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Naturally occurring phenylethanoids and phenylpropanoids: antimalarial potential†

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Malaria as an infectious disease is one of the world's most dangerous parasitic diseases. There is an urgent need for the development of new antimalarial drugs. Natural products are a very rich source of new bioactive compounds. Our research aims to shed light on the recent studies which demonstrated the antimalarial potential of phenylpropanoids as a major natural-products class. This study involves an *in silico* analysis of naturally-occurring phenylpropanoids and phenylethanoids which showed 25 compounds with moderate to strong binding affinity to various amino acid residues lining the active site; *P. falciparum* kinase (PfPK5), *P. falciparum* cytochrome bc1 complex (cyt bc1), and *P. falciparum* lysyl-tRNA synthetase (PfKRS1); of *Plasmodium falciparum* parasite, a unicellular protozoan which causes the most severe and life-threatening malaria. Furthermore, the study was augmented by the assessment of antiplasmodial activity of glandularin, a naturally occurring dibenzylbutyrolactolic lignan, against chloroquine-sensitive 3D7 strain of *P. falciparum* using SYBR green I-based fluorescence assay, which showed high antimalarial activity with IC_{50} value of 11.2 μM after 24 hours of incubation. Our results highlight phenylpropanoids and glandularin in particular as a promising chemical lead for development of antimalarial drugs.

Introduction

Vector-borne protozoan illnesses like trypanosomiasis, leishmaniasis, and malaria are well-known public health threats due to their high morbidity and mortality rates. They are widely distributed in tropical regions where the presence of poverty and conditions that are conducive to vectors responsible for the transmission of diseases are found. Numerous strategies have been applied to reduce malaria burden either by vector control or by using vaccines.[1,2]

Quinine (Fig. 1) was the first drug, from natural source, used in treatment of malaria. It was used as the first-choice drug in treatment of malaria for around 100 years, until the emergence of resistant parasites. Later on, quinine was replaced by artemisinin (Fig. 1), isolated from *Artemisia annua*, which has been widely used in Chinese traditional medicine and has proven effectiveness against all multi-drug resistant *P. falciparum* strains. Unfortunately, high failure rates of artemisinin combinations therapy was detected in the Greater Mekong sub-regions in Southeast Asia. This was attributed to the emergence of artemisinin resistance. Recently, independent emergence of artemisinin resistance in East Africa (Rwanda and Uganda) has arisen.[3]

Secondary metabolites (specialized metabolites) are natural compounds with a variety of biological activities and chemical configurations.[4–8] Among which are simple phenolics such as phenylethanoids and phenylpropanoids classed as (C6–C2) and C6–C3 compounds. Additionally, polyphenolics as lignans and neolignans constitute a significant class of secondary metabolites.[9–11] In a more specific context, lignans are phenylpropanoid dimers linked by a C–C-bond between carbons 8 and 8′ in the side chain[12–15] including many subtypes according to the nature and position of the linkage between the phenylpropane units (Fig. 2). Neolignans are a class of lignans that lack the β-β′ (also termed 8-8′) phenylpropane linkage that are characteristic of classical lignans.[16–19]

Different classes of phenylethanoids and phenylpropanoids are spread over various species of higher plants, however according to chemotaxonomy, the specific pattern of substitution

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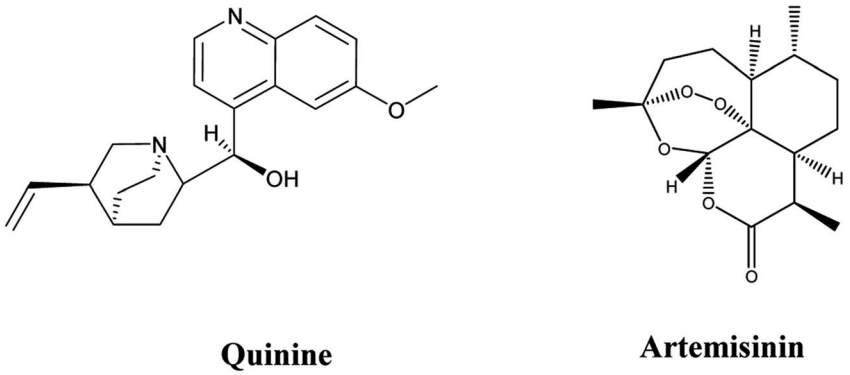

Fig. 1 The antimalarial quinine and artemisinin.

