Chapter

Development of Phytomedicines as Novel Antimalarial Lead Molecules: Progress towards Successful Antimalarial Drug Discovery

Mithun Rudrapal, Dipak Chetia and Soumya Bhattacharya

Abstract

Among numerous life-threatening infectious diseases (HIV/AIDS, TB, NTDs and EIDs), malaria continues to be the deadliest parasitic disease caused by *Plasmodium* protozoa transmitted by an infective female *Anopheles* mosquito. *Plasmodium falciparum*, the potentially fatal malaria parasite, is believed to be responsible for most of the morbidities and mortalities associated with malaria infections. Artemisinin-based Combination Therapies (ACTs) are currently considered to be the frontline therapy against malaria caused by *P. falciparum*. Despite significant progresses in antimalarial drug discovery, the control and prevention of malaria is still a challenging task. It is primarily because of the reduced clinical efficacy of existing antimalarial therapies including ACTs due to the widespread emergence of drug-resistant strains of malaria parasites, especially *P. falciparum*. It is, therefore, necessary to discover and develop novel drug candidates and/or alternative therapies for the treatment as well as prevention of resistant malaria. In this chapter, the potential of phytomedicines as natural sources of novel antimalarial lead molecules/ drugs with recent advances in phytomedicine-based antimalarial drug discovery has been reviewed.

Keywords: antimalarials, phytomedicines, *P. falciparum*, lead molecules, drug discovery

1. Introduction

Malaria is a potentially life-threatening parasitic disease caused by *Plasmodium* protozoa transmitted by an infective female *Anopheles* mosquito. Along with human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB), neglected tropical diseases (NTDs) and viral hepatitis (hepatitis B), malaria affects billions of people, and causes more than 4 million deaths every year globally [1]. Apart from these infectious diseases, emerging infectious diseases (EIDs) are serious public health threats in the twenty-first century. Some deadly EIDs include severe acute respiratory syndrome (SARS), Ebola virus disease (EVD), Zika virus disease (ZVD), swine flu (H1N1 influenza), bird flu (avian influenza), chikungunya

(CHIKV), dengue fever (DENV), hanta pulmonary syndrome (HPS, hanta virus), antibiotic-resistant infections (superbugs) and coronavirus disease (COVID-19, SARS-CoV-2) [2, 3].

According to the latest report by World Health Organization (WHO), about 229 million clinical cases of malaria with a death toll of 409,000 have been documented for the year 2019. In the same year, 94% of all malaria cases and deaths were found in the WHO African region. In the Southeast Asian region of WHO, there were an estimated 7.9 million cases of malaria in 2018. Children under 5 years of age are considerably at higher risk of malaria. They have been accounted for 67% of all malaria deaths worldwide in 2019 [4–6]. However, *Plasmodium falciparum*, the deadliest malaria parasite, is attributed to be responsible for most of the morbidity and mortality associated with malaria [7, 8]. Artemisinin-based Combination Therapies (ACTs) are currently considered as the frontline therapy against malaria caused by *P. falciparum* [9, 10]. Due to the widespread emergence and spread of drug resistant strains of *P. falciparum*, the clinical utility of existing antimalarial therapies including ACTs has been drastically declined [11, 12]. It has, therefore, become a serious health concern, which urgently necessities the discovery and development of novel drug candidates and/or alternative therapies for the treatment as well as prevention of resistant malaria. In this chapter, the potential of phytomedicines as natural sources of novel antimalarial lead molecules/ drugs with recent advances in phytomedicine-based antimalarial drug discovery has been briefly summarized.

2. Phytomedicines and antimalarial drugs

The discovery of antimalarial drugs from plant sources was started in 200 years back when quinine (QN), a cinchona alkaloid, was isolated from *Cinchona* bark in the year 1820. Earlier, the extract of *Cinchona* bark (also known as Peruvian Bark) was traditionally used for the treatment of fever by native Peruvian Indians in 1600s [13]. QN was the only known antimalarial drug for more than three centuries, and until the 1930s was the only effective therapeutic agent for the treatment of malaria. Later, the structure of quinine served as a template for the development of several synthetic congeners as potent antimalarial agents [13, 14]. The introduction of CQ, a 4-aminoquinoline derivative of QN, in the mid-twentieth century (1940) ceased the wide spread use of QN. Soon after its introduction, CQ became the mainstay of malaria chemotherapy, since it was clinically effective, less toxic and cheaper drug [15]. Another synthetic antimalarial, primaquine (PQ, 1950) was also developed thereafter based on the

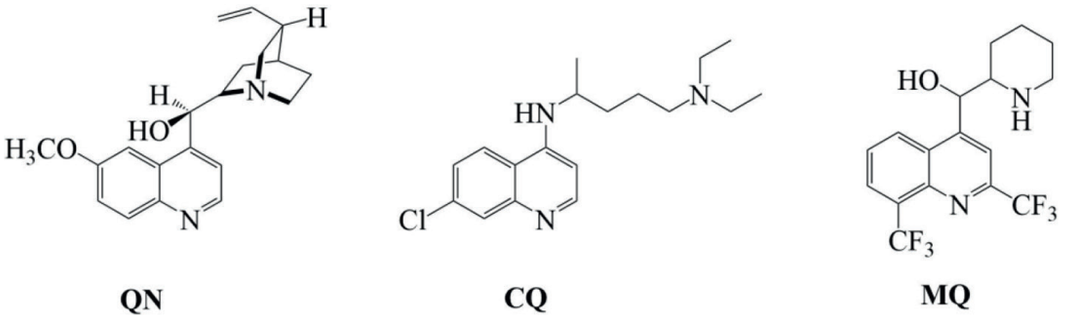

Figure 1.
Some QN-based antimalarial drugs.

structure of lead QN molecule. PQ is a 8-aminoquinoline analogue of QN. Mefloquine (MQ), a synthetic quinoline methanol derivative of QN, was developed (1975) after CQ to treat resistant cases of malaria. Malaria parasites resistance to CQ and MQ began to appear within a few decades of introduction [16]. Later, several quinoline derivatives related to CQ (amodiaquine, AQ and isoquine, IQ) and MQ [halofantrine (HL), lumefantrine (LUM) and pyronaridine (PYN)] were developed and found effective (in combination with ART-based drugs such as dihydroartemisinin, artemether and artesunate) against CQ-resistant and/or multi-drug resistant (MDR) *P. falciparum* infections. Hepatotoxicity and cardiotoxicity are some serious toxic effects associated with these drugs [17]. Moreover, rapid development of resistance has severely limited the use of QN-based drugs alone, and therefore, they are used in combination with other drugs in the treatment of resistant malaria. The increasing prevalence of MDR strains of malaria parasites, particularly *P. falciparum* in most malaria endemic areas (Southeast Asia including Myanmar, Thailand, Vietnam and India, African continent and Eastern Mediterranean region) has significantly reduced the efficacy of CQ and other potent QN-based antimalarials in the treatment of malaria [8]. **Figure 1** depicts structures of some QN-based antimalarial drugs.

QN-based antimalarials are used widely in the treatment and prophylaxis of malaria. QN still remains an important antimalarial drug due to the emergence of CQ-resistant and MDR strains of malaria parasites, especially *P. falciparum*. Due to its undesirable side effects, it is now only used as an intravenous injection (as sulphate salt) to treat severe malaria. CQ (as phosphate salt) still remains the first-line drug in the treatment of uncomplicated sensitive *P. falciparum* malaria, despite its increasing resistance to parasites, due to its easy availability, low cost and good tolerability. In CQ-resistant malaria, the next drug of choice is MQ, followed by QN in combination with tetracycline, doxycycline or sulphadoxine-pyrimethamine (SP). MQ and AQ are widely available and are used to treat cases of uncomplicated malaria in areas where CQ resistance is prevalent [18, 19].

QN-based drugs are blood stage schizonticidal. CQ/MQ is selectively active against the intra-erythrocytic mature forms (trophozoites) and also younger ring forms of malaria parasites, without any activity against gametocytes. QN-based drugs inhibit the heme polymerase enzyme resulting in specific toxicity during the developmental stage of the parasite. CQ accumulates by a weak base mechanism in the acidic food vacuole of trophozoite-infected cells and act by forming a complex with heme in the parasite food vacuole, which prevents heme polymerization and consequently, hemozoin formation. Simply, they these drugs block the polymerisation of heme to haemozoin (malaria pigment). As a result, the heme which is released during haemoglobin degradation builds up toxic accumulation of heme (haematin), thereby kills the parasite with its own toxic effects. The mode of action of QN is similar to CQ. QN binds strongly to heme protein and forms complexes that are toxic to the malaria parasite, as already delineated above. MQ also acts by inhibiting the heme polymerase, similar to CQ [8, 18–20].

