t~~T~~etradehydrocuran-17-oic a~~A~~cid m~~M~~ethyl e~~E~~ster		Indole a~~A~~lkaloids	*Picralima nitida*	In vitro [34]	0.45 0.73
Methyl (1S,9S,14Z,15R)-14-ethylidene-6-hydroxy-2-methyl-18-oxa-2,12-diazahexacyclo[13.3.2.01,9.03,8.09,16.012,19]icosa-3,5,7-triene-16-carboxylate		Indole alkaloids	*Picralima nitida*	In vitro [34]	0.95 0.66
(19α,20α)-16-(Methoxycarbonyl)-19-methyl-3,4,5,6,16,17-hexadehydro-18-oxayohimban-4-ium		Indole a~~A~~lkaloids	*Picralima nitida~~;~~* *Alstonia scholaris*	In vitro [34] In vivo [35]	0.01 0.03
5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium		Indole a~~A~~lkaloids	*Enantia C~~c~~hlorantha*	In vitro [36] In vitro and in vivo [37]	0.14 0.15
5-methylindolo[3,2-b]quinoline		Indole alkaloids	*Quassia indica*	[23]	0.19 0.05

3,8,9-trimethoxy-5-methylbenzo[c]phenanthridin-5-ium-2-ol		Indole alkaloids	*Fagara zanthoxyloides*	In vitro [40]	0.01
2,9,10-tTrimethoxy-5,6-dihydroisoquinolino[2,1-b]isoquinolin-7-ium-3-ol		Indole alkaloids	*Enantia Cchlorantha; Penianthus longifolius*	In vitro [41] In vitro and in vivo [42]	0.42 1.61
2,3,9,10-tetramethoxy-5,6-dihydroisoquinolino[2,1-b] isoquinolin-7-ium		Indole alkaloids	*Enantia Cchlorantha; Penianthus longifolius*	In vitro [41;43] In vitro and in vivo [42]	0.28 0.16
Methyl (1R,9S,11S,14Z,15S,17S,19S)-19-[(acetyloxy)methyl]-14-ethylidene-18-oxa-2,12-diazahexacyclo[9.6.1.1^{9,15}0.0^{1,9}0.0^{3,8}0.0^{12,17}]nonadeca-3,5,7-triene-19-carboxylate		Indole alkaloids	*Picralimanitida Picralima nitida*	[45]	0.44 0.53
(7aS,8S,11aS,12aR)-8-Methyl-5,6,7a,8,11a,12,12a,13-octahydro-7H-9-oxa-6a,13-diaza-indeno[2,1-a]anthracene-11-carboxylic acid methyl ester		Indole alkaloids	*Picralima nitida*	[45]	0.42 0.10
Methyl 2-[(1R,2S,5R,6R,13R,14S,16S)-14-(acetyloxy)-6-(furan-3-yl)-13-hydroxy-1,5,15,15-tetramethyl-8,17-dioxo-7-oxatetracyclo[11.3.1.0^{2,11}0.0^{5,10}]heptadec-10-en-16-yl]-2-hydroxyacetate		Limonoids	*Khaya senegalensis*	In vitro [46]	0.12 (chlo sens (3D *Falc* strai
(4aR,6R,6aS,6bR,7aS,10S,10aS,12aR,12bR)-10-(3-Furyl)-4,4,6a,10a,12b-pentamethyl-3,8-dioxo-3,4,4a,5,6,6a,7a,8,10,10a,11,12,12a,12b-tetradecahydronaphtho[2,1-f]oxireno [d]isochromen-6-yl acetate		Limonoids	*Azadirachta indica; Cedrela odorata; Khaya grandifoliola*	In vitro [47, 48] In vivo [49]	0.03 0.02 1.25 Indo clon
2-[(3S)-6,8-dimethoxy-1,3-dimethyl-3,4-dihydroisoquinolin-7-yl]-8-methoxy-3-methylnaphthalen-1-ol		Naphthoisoquinolines	*Ancistrocladustanzaniensis*	In vitro [51]	0.3 (1.9 (
(1R,3S)-7-(1-hydroxy-8-methoxy-3-methylnaphthalen-2-yl)-8-methoxy-		Naphthoisoquinolines	*Ancistrocladustanzaniensis*	In vitro	0.1 (