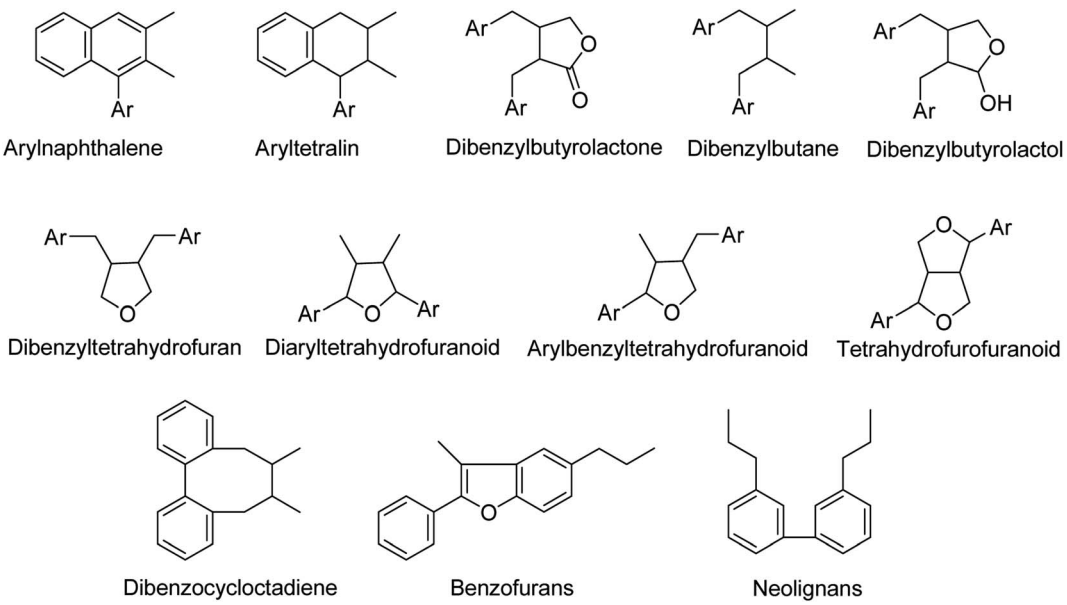

Fig. 2 Structure of different classes of naturally occurring lignans and neolignans.

of these classes may restrict their existence to certain genera and species.[20,21] On the other hand, more than 200 lignans have been chemically and biologically characterized in different organs of about 70 plant families.[19]

Several studies reported that phenylethanoids possess antibacterial, anticancer, antidiabetic, anti-inflammatory, antiobesity, antioxidant, antiviral, and neuroprotective properties.[21] Whereas, plants rich in phenylpropanoids have been reported to be used traditionally for treatment of several skin inflammatory disorders as sores, wound healing purposes, sedative activity, and relief of general body exhaustion.[15,22] Through the last few years, many research studies have revealed their anti-inflammatory, anti-atherosclerosis, anti-platelet-aggregation, antihypertension, antifatigue, analgesic, hepatoprotective and immunostimulant benefits.[23–25] Furthermore, they are known for their potent antioxidant capacity,[26–28] their capabilities to control diabetes,[29,30] in addition to their notable effects as anticancer, nephroprotective, cardioprotective and neuroprotective agents.[10,26,27] Moreover, they were reported to inhibit the growth of bacteria, fungus, and yeast in several investigations and also showed potent activity even against resistant microbes.[10,14] Some studies also discussed their antiviral activity against different viruses as HIV-1, H1N1, SARS-CoV and hepatitis C viruses, and highlighted the possible mechanism of action of these compounds.[10,17–19,24,31,32]

In 2016, a study conducted by Hematpoor and co-workers reported the larvicidal and ovicidal activity against *Aedes aegypti*, *Aedes albopictus* and *Culex quinquefasciatus* of *Piper sarmentosum* phenylpropanoids.[33]