ART, an active constituent of *Artemisia annua* L. (Sweet wormwood) and related compounds (semi-synthetic derivatives) showed promising antimalarial efficacy in clinical trials in 1970s (1972) and till date they are considered as the most effective and potent antimalarial agents [21]. Since ART is not soluble in water or oil, it has several limitations such as poor aqueous solubility, oral absorption and bioavailability. Reduction of ART (sesquiterpene lactones or cyclic endoperoxide) produced dihydroartemisinin (DHA), a sesquiterpene lactol, which served later as a template for the synthesis of a series of semi-synthetic analogues such as artemether (AM), arteether

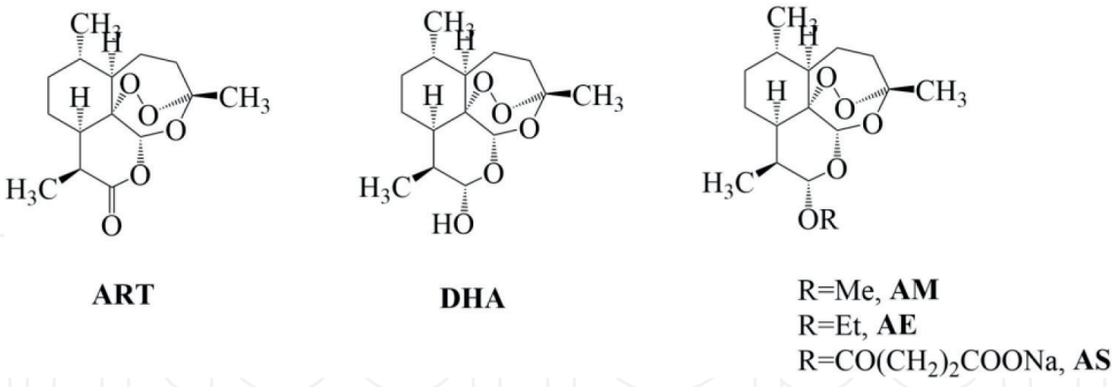

Figure 2.
ART and some ART-based antimalarials.

(AE) and artesunate (AS). They are collectively termed as the first-generation derivatives of ART [22, 23]. First-generation ART derivatives can be further grouped into oil soluble C(10) β-alkyl ethers (AM and AE) and water soluble C(10) β-(substituted) esters (sodium artesunate and sodium artelinate). These drugs possess better oil/water solubility, and therefore, have superior pharmacokinetics properties with increased antimalarial efficacies over the parent compound, ART [8]. **Figure 2** represents the structures of ART and some ART-based antimalarial drugs.

Because of having excellent antiparasitic efficacy against resistant parasites, ART-based drugs mostly replaced the use of QN- and antifolate-based drugs. ART derivatives are fast-acting antimalarials effective against MDR strains of *P. falciparum* and are used for the treatment of severe and complicated malaria. ART-based drugs showed very rapid clearance of parasites and faster resolution of fever as compared to QN. In some areas of Southeast Asia, combinations of ART-based drug and MQ offer the only reliable treatment for uncomplicated MDR *P. falciparum* malaria [24, 25].

ART and its analogues are active against all blood stages, particularly against younger ring forms and gametocytes. They have no activity on hepatic stages of parasites. They reduce parasitemia very rapidly and are well tolerated in both adults and children. ART and related compounds are concentrated in parasite-infected erythrocytes and exert their parasiticidal activity subsequent to reductive activation by heme in an irreversible redox reaction, which produces toxic carbon-centred free radicals. Toxic free radicals may lead to alkylation of heme or bring about oxidative damage to parasite proteins/lipids. The endoperoxide group, therefore, appears to be crucial for the antimalarial activity. The antimalarial activity of ART may also result from the inhibition of a parasitic calcium ATPase enzyme [8, 24–26].

The development of atovaquone (ATO), a 2-hydroxy-1,4-napthoquinone antimalarial, began more than 50 years ago when the outbreak of World War II caused substantial shortages in the supply of QN. ATO is an analogue of lapachol (a prenylnaphthoquinone isolated from *Tabebuia* species, Lapacho tree, 1892). Lapachol was used as an antimalarial lead molecule for the development of ATO. It is effective against CQ-resistant *P. falciparum*, but because, when used alone, resistance develops rapidly, ATO is often given in combination with proguanil (PG). A new fixed-dose antimalarial combination of ATO and PG (Malarone, 1998) is available in the market worldwide. Malarone shows good tolerability with minimal side effects in children and adults with uncomplicated malaria. It is used as chemoprophylaxis for the prevention of malaria in travellers. ATO represents a novel class of expensive antimalarial drug.

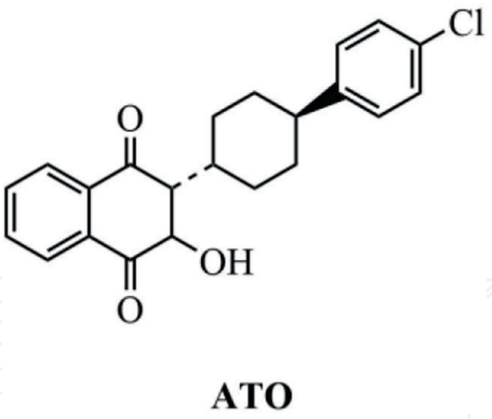

Figure 3.
Structure of ATO.

ATO is used in combination with PG (a selective inhibitor of dihydrofolate reductase, DHFR) or tetracycline for the prevention as well as treatment of CQ-resistant malaria, including cerebral malaria caused by *P. falciparum*. It is as effective as MQ or doxycycline. ATO acts through the inhibition of electron transport at the *Plasmodium* mitochondrial cytochrome bc1 complex and depolarizes the membranes of *Plasmodial* mitochondria[15, 16]. The structure of ATO is given in **Figure 3.**

3. Approaches to antimalarial drug discovery

The objective of antimalarial drug discovery is to find out new and potent drug candidates based on the knowledge of existing and/or novel drug targets. It is necessary to develop affordable and safe drugs that would be reasonably cheaper, non-toxic to host tissues, and clinically effective against resistant malaria parasites. Suitable *in vitro* and *in vivo* experimental methods are, therefore, used for the evaluation of efficacy as well as toxicity of newer antimalarial agents. However, there are several traditional and modern approaches to antimalarial drug discovery programme, which include traditional evaluation of bioactive natural products/phytomedicines, molecular modifications of existing lead molecules, reverse pharmacological or drug repurposing approach and drug discovery based on CADD/SBDD approach [8]. Brief explanations of these approaches are given here under (**Figure 4**).

3.1 Ethnomedicinal evaluation based approach

The investigation of medicinal plants having traditional/ folkloric uses as antimalarial medicine may be potential sources of novel bioactive compounds that can be further developed into potent antimalarial drugs and/or lead molecules. Several tribes and aboriginals of Asian, African and South American continents still rely on plant-based ethnomedicines for the management of fever and malaria-like illness. QN and ART were discovered from the ethnomedicinal use of *Cinchona* and *Artemisia* plants, respectively. They served as lead structures in the development of many more potent antimalarial drugs of current use. Considering the above fact, thousands of medicinal plants and traditional formulations have been screened (*in vitro* and *in vivo*) to aid bioactive fraction guided discovery of antimalarial lead molecules [27].