1,2,3-trimethyl-3,4-dihydro-1H-isoquinolin-6-ol				[51]	4.2 (
2-[(1R,3S)-6,8-dimethoxy-1,2,3-trimethyl-3,4-dihydro-1H-isoquinolin-7-yl]-8-methoxy-3-methylnaphthalen-1-ol		Naphthoisoquinolines	*Ancistrocladustanzaniensis*	In vitro [51]	0.7 (9.1 (
(1R,3R)-7-[5-hydroxy-2-(hydroxymethyl)-4-methoxynaphthalen-1-yl]-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-8-ol		Naphthoisoquinolines	*Triphyophyllumpeltatum*	In vitro and in vivo [52, 53]	0.00 0.00 (NF
(1R,3R)-5-(5-hydroxy-4-methoxy-2-methylnaphthalen-1-yl)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-8-ol		Naphthoisoquinolines	*Triphyophyllumpeltatum*	In vitro and in vivo [52, 53]	0.01 form *falci* 0.01 form *berg*
(1R,3R)-7-[2-(hydroxymethyl)-4,5-dimethoxynaphthalen-1-yl]-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-8-ol		Naphthoisoquinolines	*Triphyophyllumpeltatum*	In vitro [55]	0.00 0.00 (NF
2,3,7,8-Tetrahydroxychromeno[5,4,3-cde]chromene-5,10-dione		Polyphenoliccompounds	*Alchorneacordifolia*	In vitro [56]	0.10 0.03 0.09 0.10 0.05
(1β,11β,12α)-1,11,12-Trihydroxy-11,20-epoxypicrasa-3,13(21)-diene-2,16-dione		Quassinoids	*Ailanthus altissima*	In vitro [57]	0.00
		Quassinoids	*Ailanthus altissima*	In vitro [57]	0.06
(1β,11β,12α,15βb)-1,11,12-trihydroxy-2,16-dioxo-13,20-epoxypicrasa-3-en-15-yl (2R)-2-methylbutanoate		Quassinoids	*Simaba orinocensis*	In vitro [58]	0.00 0.00 (W2
(3aR,4R,6R,7E,10Z,11aR)-6-hydroxy-6,10-dimethyl-3-methylidene-2,9-		Sesquiterpenes	*Tithonia diversifolia*	In vitro	0.33

dioxo-3a,4,5,11a-tetrahydrocyclodeca[b]furan-4-yl] 2-methylpropanoate				[59]	Cyt IC5 (HT
(3aR,4R,6E,10Z,11aR)-6-formyl-4-hydroxy-3-methylidene-2-oxo-3a,4,5,8,9,11a-hexahydrocyclodeca[b]furan-10-yl]methyl acetate		Sesquiterpenes	*Dicoma tomentosa*	In vitro [60]	0.92 0.77
(4S,5R,8S,9R,12S,13R)-1,5,9-Trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.04,13.08,13]hexadecan-10-one		Sesquiterpenes	*Artemisia annua*	In vitro [61]	0.00 W2)
M methyl 2-[(3R,4R,6S)-4-ethyl-6-[(E,2R)-2-ethylhex-3-enyl]-6-methyldioxan-3-yl]acetate		Endoperoxyketal polyketides	*Plakortiscfr. Simplex*	In vitro [63, 64]	0.12 0.27

n.a not available

27.5. Conclusions

This work has revealed a wide range of natural products with potent antimalarial activity, belonging to some specific chemical group, mainly alkaloids, terpenoids, quassinoids, limonoids, and polyphenols.

Selected compounds from a physicochemical point of view are characterized for larger molecular mass and higher hydrophobicity index (logP). These properties may be considered necessary for the achievement of the intracellular target [66]. Furthermore, most of these compounds are hydrogen bond acceptors. Structurally, there are recurrent chemical groups that share these molecules. Most compounds present a rigid scaffold of at least 3 cycles which confers high rigidity to the molecule. However, further structure-activity relationship studies are necessary for the possible identification of a pattern of functional groups (pharmacophore) responsible for the antimalarial activity.

Many of the selected compounds, including artemisinin, are likely expected to exert redox activity in biological systems, but, in most instances, a direct evidence is missing.

At this regard, it should be considered that the erythrocyte-plasmodium system represents a unique environment combining two interconnected oxidative ~~defence~~defense systems, extremely high concentration of heme iron contained in the host compartment and intense hemoglobin~~aemoglobin~~ digestion and heme detoxification in the parasite [22].

Experiments to test the interference with the host-parasite redox state of any potential antimalarial ~~malarial~~ compounds should be, therefore, tested in infected erythrocytes at different development stages.

It should be also noticed that, the antimalarial mechanism of action of redox compounds is complex involving very sensitive host targets [67] that could be considered for the screening of antimalarial drug candidates.

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