Only few studies reported their antiprotozoal activity for compacting vector-borne protozoan illnesses. Oketch-Rabah and his co-workers, in 1997, reported the antiprotozoal activity of *Asparagus africanus* Lam. (Liliaceae) roots. The lignan (+)-nyasol (Fig. 3) potently inhibits the growth of *Leishmania major* promastigotes, the IC_{50} being 12 μM, and moderately inhibits *P. falciparum schizonts* with the IC_{50} 49 μM.[34] Also, tetrahydrofuran lignans, isolated from *Nectandra megapotamica* (Lauraceae), showed *in vitro* activity against *Leishmania donovani* and *P. falciparum*.[35]

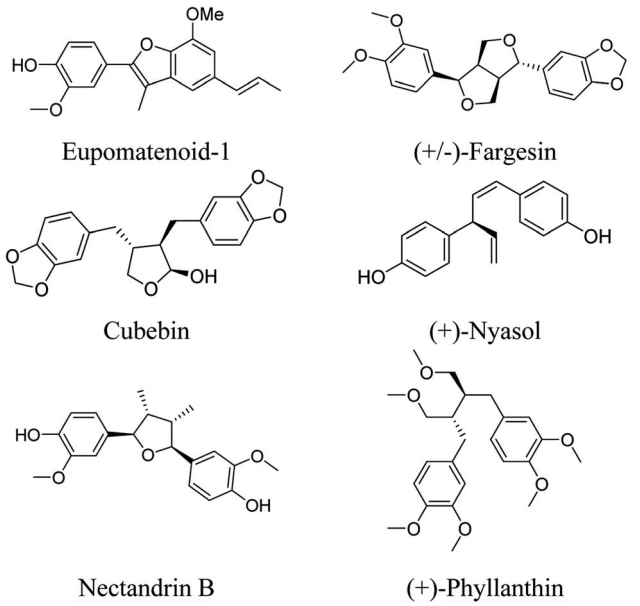

Fig. 3 Literarily-reported natural antimalarial agents.

Furthermore, it had been reported that the rhizomes of *Aristolochia elegans* Mast (F. Aristolochiaceae) exhibited antiprotozoal activities against *Entamoeba histolytica* and *Giardia lamblia* due to eupomatenoid-1 which was very active (IC_{50} < 0.624 μg mL^{-1}); in contrast, fargesin and cubebin (Fig. 3) were moderately active (IC_{50} < 275 μg mL^{-1}).[36]

In 2017, Otero and co-workers demonstrated the antiprotozoal activity of some hybrids of caffeic acid against *Trypanosoma cruzi* and amastigotes of *Leishmania* (*Viannia*) *panamensis* protozoa.[10,37] In 2020, Maia and co-workers had been reported the virtual screening and the *in vitro* assessment of the antileishmanial activity of lignans.[38]

Additionally, lignans isolated from *Haplophyllum tuberculatum* (Rutaceae) exhibited antiprotozoal activity against *L. donovani amastigotes*, *P. falciparum*, and *Trypanosoma brucei* rhodesiense bloodstream forms. Nectandrin B (Fig. 3) exhibited the highest activity against *L. donovani* (IC_{50} 4.5 μM) and the highest selectivity index of 25.5.[39]

Lignans isolated from *Holostylis reniformis* Duch. (Aristolochiaceae) and *Rhaphidophora decursiva* possessed high antiplasmodial activity against *P. falciparum*.[40–42] 4-(1,3-dimethoxypropyl)phenol, a compound isolated from *Alpinia galanga* (L.) (Zingiberaceae), showed significant activity against *L. major* ($IC_{50} = 27.8 \pm 0.34$ μg mL^{-1}) and was selectively active against *T. brucei gambisense* and *T. brucei rhodeisense* with potent activity with IC_{50} 23.66 ± 0.87 μg mL^{-1} and 26.85 ± 2.20 μg mL^{-1}, respectively.[43] Moreover, Komlaga and co-workers, reported isolation of a dibenzyl lignan, named as (+)-phyllanthin (Fig. 3), which displayed potent antiplasmodial activity against chloroquinine-resistant *P. falciparum* strains W2 and 3D7 ($IC_{50} = 26.23 \pm 3.47$ & 5.65 ± 1.48 μM, respectively).[44]