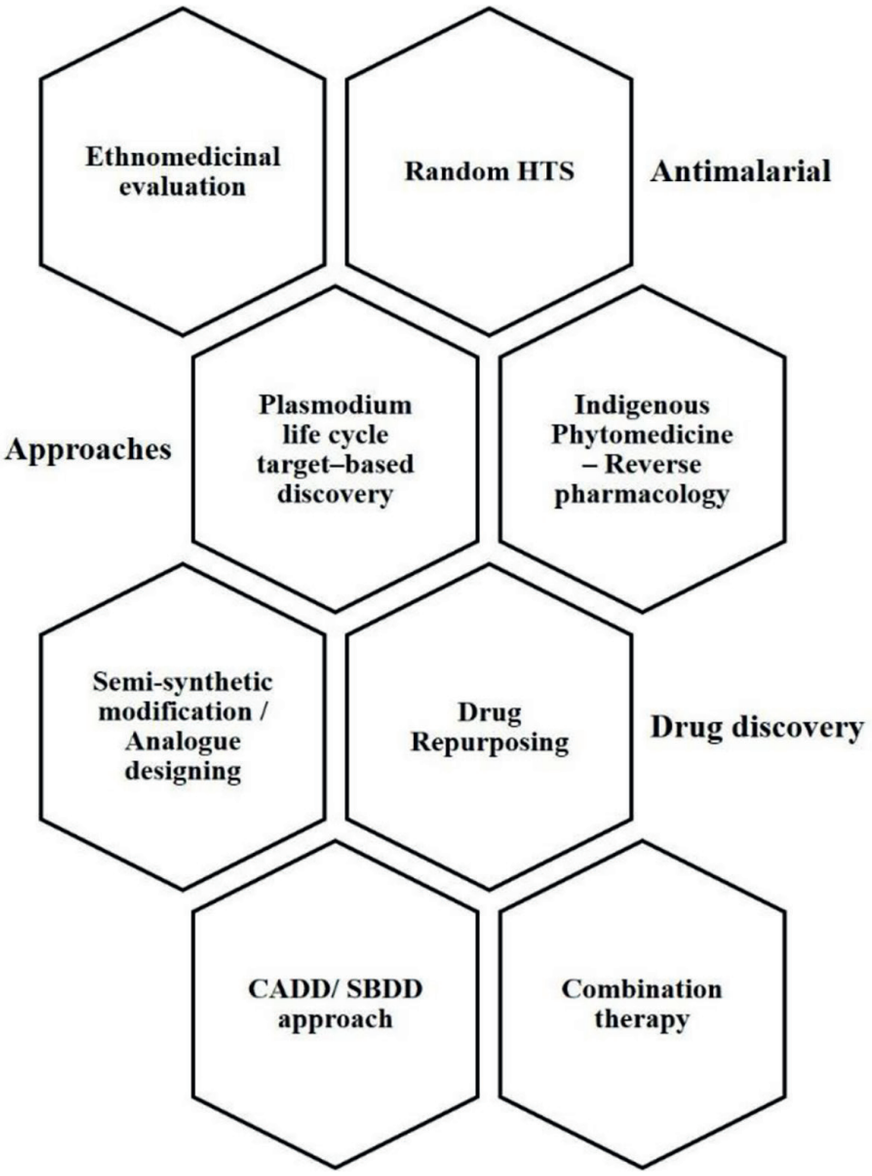

Figure 4.
Approaches to antimalarial drug discovery.

3.2 Random high-throughput screening

Random high-throughput screening of plant extracts is one of the common approaches for antimalarial drug discovery. Scientists and researchers perform random screening of plant extracts against *Plasmodium* strains by various *in vitro* methods in search for novel antimalarial compounds. Depending upon preliminary antimalarial efficacy (IC_{50}) and cytotoxicity profile (CC_{50}) obtained *in vitro*, plant extracts and/or isolated pure compounds can be further subjected to *in vivo* experimental (ED_{50} and Pharmacokinetics) studies [28].

3.3 *Plasmodium* life cycle targeted drug discovery

This is believed to be the most potential approach in antimalarial drug discovery programme. Specific proteins or enzymes that are essential biological components in the life cycle of *Plasmodium* parasite may provide novel targets for the discovery

of drug molecules. For instance, falcipains (FP), plasmepsins (PM), dihydrooroate dehydrogenase (DHOH), phosphatidylisositol-4-kinase (PI4K), cytochrome *bc1* (Cyt *bc1*) and Na^+-ATPase 4 are some novel drug targets discovered from the biology of *P. falciparum* [8].

3.4 Indigenous phytomedicine-based reverse pharmacological approach

Reverse Pharmacology deals with the precisely designed preclinical and clinical research of age old herbal medicine used in well documented indigenous system of medicine (*Ayurvedic* medicine, Chinese medicine etc.) with a view of better understanding of the mechanism of action (even at molecular level) followed by the isolation of bioactive molecule(s) and finally the development of lead molecule(s). In fact, the discovery and development of ART (from *A. annua*) and its derivatives are the result of reverse pharmacological approach. Another interesting example is the discovery of antiplasmodial protoberberine type alkaloids allocryptopine and protopine from *A. mexicana*. This approach is considered to be quite reliable and faster technique due to the availability of prior information about therapeutic and toxic properties of the plant species under investigation. However, the discovery of potent lead molecule(s) with desired pharmacological/toxicity profile may sometimes be difficult because herbal medicine/ plant extracts possess therapeutic efficacy due to the synergistic activity of multiple ingredients in the crude mixture [26, 29].

3.5 Drug repurposing approach

Repurposing of existing drugs with new therapeutic indications is also considered as one of the effective alternatives for the discovery of antimalarial drugs. The notable advantage of this approach is that the mechanism of action and toxicity of drugs have already been established in clinical trials for other diseases. Folate antagonists (sulphonamides, sulphones, biguanides, pyrimethamine, triazines, etc.) and several antibacterials/ antibiotics (tetracycline, doxycycline, clindamycin etc.) have been reported to exhibit promising antiplasmodial efficacy against malaria parasites. In recent days, drug repurposing involves the combined efforts of *in silico* and *in vitro* methods to identify new therapeutic uses of existing drug molecules on a rational basis. Using the same strategy, researchers have been working on existing drugs in search for new antimalarial drug candidates. Repurposing of azithromycin, auranofin, loperamide hydrochloride, amlodipine besylate, cyclosporin A, esomeprazole magnesium, omeprazole etc. with antimalarial activity have been reported in literature [30, 31].

3.6 Semi-synthetic modifications or designing of analogues

Novel antimalarial drugs can be developed from the semi-synthetic modification of naturally derived lead molecules and/or by designing of newer synthetic analogues/ derivatives of existing drugs based on the structure-activity relationship (SAR) approach. This approach mainly emphasizes on reducing the toxicity with retaining and/or enhancing the therapeutic efficacy of the basic template structure/ lead molecule. Synthetic quinolines like CQ, AQ, IQ (4-aminoquinolines), PQ (8-aminoquinolines) MQ, HL, LUM (quinoline amino alcohols), piperaquine (PIP, bisquinoline analogue) and PYN (benzonaphthyridine derivative) were developed based upon the structural template of QN. Several chemical strategies were involved in structural

modification of QN or other lead molecules in order to improve the therapeutic efficacy as well as toxicity of the parent molecule. Tebuquine (4-aminoquinoline derivative, a CQ analogue) and tafenoquine (8-aminoquinoline derivative, a derivative of PQ), are two newer drugs developed recently. Ferroquine (4-aminoquinoline derivative, a CQ analogue, Phase II terminated), AQ-13 (4-aminoquinoline analogue, Phase II) are presently under development. Following similar approach, DHA, AM and AS were also developed from ART. Some newer drugs (belonging to different classes) that are under development include DSM265 [Pf dihydrooroate dehydrogenase (DHOH) inhibitor, a triazolopyrimidine-based drug, Phase II], MMV390048 [Pf phosphatidylisositol-4-kinase (PI4K) inhibitor, Phase I] and KAE609 or cipargamin (Na+-ATPase 4 inhibitor) [8, 32–38].

3.7 Combination therapy approach

The concept of combination therapy (CT) is based on the synergistic or additive activity of two or more drugs, which improves therapeutic efficacy and also delays the development of resistance to the individual drugs of the combination. In antimalarial combination therapy, two or more drugs are used together that act with independent mode of action probably at different biochemical targets in the life cycle of *Plasmodium* parasite. WHO recommended combining the rapid schizonticidal ART derivative (DHA, AM or AS) with one or more partner drugs (from different class of antimalarials having longer biological half-lives) for the treatment of resistant *P. falciparum* malaria. Such combined antimalarial drug regimens (for examples, AM + LUM (Co-Artem, fixed dose, AL), AS + MQ (AM), AS + CQ, AS + SP, AS + DOX, AS + DOX + CQ etc.) are known as ACTs. Some ACTs which are in pipeline include AS + PYN, DHA + PIP (Artekin), DHA-PIP- Trimethoprim and DHA + PIP + MQ [8, 25].

3.8 Drug discovery by CADD/SBDD approach

Traditionally, drugs are discovered by testing naturally derived or synthetically obtained compounds in time-consuming multi-step processes against a battery of *in vitro* and *in vivo* screening methods. Compounds having promising therapeutic potential are further investigated for their development as drug candidates after pharmacokinetic, metabolism and toxicity studies. Today's modern drug discovery process involves rational design and development of novel drug molecules based on a particular disease target using modern tools and techniques of virtual and experimental screening techniques. In virtual screening, computational methods screen large chemical libraries targeted towards a specific biological receptor, using advanced high performance computing environments, data management software and internet. It delivers new drug candidates quickly and at lower costs. Virtual screening is an approach of structure-based drug design (SBDD) that uses computer-based (*in silico*) methods to discover and develop new drug molecules on the basis of biological structures of particular disease of interest. SBDD methods mainly focus on the design of molecules for a disease target with known three dimensional structures followed by the determination of their binding affinity for the target by molecular docking along with other *in silico* screening methods (ADMET and toxicity screening) for optimization of molecules during development. The process of SBDD proceeds through design and development of a series of consecutive steps from hit identification to lead optimization followed by preclinical and clinical development of drug candidates [38, 39]. Antimalarial drug

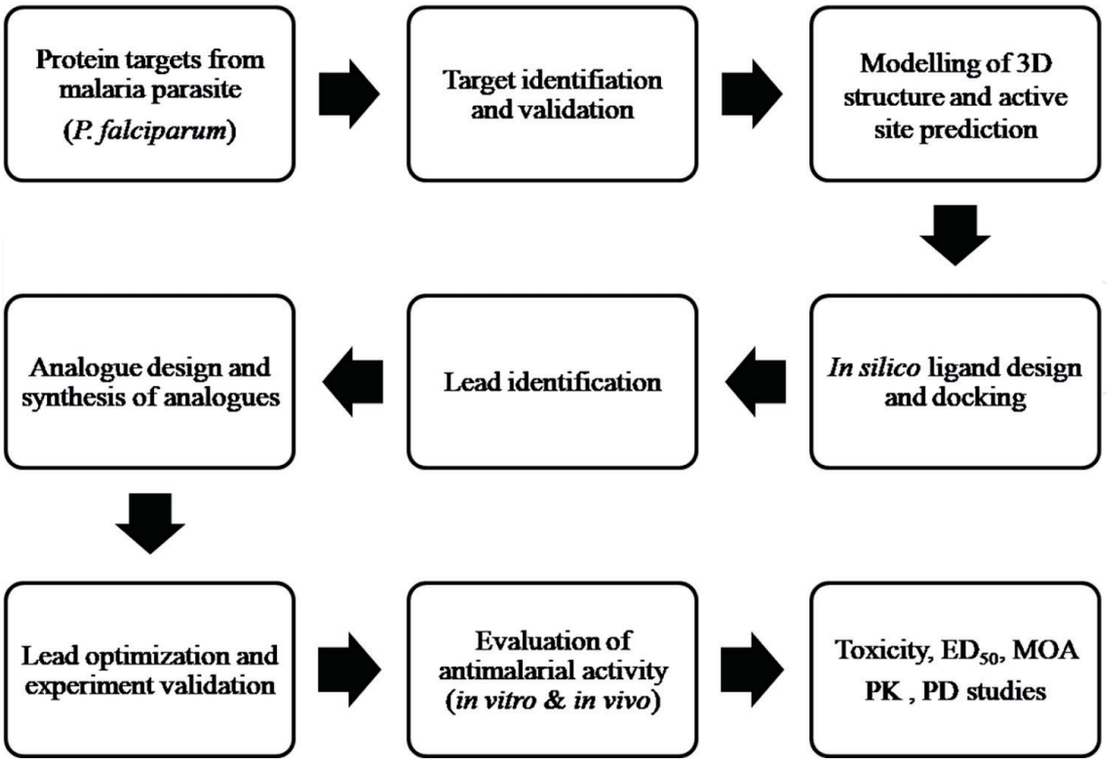

Figure 5.
Antimalarial drug discovery based on SBDD approach.

discovery based on SBDD approach involves the application of modern tools of molecular modelling and other *in silico* techniques in the development of novel antimalarial drug candidates (**Figure 5**).

4. Phytomedicines and antimalarial lead molecules: recent developments

Phytomedicines (i.e., plant-based/ herbal traditional medicine systems) served as potential sources of lead molecules for the development of several clinically useful antimalarial drug candidates. For example, QN isolated from *Cinchona* bark was used as a template for the development of CQ and MQ. ART isolated from *Artemisia annua* has been utilized for the successful development of various semi-synthetic derivatives (DHA, AM and AS) which are currently used in the treatment of CQ-resistant *P. falciparum* malaria [40, 41]. Apart from QN and ART, some examples of antimalarial natural products that were developed from plants include yingzhausu A, febrifugine, sergeolide, chaparrin, glaucarubin, tehranholide and brusatol [42].

During the last few decades, a large number of plant species have been identified to be effective as antimalarial agents. Pure phytochemicals isolated from these plants have been reported to exhibit antimalarial effectiveness, particularly, against CQ-sensitive and CQ-resistant strains of *P. falciparum*. It is, therefore, imperative that antimalarial phytochemicals reported with promising *in vitro* and *in vivo* activities can be further subjected to preclinical and clinical confirmation for their development as novel antimalarial lead molecules and/ drug candidates. Plant-derived antimalarial compounds belong to several phytochemical classes of natural products such as alkaloids, terpenoids, quassinoids, limonoids, Polyphenols and flavonoids, coumarins, steroids, anthraquinones, naphthoquinones etc.

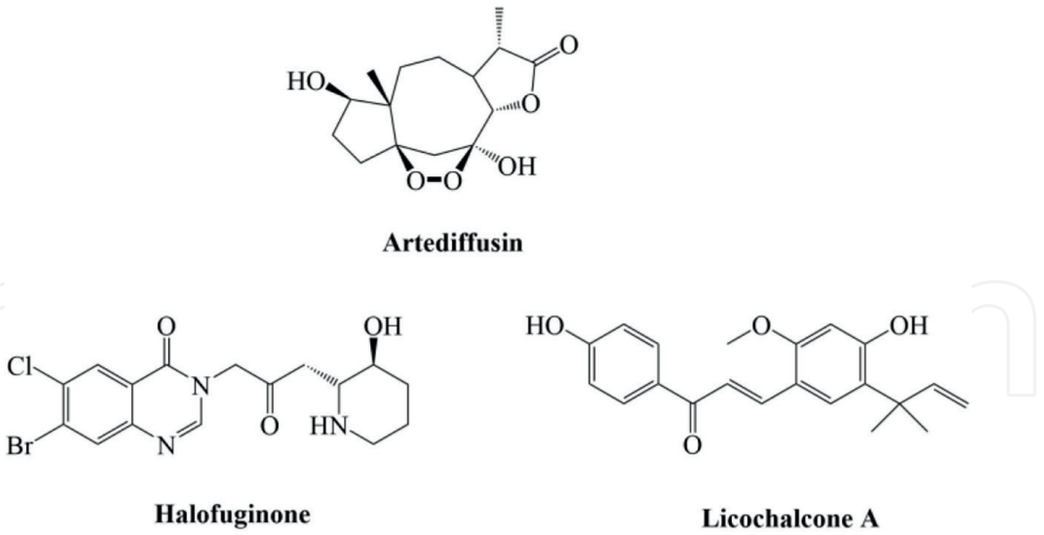

Figure 6.
Structures of some recently developed plant-derived antimalarial compounds.