According to previous studies, the mechanisms underlying the antimalarial activity of natural products are most likely through interfering with the parasite's haem detoxification, triggering oxidative stress and lipid peroxidation, inhibition of the enzymes involved in fatty acid, protein and calcium metabolism.[45,46]

Clearly, we highlighted the pivotal role of natural products (especially secondary metabolites) in compacting malaria as an epidemic disease. Hence, this study encompasses screening of the antimalarial activities of both phenylethanoids and phenylpropanoids, in addition to their derivatives *via* computational approaches using *in silico* molecular docking studies, aiming at discovery of novel scaffolds that afford safer and effective medicinal treatments to reduce the high malaria mortality and morbidity rates and to overcome the limitations of the conventional antimalarial drugs. Also, exploring antimalarial activity of glandularin isolated from isolated from the leaves of *Glandularia* × *hybrida* against 3D7 strains of *P. falciparum*, in addition to its binding interactions within crystal structure of three known *P. falciparum* active sites.

Experimental

Molecular docking simulations

In silico simulations of 25 molecules were performed using Molecular Operating Environment (MOE ® software) within crystal structure of three *P. falciparum* proteins; *P. falciparum* cell cycle regulator and non-human derived cyclin-dependent kinase (CDK) which called the *P. falciparum* kinase (PfPK5; PDB ID: 1V0P), *P. falciparum* cytochrome bc1 complex (cyt bc1; PDB ID: 4PD4), and *P. falciparum* lysyl-tRNA synthetase (PfKRS1; PDB ID: 6AGT) revealed from protein data bank (RCSB Protein data bank; **https://www.rcsb.org/**). Crystal structure of three proteins were validated by re-docking of co-crystallized ligands and their docking score and RMSD (Å) were in the acceptable range. Structure of 25 test molecules were drawn using Chem®Draw program and were energy minimized using MOE ligand preparation tool. Finally, docking protocol and visual inspection of obtained docking poses was done as reported (diterpenoids profile of the marine sponge *Chelonaplysilla erecta* and candidacy as potential antitumor drugs investigated by molecular docking and pharmacokinetic studies, Natural Product Research, **https://doi.org/10.1080/14786419.2022.2063856**), and data were listed in Table S3† and represented as schematic diagrams in Fig. 4, 5 and S3.†

Plant preparation and glandularin isolation

In a previous study, leaves of *Glandularia* × *hybrida* were extracted using ethanol and the ethanolic extract was further defatted using *n*-hexane. The defatted extract was subjected to a series of chromatographic procedures to isolate glandularin. Glandularin, a dibenzylbutyrolactolic lignin, was obtained as colorless residue, identified using different spectroscopic techniques, and the stereocenters were determined using X-ray crystallographic analysis. Glandularin has been previously characterized.[47]

P. falciparum culture medium and maintenance

The parasites were cultured as described previously.[48] In brief, parasites were grown RPMI 1640 medium supplemented with 5% pooled human sera A^+, along with 11 mM glucose, 25 mM HEPES, and 29 μM hypoxanthine. Human sera were heat-deactivated,