Terhanolide (artediffusin), a sequiterpene lactone isolated from *A. diffusa* exhibited antimalarial efficacy against *P. falciparum* (*in vitro*) and *P. berghei* (*in vivo*) [43]. Halofuginone, an analogue of febrifugine (an alkaloid originally isolated from the plant *Dichroa febrifuga*) exhibited antiplasmodial effects against CQ-sensitive and CQ-resistant *P. falciparum (in vitro*) with curative effects in *P. berghei*-infected mice [44]. Sergeolide, a quassinoid from *Picrolemma pseudocoffa* showed antimalarial activities *in vitro* against *P. falciparum* and *in vivo* against *P. berghei* in mice [45]. Further, the antimalarial property licochalcone A (oxygenated chalcone) obtained from Chinese licorice has been reported to exhibit antimalarial activity against CQ-sensitive and CQ-resistant *Plasmodium* strain. Lichochalcone-A was the first natural

Name of specific phytochemical(s)	**Type of compound(s)**	**Plant source (Family)**	**Antimalarial/ Antiplasmodial activity**
Alkaloids			
Strychnogucine B Strychnobaillonine	Bisindole alkaloid	*Strychnos icaja* Baill. (Loganiaceae)	*In vivo* antimalarial activity (30 mg/kg/d dose) against *P. berghei* in murine model Potent *in vitro* antimalarial activity against CQ-sensitive 3D7 strain of *P. falciparum* with IC_{50} value of 1.1 μM
Lycorine	Indolizidine alkaloid	Plants from Amaryllidaceae family	*In vitro* antimalarial activity with IC_{50} value of 0.029 μg/mL against FCR-3 African strain of *P. falciparum*
Caesalminines A & B	Tetracyclic cassane-type diterpenoids alkaloids	*Caesalpinia minax* Hance (fabaceae)	Antiplasmodial activity with IC_{50} values between 0.42 and 0.79 μM

Name of specific phytochemical(s)	**Type of compound(s)**	**Plant source (Family)**	**Antimalarial/ Antiplasmodial activity**
8α-Polyeolinone, polyalthenol, *N*-acetyl-8α-polyeolinone and *N*-acetyl-polyveoine	Indolosesquiterpene alkaloid	*Polyalthia oliveri Pellegr. (Annonaceae) Polyalthia suaveolens* Engl. & Diels. (Annonaceae) (syn.*Greenwayodendron suaveolens* Engl. & Diels. Verdc. (Annonaceae)	Antiplasmodial activity against NF54 strain of *P. falciparum* with IC_{50} of 2.8 μM
Strychnochrysine	Bisindolomonoterpenoid alkaloid	Strychnos nux-vomica Linn. (Loganiaceae)	Antiplasmodial activity against CQ-sensitive and CQ-resistant strains of *P. falcipaum*
Conessine	Steroidal alkaloid	*Holarrhena antidysenterica* (L.) Wall. Ex A. DC. (Apocynaceae)	Antimalarial activity against CQ-sensitive *P. berghei* NK65 strain in BALB/c mice
Conessine	Steroidal alkaloid	*Holarrhena antidysenterica* (L.) Wall. Ex A. DC. (Apocynaceae)	IC_{50} values of 1.9 μg/ml and 1.3 μg/ml in the schizont maturation and pLDH assays,
Mokluangin D irehline and mokluangin A	Pregnene-type alkaloid	*Holarrhena pubescens* (Buch.-Ham.) Wall. Ex G. Don. (Apocynaceae)	Antimalarial activity against MDR *P. falciparum* K1 strain with IC_{50} values between 1.2 and 2.0 μM
N-3-benzoyldihydrocyclomicrophylline F	Steroidal alkaloid	*Buxus cochinchinensis* Pierre ex Gagnep. (Buxaceae)	Antimalarial activity against DR Dd2 strain of *P. falciparum* with IC_{50} value of 2.07 μM
Alstonisine	Indole alkaloid	*Alstonia macrophylla* Wall. ex G.Don (Apocynaceae)	Antiplasmodial activity against *P. falciparum* with IC_{50} value of 7.6 μM
20-Epi-dasycarpidone	Indole alkaloid	*Aspidosperma ulei* Markgr. (Apocynaceae).	Active against MDR K1 strain of *P. falciparum* with IC_{50} value of 16.7 μM
16-demethoxycarbonylvoacamine	Sarpagine-type indole alkaloids	*Tabernaemontana macrocarpa* Jack. (Apocynaceae)	Antiplasmodial activity against 3D7 strain of *P. falciparum*
Dehydrotylophorine, dehydroantofine and tylophoridicine D	Phenanthroindolizine alkaloids	*Ficus septica* Burm.f. (Moraceae)	Antimalarial activity against 3D7 strain of *P. falciparum* with IC_{50} values of 0.42, 0.028, 0.058 μM
10-Demethylxylopinine	Isoquinoline alkaloids	*Actinodaphne macrophylla* (Blume)Nees (Lauraceae)	*In vitro* antiplasmodial activity against 3D7 strain of *P. falciparum*
(+)-*N*-methylisococlaurine, atherosperminine, 2-hydroxyathersperminine	Isoquinoline	*Cryptocarya nigra* R.Br. (Lauraceae)	Antiplasmodial activity against CQ-resistant strain of *P. falciparum* (K1 strain) with IC_{50} values of 5.40, 5.80, and 0.75 μM

Name of specific phytochemical(s)	**Type of compound(s)**	**Plant source (Family)**	**Antimalarial/ Antiplasmodial activity**
Dihydronitidine	dihydronitidine	*Zanthoxylum heitzii* (Aubrey. & Pellegr.) P.G. Waterm. (Rutaceae)	Potent against *P. falciparum* with IC_{50} value of 25 nM
(−)-Pseudocurine	Bisbenzylisoquinoline	*Stephania abyssinica* Oliv. (Menispermaceae)	Antiplasmodial activity against both CQ-susceptible D6 and CQ-resistant W2 strains of *P. falciparum* (IC_{50} = 0.29±0.00 and 0.31±0.01 μg/ml, respectively)
(+)-laurotetanine, (+)-norstephasubine	Bisbenzylisoquinoline	*Alseodaphne corneri* Kosterm. (Lauraceae)	*In vitro* antiplasmodial efficacy with IC_{50} values of 0.189 and 0.116 μM
Dioncophylline F	Naphthylisoquinoline alkaloid	*Ancistrocladus ileboensis* Heubl, Mudogo & G. Bringmann. (Ancistrocladaceae)	Highly effective and specifically active against *P. falciparum*
Pseudopalmatine Obtusipetadione Anonaine Tavoyanine A, roemerine, Laurolitsine and boldine	Aporphine alkaloid	*Stephania rotunda* Lour. (Menispermaceae) *Dasymaschalon obtusipetalum* Jing Wang & R.M.K. Saunders. (Annonaceae) *Xylopia sericea* A.St.-Hil. (Annonaceae) *Phoebe tavoyana* (Meissn.) Hook f. (Lauraceae)	Effective against W2 strain of *P. falciparum* with IC_{50} value of 2.8 μM *In vitro* antiplasmodial activity against MDR *P. falciparum* strains (TM4 and K1) with IC_{50} values of 2.46 ± 0.12 and 1.38 ± 0.99 μg/mL Antiplasmodial activity against CQ-resistant W2 strain of *P. falciparum* With IC_{50} value of 23.2 ± 2.7 μg/ml Potent inhibitory activity against 3D7 strain of *P. falciparum* 3D7 with IC_{50} values of 0.89, 1.49 and 1.65 μg/ml
Sebiferine	Morphinandienone type alkaloid	*Phoebe tavoyana* (Meissn.) Hook f. (Lauraceae)	Potent inhibitoryactivity against the growth of *P. falciparum* 3D7 clone, with IC_{50} values of 2.76 μg/ml
Simplicifolianine	Protoberberine	*Meconopsis simplicifolia* (D. Don) Walpers (Papaveraceae)	Antiplasmodial activity against *P. falciparum* strains, TM4/8.2 (CQ-antifolate-sensitive strain) and K1CB1 (MDR) with IC_{50} values of 0.78 μg/mL and 1.29 μg/mL, respectively
Coptisine	Protoberberine-type alkaloid	*Coptis chinesis* Franch. (Ranunculaceae)	Potent inhibitory activity against *P. falciparum* dihydroorotate dehydrogenase (Pf DHODH) with IC_{50} value of 1.83 ± 0.08 μM