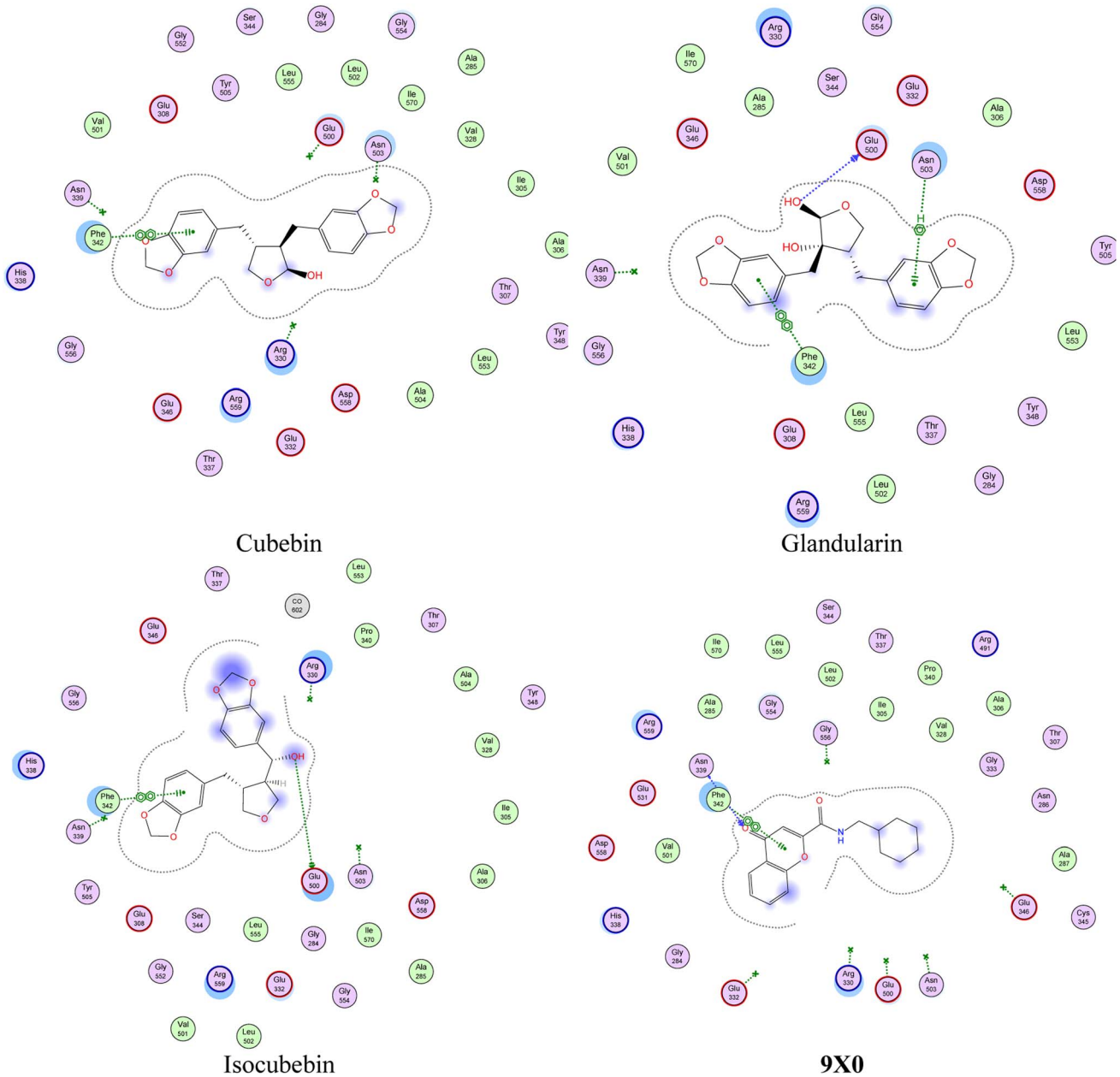

Fig. 4 Presumptive mode of interaction of test molecules and **9X0** within active site of *P. falciparum* lysyl-tRNA synthetase (PfKRS1; PDB ID: 6AGT).

aliquot and stored frozen at −20 °C until use. Complete medium was prepared fresh just before use and pre-warmed at 37 °C.

Synchronization of parasite culture

Sorbitol treatment or ring stage isolation is a strategy for synchronizing parasite culture. Sorbitol synchronization method is based on parasitized RBC membrane differential permeability. Although RBCs are impermeable to sorbitol, infected RBCs with mature stages have a permeable membrane due to parasite-induced structural changes. This feature is utilized to selectively destroy mature forms of the parasite using osmotic shock while leaving uninfected RBCs and RBCs parasitized by ring stages unaffected. Synchronization was done using the procedure as reported before.[49] Primarily, Sorbitol synchronized parasites (100 µl) at 2% haematocrit and 1% parasitaemia were incubated under normal culture conditions in the absence or presence of increasing concentrations of the tested compound. Artemisinin was used as positive controls, while 0.4% (v/v) DMSO was used as the negative control. Individual samples were seeded in 96 well plates and incubated at 37 °C for 48 h.

SYBR green-I fluorescence assay for parasitemia determination

The SYBR green-I-based fluorescence assay was performed to measure the growth inhibition effect of glandularin against 3D7 strains of *P. falciparum* as described by Johnson, *et al.* 2007.[50,51]

After 12, 24 and 48 h of incubation, 100 μl of SYBR green I lysis buffer was added to each well and mixed gently twice with a multi-channel pipette and incubated in dark at 37 °C for 1 h. Fluorescence was measured with a Victor fluorescence multi-well plate reader (PerkinElmer, Waltham, MA) with an excitation and emission wavelength of 485 and 530 nm, respectively. The fluorescence counts were plotted against the drug concentration and the 50% inhibitory concentration (IC_{50}) was determined by analysis of dose response curves.

Results were validated microscopically by examination of Giemsa-stained smears of glandularin treated parasite cultures. Blood films were stained with a 7.5% Giemsa solution (pH of 7.2) for 15 min. Parasitemia was counted using a bright field microscope, and the morphological changes were noted *via* imaging.

Results and discussion

The main problem facing malaria transmission areas is the development of drug resistant parasite strains. This enhances the importance of discovering new antimalarial agents with better activity.[52] Our study aimed to spot the light on antimalarial active phenylethanoids and phenylpropanoids through *in silico* and *in vitro* assessments.

Molecular docking simulations

A series of 261 naturally occurring phenylethanoids and phenylpropanoids from different plant families (Tables S1, S2 and Fig. S1†) including 27 representatives with previously reported antiprotozoal activity (Table S1 and Fig. S2†) were investigated for their antimalarial potential.

Based on Gao *et al.* findings about the effect of quinone on ubiquitin in bc1 complex and inhibition of Qi site of *P. falciparium* cyt bc1,[53] and Hoepfner *et al.* who utilized the reverse genomic approaches to identify *P. falciparum* lysyl-tRNA synthetase as the novel druggable drug target for both blood and liver stages for a compound identified from such phenotypic screening, we run two different virtual screening experiments, one through target predication simulations using Swiss Target Predication facility which gave insights about major target for such class of compounds as inhibitors of both kinases and secreted proteins[54] and other one using *in silico* molecular docking screening within active site of 3 proteins; *P. falciparum* kinase, *P. falciparum* cytochrome bc1 complex, and *P. falciparum* lysyl-tRNA synthetase; isolated from *P. falciparum* malarial strain. As shown in Table S3,† most of selected compounds have moderate to strong docking score within active site of selected proteins, as shown in Fig. S4.†

Remarkably, some of these molecules were found to have a docking score higher with tighter binding interactions (in the form of H-donor and H-acceptor, in addition to hydrophobic interactions) with various amino acids lining active sites than did the co-crystallized ligands, as shown in Fig. S3 and S5.† Moreover, exploration of binding interactions of glandularin and its structurally-related compounds; cubebin and isocubebin; within one of the most popular proteins affecting *P. falciparum* activity; lysyl-tRNA synthetase (PfKRS1),[55] as shown in Fig. 4, revealed interestingly that glandularin showed comparable binding energy to that of co-crystallized ligand; **9X0**; with strong binding interactions with key amino acid residues lining PfKRS1 active site in the form of three stabilizing H-bonds and hydrophobic interactions indicating its possibility as antimalarial target, as shown in Fig. 5.

Interestingly, there isn't much data in available literature discussing the structural activity relationship of these compounds selected for molecular docking study and how their structures might affect their biological activity on target proteins. Hence, few of these well-characterized compounds were selected and checked for their affinity for the study's chosen target proteins correlated with their structures to get a good idea of their biological activity in upcoming *in vitro* tests.

Firstly, by examining the docking score of the well-known polyphenols (feddeiphenol A and C, and surinamensin) within the active site of *P. falciparum* kinase (PfPK5; PDB ID: 1V0P) (Table S3†), we found that there is no big difference between the C-linked polynuclear compound, feddeiphenol A,