Name of specific phytochemical(s)	**Type of compound(s)**	**Plant source (Family)**	**Antimalarial/ Antiplasmodial activity**
Miliusacunines A	Oxoprotoberberine	*Miliusa cuneata* (Graib). (Annonaceae)	*In vitro* antimalarial activity against TM4 strain of *P. falciparum* with IC_{50} value of 19.3 ± 3.4 μM
Hymenocardine *N*-oxide	Cyclopeptide alkaloids	*Hymenocardia acida* Tul. (Phyllanthaceae)	Antiplasmodial activity against *P. falciparum* with IC_{50} value of 12.2 ± 6.6 μM
Microthecaline A	Quinoline alkaloid	*Eremophila microtheca* F.Muell. (Scrophulariaceae)	Moderate antimalarial activity against *P. falciparum* (3D7 strain) with IC_{50} value of 7.7 *μM*
Sauristolactam	Pyridocoumarin alkaloid	*Goniothalamus australis* Jessup. (Annonaceae)	Potent antimalarila activity against CQ-sensitive *P. falciparum* (3D7 strain) with IC_{50} value of 9.0 μM
Normelicopidine	*Acridone Alkaloid*	*Zanthoxylum simullans* Hance (Rutaceae)	Active against drug resistant Dd2 strain of *P. falciparum* with IC_{50} value of 18.9 ug/mL
Carpaine	Macrocyclic dilactone	*Carica papaya* L. (Caricaeae)	Potent antimalarial activity activity against 3D7 (sensitive) and Dd2 (resistant) strains of *P. falciparum* with IC_{50} values of 4.21 μM and 4.57 μM, respectively
Palmitine and jatrorrhizine	Indole alkaloid	*Penianthus longifolius* Miers. (Menispermaceae)	In vitro antimalarial activity against *P. falciparum* with IC_{50} values ranging from 0.28 to 0.35 μg mL^{-1}
Liriodenine	Indole alkaloid	*Glossocalyx brevipes* Benth. (Siparunaceae)	Antimalarial activity against drug sensitive D-6 strain and NF54 strains of *P. falciparum* with IC_{50} values of 2.37 μM and 1.32 μM, respectively
Fagaronine	Indole alkaloid	*Fagara zanthoxyloides* (Lam). (Rutaceae)	Antimalarial activity *in vitro* against *P. falciparum* with IC_{50} value of 0.018 μg mL^{-1}
Strychnopentamine chrysopentamine	Indole alkaloid	*Strychnos usambarensis* Glig ex Engl. (Loganiaceae)	Antimalarial activity against CQ-sensitive (FCA 20) (IC_{50} = 117 to 579 nM), moderately CQ-resistant (FCB1-R) (IC_{50} = 107–550 nM) and CQ-resistant (W2) (IC_{50} = 145–507 nM) strains of *P. falciparum*

Name of specific phytochemical(s)	**Type of compound(s)**	**Plant source (Family)**	**Antimalarial/ Antiplasmodial activity**
Ancistrobrevine; Ancistrobertsonine A, Ancistrobertsonine B, Ancistrobertsonine C, Ancistrobertsonine D	Naphthoisoquinolines	*Ancistrocladus robertsoniorum* J. Leonard. (Ancistrocladace)	Moderate antimalarial activity against K-1 and NF54 strains of *P. falciparum* (IC_{50} values ranges from 2.0 to 15.9 μM)
Habropetaline A, 5′-Odemethyl-dioncohylline A	Naphthoisoquinolines	*Triphyophyllum peltatum* (Hutch. & Dalz.) Airy Shaw (Dioncophyllaceae)	Antiplasmodial activities against K1 (CQ and pyrimethamine resistant) and NF54 (sensitive to all known drugs) strains of *P. falciparum* with IC_{50} values of 5.0 and 2.3 ng mL^{-1}, respectively
Nitidine	Furoquinolines alkaloid	*Toddalia asiatica* (L.) Lam. (Rutaceae)	*In vitro* antiplasmodial activity against K39 strain of *P. falciparum* with IC_{50} value of 0.045 μg mL^{-1}
β-hydroxydihydrochalcone Deguelin, obovatin	Flavonoids	*Tephrosia elata* Deflers . (Fabaceae)	Antiplasmodial activity against D6 and W2 strains of *P. falciparum* with IC_{50} values of 8.2 ± 0.8 and 16.3 ± 0.9 μM, respectively Antimalarial activity against D6 and W2 strains of *P. falciparum* with IC_{50} values ranging from 12.4 to 27.6 μM
Chrobisiamone A	Bischromone	*Cassia siamea* (Lam). (Fabaceae)	*In vitro* antiplasmodial activity against 3D7 strain of *P. falciparum* 3D7 (IC_{50} = 5.6 μM)
Series of twelve biflavonoids (amentoflavone and hinokiflavone derivatives)	Flavonoids	*Selaginella bryopteris* L. (Selaginellaceae)	Antiplasmodial activity against *P. falciparum* strains with IC_{50} value between 0.30 and 0.26 μM
Citflavanone lonchocarpol A 8-prenyldaidzein	Flavonoids	*Erythrina fusca* Lour. (Fabaceae)	*In vitro* antiplasmodial activity against *P. falciparum* at 12.5 μg/mL
Butyraxanthones A-D	Xanthone	*Pentadesma butyracea* Sabine (Clusiaceae)	Antiplasmodial activity against *P. falciparum* with IC_{50} values ranging from 4.4 to 8.0 μM

Name of specific phytochemical(s)	**Type of compound(s)**	**Plant source (Family)**	**Antimalarial/ Antiplasmodial activity**
Kaempferol	Flavonols	Onions, kale, broccoli, apples, cherries, fennel, sorrel, berries, tea	*In vitro* antiplasmodial activity against *P. falciparum* with IC_{50} values 33 ± 7 μM(3D7 strain) and 25 ± 2 μM (7G8 strain)
Myricetin	Flavonols	Onions, kale, broccoli, apples, cherries, fennel, sorrel, berries, tea	*In vitro* antiplasmodial activity against *P. falciparum* with IC_{50} values 40 ± 10 μM (3D7) and 76 ± 2 μM (7G8)
Quercetin	Flavonols	Onions, kale, broccoli, apples, cherries, fennel, sorrel, berries, tea	*In vitro* antiplasmodial activity against *P. falciparum* with IC_{50} values 15± 5μM μM (3D7) and 14 ± 1 μM (7G8)
Isoquercitrin	Flavonols	Onions, kale, broccoli, apples, cherries, fennel, sorrel, berries, tea	*In vitro* antiplasmodial activity against *P. falciparum* with IC_{50} values 66± 10μM (3D7) and 66± 10μM (7G8)
Luteolin	Flavones	Parsley, thyme, celery, sweet red pepper	*In vitro* antiplasmodial activity against *P. falciparum* with IC_{50} values 11± 1μM (3D7) and 12 ± 1 μM (7G8)
Chrysin	Flavones	Parsley, thyme, celery, sweet red pepper	*In vitro* antiplasmodial activity against *P. falciparum* with IC_{50} values 18± 3μM (3D7) and 22 ± 4 μM (7G8)
Okundoperoxide	bicyclofarnesyl sesquiterpene endoperoxide	*Scleria striatinux* de Wild (syn. *S. striatonux*) (Cyperaceae)	Antiplasmodial activity against CQ-sensitive (D6) and CQ-resistant (W2) strains of *P. falciparum* with IC_{50} values ranging from 176 to 180 μM
Fagraldehyde	Secoiridoid aglycone	*Fagraea fragrans* (Roxb.) DC. (Gentianaceae)	Effective *in vitro* against *P. falciparum*, exhibiting an IC_{50} value of 116.6 ± 9.4 μM (W2 strain)
6α,7β-Diacetoxyvouacapane	Diterpene	*Bowdichia nitida* Benth. (Fabaceae)	*In vitro* antiplasmodial activity against 3D7 strain of *P. falciparum* (IC_{50} = 1 μM)

Name of specific phytochemical(s)	Type of compound(s)	Plant source (Family)	Antimalarial/ Antiplasmodial activity
Geraniol	Monoterpene	Pure isolated compound	Antiplasmodial activities against CQ-resistant FcM29-Cameroon strain of *P. falciparum* (IC_{50} = 52 μM)
Limonene	Monoterpene	Pure isolated compound	IC50 = 66 μ Mantiplasmodial activities against the chloroquine-resistant FcM29-Cameroon strain of *P. falciparum*
Ineupatorolide A	Sesquiterpene lactone	*Carpesium rosulatum* (Asteraceae)	*In vitro* antiplasmodial activity against CQ-resistant D10 strain of *P. falciparum* (IC_{50} = 0.019 μM) *In vivo* antimalarial activity against *P. berghei* in mice at doses of 2, 5 and 10 $mg.kg^{-1}{\cdot}day^{-1}$

Table 1.
Phytomedicines as potential sources of antimalarial compounds [41, 47, 48, 52–58].

derivative of chalcones with antimalarial effectiveness against CQ-resistant strain of *P. falciparum* [43]. **Figure 6** displays structures of some recently developed plant-derived antimalarial compounds.

Herein, phytomedicine-derived antimalarial compounds are categorized into two broad groups, viz. alkaloids and non-alkaloids [46]. Different alkaloids such as indoles, bisindols, isoquinolines (naphthyl and benzyl), piperidines, pyrroles, quinolones, steroidal alkaloids have been reported to possess antimalarial effectiveness. Polyphenolic compounds and bioflavonoids including dietary flavonoids such as kaempferol, myricetin, quercetin and isoquercitrin possess *in vitro* antimalarial activities. Different terpenenoids (farnesol, nerolidol, limonene, and linalool), quassinoids, coumarins and limonoids also exhibited antiplasmodial activity when tested *in vitro* against *P. falciparum* strains [47, 48]. Semi-synthetic triterpenes such as balsaminoside B, karavilagenin C, *S*-farnesylthiosalicylic acid, and karavoates B and D have been reported to exhibit *in vitro* and *in vivo* antimalarial activity [49–51]. **Table 1** describes phytomedicines as potential sources of novel antimalarial compounds.

5. Challenges in antimalarial drug discovery

There are several challenges that exist in the domain of antimalarial drug discovery from plant sources. Some major challenges are low natural abundance of phytoconstituents, difficulty in isolation of the specific active compound in pure form, safety/toxicity and ADMET/pharmacokinetics issues, and high cost of production. Due to synergistic nature of crude plant extracts, it is also difficult to select the specific phytochemical responsible for the antimalarial action for isolation. Other issues include limited oral bioavailability and target specificity of natural molecules isolated

from plants [59, 60]. Natural products with high degree of structural complexity and chemical instability are the other notable hindrances in the drug discovery pipeline of antimalarial drugs from plants. *In vitro* screening using parasitic cell cultures is a tedious work protocol which requires an expensive experimental set up and skilled laboratory personnel for the successful evaluation of antiparasitic activity. Similarly, the *in vitro* toxicity evaluation on normal cell lines requires extensive efforts, skills and labours. Compounds having high *in vitro* efficacy ($IC_{50} \leq 1\mu M$) and sufficient oral bioavailability can be considered for further *in vivo* testing. Compounds with ED_{90} values of less than 10 mg/kg per os in *in vivo* murine model is essential for further development [12, 17]. An important challenge is the lacking of efficacy in preclinical trials after the successful *in vitro* and *in vivo* studies. Further, development of semi-synthetic derivatives from the natural lead(s) is a challenging task in context of designing scheme of synthesis, synthetic modification, purification of compounds and finally chemical characterization of pure compounds. High-throughput experimental assays eliminate potent antimalarial compounds due to toxicity issues and lack of pharmacokinetic properties [42]. Another challenge is the geochemical and climatic variation of plants. One more important challenge is that since no molecular mechanism and target specificity is known, it is very difficult to choose the *in vitro* or *in vivo* models for preliminary screening, and final confirmation of antimalarial efficacy with the exploration of mode(s) of action [59, 60]. Recently, *in silico* techniques based discovery of antimalarial drugs could reduce the chances of failure in the discovery pipeline. However, newer assays and target based approaches are required to be developed for discovery of newer congeners/ derivatives of naturally occurring potent molecules with desired antimalarial potency and less toxicity.

6. Conclusion

Re-emergence of resistance of existing drugs against *P. falciparum*, toxicity and unsatisfactory pharmacokinetics and less cost-effectiveness and poor patient compliance, particularly in South-east Asian and African regions are some major concerns in the malaria control and prevention programme worldwide. Although QN- and ART-based existing drugs/ therapies are considered as gold standards in malaria chemotherapy, the clinical utility of these drugs is challenging. Potent antimalarial compounds derived from phytomedicines could serve as potential sources of future antimalarial leads/ agents after a plethora of drug development (pre-clinical and clinical studies) processes. Target-based discovery of bioactive phytochemical entities is required for their successful development as effective and safe antimalarial drug molecules.

Conflict of interest

Authors declare that there is no conflict of interest.

Author details

Mithun Rudrapal[1*], Dipak Chetia[2] and Soumya Bhattacharya[3]

1 Rasiklal M. Dhariwal Institute of Pharmaceutical Education and Research, Pune, Maharashtra, India

2 Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India

3 Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata, India

*Address all correspondence to: rsmrpal@gmail.com

IntechOpen

References

[1] Communicable Diseases (CDS) ((World Health Organization). Available from URL: https://www.who.int/about/structure/organigram/htm/en/ [Accessed: 18 February 2021]

[2] McArthur DB. Emerging infectious diseases. The Nursing Clinics of North America. 2019;**54**(2):297-311

[3] World Malaria Report 2020 (World Health Organization). Available from URL: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2020 [Accessed: 15 February 2021]

[4] Kalita J, Chetia D, Rudrapal M. Design, synthesis, antimalarial activity and docking study of 7-Chloro-4-(2-(substituted benzylidene)hydrazineyl) quinolines. Medicinal Chemistry. 2020;**16**(7):928-937

[5] Rudrapal M, Khairnar SJ, Borse LB, Jadhav AG. Coronavirus disease-2019 (COVID-19): An updated review. Drug Reseaarch. 2020;**70**:389-400

[6] Rudrapal M, Banu ZW, Chetia D. Newer series of trioxane derivatives as potent antimalarial agents. Medicinal Chemistry Research. 2018;**27**(2):653-668

[7] Rudrapal M, Chetia D, Singh V. Novel series of 1,2,4-trioxane derivatives as antimalarial agents. Journal of Enzyme Inhibition and Medicinal Chemistry. 2017;**32**(1):1159-1173

[8] Rudrapal M, Chetia D. Endoperoxide antimalarials: Development, structural diversity and pharmacodynamic aspects with reference to 1,2,4-trioxane-based structural scaffold. Drug Design Devlopmental Therapy. 2016;**10**:3575-3590

[9] Kalita J, Chetia D, Rudrapal M. Molecular docking, drug-likeness studies and ADMET prediction of quinoline imines for antimalarial activity. Journal of Medical and Chemical Drugs Design. 2019;**2**(1):1-7

[10] Medhi A. Synthesis and antimalarial activity of lawsone mannich base derivatives. Indian Journal of Pharmaceutical Education and Research. 2018;**52**(3):472-479

[11] Patowary P, Chetia D, Kalita J, Rudrapal M. Design, synthesis and antimalarial activity of flavonoid derivatives. Indian Journal of Heterocyclic Chemistry. 2019;**29**(1):53-58

[12] Rudrapal M, Chetia D. *In vitro* and *in vivo* models used for antimalarial activity: A brief review. Asian Journal of Pharmaceutical and Pharmacology. 2019;**5**(6):1251-1255

[13] Biamonte MA, Wanner J, Le Roch KG. Recent advances in malaria drug discovery. Bioorganic & Medicinal Chemistry Letters. 2013;**23**:2829-2843

[14] Rudrapal M, Chetia D. Malaria: Chemotherapy and Development of Novel Antimalarial Agents. Germany: LAP LAMBERT Academic Publishing; 2014

[15] Bhagavathula AS, Elnour AH, Shehab A. Alternatives to currently used antimalarial drugs: In search of a magic bullet. Infectious Diseases of Poverty. 2016;**5**:103

[16] Robert A, Benoit-Vical F, Dechy-Cabaret O, Meunier B. From classical antimalarial drugs to new compounds based on the mechanism of action of artemisinin. Pure and Applied Chemistry. 2001;**73**:1173-1180

[17] Meshnick SR, Dobson MJ. History of antimalarial drugs. In: Rosenthal PJ, editor. Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery. New Jersey: Humana Press; 2001. pp. 2-25

[18] Rudrapal M, Chetia D. Novel 4-aminoquinoline analogues as antimalarial agents: A review. Der Pharmacia Letter. 2011;**3**(3):29-36

[19] Rudrapal M. A brief review on malaria and current antimalarial drugs. Current Pharmaceutical Research. 2011;**1**(3):286-292