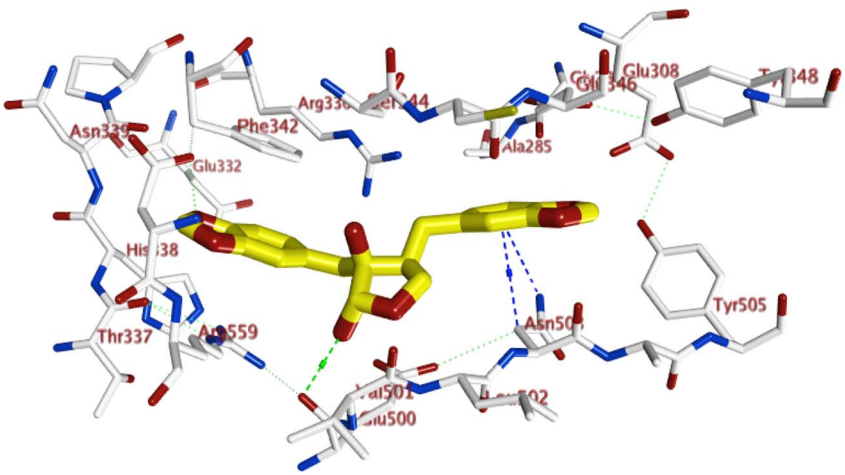

Fig. 5 3D binding interactions of glandularin within 6AGT active site; showing H-bonding (red-dotted lines) and various hydrophobic interactions (blue-dotted lines).

and its ether-analog feddeiphenol C. This might be because the chelate-type intramolecular H-bond formed between etherial O-atom and neighbouring OH-group which impairs free rotation around the central atom and hence it does not significantly improve docking efficiency compared to non-etherial analog. However, when we worked on docking simulations of these compounds within *P. falciparum* lysyl-tRNA synthetase (PfKRS1; PDB ID: 6AGT) to examine the significance of the presence of additional methoxy group in one of surinamensin's aromatic rings, we found that it didn't significantly improve the docking profile of surinamensin compared to its dimethoxy-analog, feddeiphenol C, and by visually inspecting its docking poses, indeed none of the 3,4,5-OMe groups participate in any binding interactions. Moreover, the hydroxy propanone side chain of feddeiphenol C was found to participate in a strong H-bond interaction with ASN 339, which could be responsible for raising its docking score above the surinamensin one.

Secondly, examining caffeic acid derivatives with moderate to strong docking score (rosmarinic acid, ethyl rosmarinate, and shimobashiric acid B) (Table S3†), we found that the introduction of lipophilic group as ethyl group of ethyl ester derivative (ethyl rosmarinate) significantly improved docking score compared to free acids, rosmarinic acid and shimobashiric acid B within *P. falciparum* kinase (PfPK5; PDB ID: 1V0P) active site which was the opposite found within both *P. falciparum* cytochrome bc1 complex (cyt bc1; PDB ID: 4PD4), and *P. falciparum* lysyl-tRNA synthetase (PfKRS1; PDB ID: 6AGT) active sites. Additionally, by examining the docking pose of rosmarinic acid, we found that the carboxylic group has no participation in any binding interactions with amino acid residues lining the 1V0P active site. So, all these interesting results could be attributed to the addition of lipophilicity *via* a lipophilic alkyl group to these caffeic acid derivatives (as in ethyl rosmarinate and shimobashiric acid B). Finally, the presence of hydroxyl group either on tetrahydrofuran ring or the methylenic carbon improved the docking score of these alcoholic derivatives (isocubebin, cubebin, and glandularin) over non-alcoholic ones (hinokinin and savinin) through the formation of H-bond with amino acid residues lining all the three active sites of *P. falciparum* kinase (PfPK5; PDB ID: 1V0P), *P. falciparum* cytochrome bc1 complex (cyt bc1; PDB ID: 4PD4), and *P. falciparum* lysyl-tRNA synthetase (PfKRS1; PDB ID: 6AGT) proteins is a common finding among members of lignan's class.

Table 1 Antimalarial activity of glandularin at different time intervals against *P. falciparum* using SYBR green-I-based fluorescence assay

Time (h)	Glandularin IC_{50} values (μM)
12	62.9
24	11.2
48	53.4

In vitro antimalarial activity

The *in silico* docking study was further augmented by *in vitro* assessment of the glandularin for their antiplasmodial activity against chloroquine-sensitive 3D7 strain of *P. falciparum* using SYBR green I-based fluorescence assay and results were listed in Table 1. According to antimalarial activity scale set by Philippe and co-workers, the results showed moderate antimalarial activity of glandularin with an IC_{50} value of 11.2 μM after 24 hours of incubation[56] (N.B. the positive control, artemisinin, showed IC_{50} of 0.02 μM at the same incubation time interval).