[20] Dinio T, Gorka AP, McGinniss A, Roepe PD, Morgan JB. Investigating the activity of quinine analogues versus chloroquine resistant *Plasmodium falciparum*. Bioorganic & Medicinal Chemistry. 2012;**20**:3292-3297

[21] Bray PG, Ward SA, O'Neill PM. Quinolines and artemisinin: Chemistry, biology and history. Current Topics in Microbiology and Immunology. 2005;**295**:3-38

[22] Luo XD, Shen CC. The chemistry, pharmacology, and clinical applications of Qinghaosu (Artemisinin) and its derivatives. Medicinal Research Reviews. 1987;**7**:29-52

[23] Balint GA. Artemisinin and its derivatives: An important new class of antimalarial agents. Pharmacology & Therapeutics. 2001;**90**:261-265

[24] Meshnick SR. Artemisinin: Mechanisms of action, resistance and toxicity. International Journal for Parasitology. 2002;**32**:1655-1660

[25] Garner P, Graves PM. The benefits of artemisinin combination therapy for malaria extend beyond the individual patient. PLoS Medicine. 2005;**2**:e105

[26] Borstnik K, Paik IH, Shapiro TA, PosnerGH. Antimalarialchemotherapeutic peroxides: Artemisinin, yingzhaosu A and related compounds. International Journal for Parasitology. 2002;**32**(4):1661-1667

[27] Liu C. Discovery and development of artemisinin and related compounds. China Herbal Medicine. 2017;**9**:101-114

[28] Achan J et al. Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. Malaria Journal. 2011;**10**:144

[29] Rosenthal PJ. Antimalarial drug discovery: Old and new approaches. The Journal of Experimental Biology. 2003;**206**:3735-3744

[30] Flannery EL, Chatterjee AK, Winzeler EA. Antimalarial drug discovery-approaches and progress towards new medicines. Nature Reviews. Microbiology. 2013;**11**:849-862

[31] Rudrapal M, Khairnar SJ. Drug repurposing: An emerging approach in drug discovery. In: Dekebo A, editor. Drug Repurposing: Hypothesis, Molecular Aspects and Therapeutic Applications. London: IntechOpen; 2020, 2020

[32] Roy S, Chetia D, Rudrapal M, Prakash A. Synthesis and antimalarial activity study of some new Mannich bases of 7-Chloro-4-Aminoquinoline. Medicinal Chemistry. 2013;**9**(3):379-383

[33] Rudrapal M, Chetia D, Prakash A. Synthesis, antimalarial and antibacterial activity evaluation of some new 4-aminoquinoline derivatives. Medicinal Chemistry Research. 2013;**22**:3703-3711

[34] Sharma D, Chetia D, Rudrapal M. Design, synthesis and antimalarial activity of new 2-hydroxy-1,4-naphthoquinone-4-hydroxyanilino

hybrid Mannich bases. Asian Journal of Chemistry. 2016;**28**(4):782-788

[35] Gogoi J, Chetia D, Kumawat MK, Rudrapal M. Synthesis and antimalarial activity evaluation of some mannich bases of tetraoxane-phenol conjugate. Indian Journal of Pharmaceutical Education and Research. 2016;**50**(4):591-597

[36] Kashyap A, Chetia D, Rudrapal M. Synthesis, antimalarial activity evaluation and drug-likeness study of some new Quinoline-Lawsone hybrids. Indian Journal of Pharmaceutical Sciences. 2016;**78**(6):892-911

[37] Rudrapal M, Chetia D. QSAR analysis of 7-chloro-4-aminoquinoline derivatives as antimalarial agents. Asian Journal of Organic Medical Chemistry. 2013;**1**:51-54

[38] Bhagat S, Gahlawat A, Bharatnam PV. Structure-based drug design PfDHODH inhibitors as antimalarial agents. In: Mohan C, editor. Structural Biinformatics: Applications in Preclinical Drug Discovery Process. Challenges and Advances in Computational Chemistry and Physics. Cham: Springer; 2019

[39] Rudrapal M, Chetia D. Virtual screening, molecular docking and f QSAR studies in drug discovery and development programme. Journal of Drug Delivery Therapy. 2020;**1094**:225-233

[40] Ashley EA, Phyo AP. Drugs in development for malaria. Drugs. 2018;**78**:861-879

[41] Rudrapal M, Chetia D. Plant flavonoids as potential source of future antimalarial leads. Systematic Review in Pharmacology. 2017;**8**:13-18

[42] Mojab F. Antimalarial natural products: A review. Avicenna Journal of Phytomedicine. 2011;**2**:52-62

[43] Mishra LC, Bhattacharya A, Bhasin VK. Phytochemical licochalcone A enhances antimalarial activity of artemisinin in vitro. Acta Tropical. 2009;**109**:194-198

[44] Pines M, Spector I. Halofuginone-The multifaceted molecule. Molecules. 2015;**20**(1):573-594

[45] Fandeur T, Moretti C, Polonsky J. *In vitro* and *in vivo* assessment of the antiomalarial activity of sergeolide. Planta Medica. 1985;**51**:20-23

[46] Oliveira BA, Dolabela MF, Braga FC, Jácome RLRP, Varotti FP, Póvoa MM. Plant-derived antimalarial agents: New leads and efficient phythomedicines. Part I. Alkaloids. Anais da Academia Brasileira de Ciencias. 2009;**81**:715-740

[47] Amoa Ntie-Kang F, Lifongo LL, Ndom JC, Sippl W, Mbaze LM. The potential of anti-malarial compounds derived from African medicinal plants, part I: A pharmacological evaluation of alkaloids and terpenoids. Malaria Journal. 2013;**12**:449

[48] Batista R, Silva Ade J Jr, de Oliveira AB. Plant-derived antimalarial agents: New leads and efficient phytomedicines. Part II. Non-alkaloidal natural products. Molecules. 2009;**14**:3037-3072

[49] Tse EG, Korsik M, Todd MH. The past, present and future of anti-malarial medicines. Malaria Journal. 2019;**18**:93

[50] Tajuddeen N, Van Heerden FR. Antiplasmodial natural products: An update. Malaria Journal. 2019;**18**:404

[51] Pawar HA. Natural product as a source of lead to the design of new drugs. Natural Products in Chemical Research. 2014;**2**:156

[52] Rustaiyan A, Nahrevanian H. An investigation on Anti-malarial Effects of Tehranolide Isolated from Artemisia diffusa against Human Malaria Parasite *Plasmodium falciparum in vitro*. Research Journal of Parasitology. 2015;**10**(2):73-78

[53] Beaufay C, Ledoux A, Jansen O, Bordignon A, Zhao S, Teijaro CN, et al. *In vivo* antimalarial and antitrypanosomal activity of Strychnogucine B, a Bisindole Alkaloid from *Strychnos icaja*. Planta Medica. 2018;**84**:881-885

[54] Dua VK, Verma G, Singh B, Rajan A, Bagai U, Agarwal DD, et al. Anti-malarial property of steroidal alkaloid conessine isolated from the bark of *Holarrhena antidysenterica*. Malaria Journal. 2013;**12**:194

[55] Nair JJ, van Staden J. Antiplasmodial lycorane alkaloid principles of the plant family amaryllidaceae. Planta Medica. 2019;**85**(8):637-647

[56] Qidwai T, Jamal F, Khan MY, Sharma B. Exploring drug targets in isoprenoid biosynthetic pathway for *Plasmodium falciparum*. Biochemistry Research International. 2014;**2014**:657189

[57] GabrielHB,SussmannRAC,KimuraEA, Rodriguez AAM, Verdaguer IB, Leite GCF. Terpenes as potential antimalarial drugs. In: Perveen S, Al-Taweel A, editors. Terpenes and Terpenoids. London: IntechOpen; 2018

[58] Lehane AM, Saliba KJ. Common dietary flavonoids inhibit the growth of the intraerythrocytic malaria parasite. BMC Research Notes. 2008;**1**:26

[59] Burrows JN, Leroy D, Lotharius J, Waterson D. Challenges in antimalarial drug discovery. Future Medicinal Chemistry. 2011:31401-31412

[60] Uzor PF. Alkaloids from plants with antimalarial activity: A review of recent studies. Evidence-based Complementary and Alternative Medicine. 2020;**2020**:8749083