Remarkably, microscopical examination of Giemsa-stained blood smears of untreated (control) and glandularin-treated parasite cultures showed clearly the antimalarial effect of glandularin on infected cells, as shown in Fig. 6.

Glandularin was of a special antimalarial concern in our study due to its antimalarial potential showed in high docking scores in the *in silico* study, together with promising antimalarial activity against 3D7 strain of *P. falciparum* in the *in vitro* study. Glandularin's structure is closely related to cubebin (8α-hydroxy cubebin). Cubebin and its analogues were assessed before for their antiprotozoal activities in many studies revealing their potent activities. Carlis and co-workers assessed cubebin, its oxidation product hinokinin, and dihydrocubebin for their *in vitro* anthelmintic activity against gastrointestinal nematodes using the egg hatch test, larval development test and L3 migration inhibition test.[57] These compounds showed ovicidal activity with EC_{50} values of 150.00 μg mL^{-1}, 186.70 μg mL^{-1} and 68.38 μg mL^{-1}, respectively. In larval development test, cubebin showed an EC_{50} value of 14.89 μg mL^{-1}, and an EC_{50} value of 30.75 μg mL^{-1} for hinokinin. On the other hand,

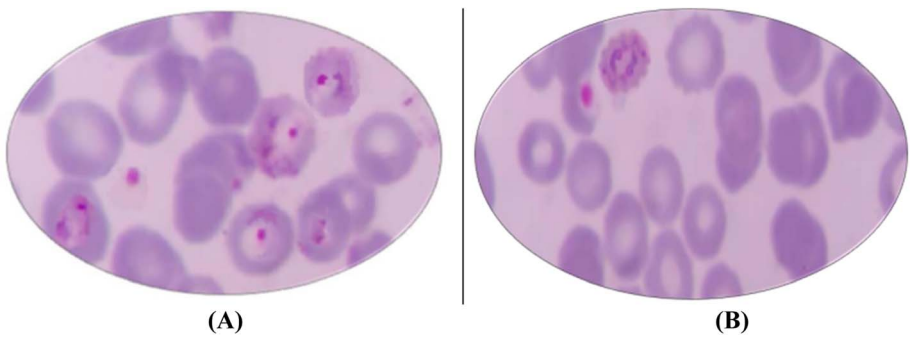

Fig. 6 (A) Giemsa-stained thin blood smears showing numerous *P. falciparum* (ring stage) in the untreated control sample; (B) after treatment with Glandularin.

hinokinin showed 100% inhibition for the larval development at all concentrations evaluated. In the L3 migration inhibition test, larval migration was inhibited by dihydrocubebin with a value of 100% in all concentrations evaluated, while cubebin and hinokinin exhibited EC_{50} values of 0.89 μg mL^{-1} and 0.34 μg mL^{-1}, respectively. Additionally, cubebein and hinokinin, were reported for their antiprotozoal activity against *T. cruzi*, the primary cause of Chagas' diseases.[58] The antiprotozoal activity was assessed *in vivo* using tissue morphometric analysis, showing significant decrease in parasitemia in the groups treated with cubebin and hinokinin orally. These compounds and their closely structural analogues are worthy to be further investigated for antiprotozoal activity including underlying mechanisms of their activities and studying of their structural activity relationships together with chemical transformations which may help in adjusting their activities.

Conclusions

The study enclosed some of the reported naturally occurring phenylethanoids and phenylpropanoids with diverse activities. Additionally, docking simulations run on 25 selected phenylpropanoids for their antimalarial activities against *P. falciparum* within active site of 3 proteins; *P. falciparum* kinase, *P. falciparum* cytochrome bc1 complex, and *P. falciparum* lysyl-tRNA synthetase; isolated from *P. falciparum* malarial strain. The *in silico* study was in agreement with all the findings reported in the literature about their potential as antiplasmodial agents. Glandularin, as a dibenzylbutyrolactolic lignan, demonstrated an example for naturally occurring antimalarial drugs. Glandularin's docking score to co-crystallized ligand within active site of *P. falciparum* lysyl-tRNA synthetase revealed its high potential as promising antimalarial drug of natural source. This was more confirmed by the high antimalarial activity of glandularin that was exerted during its *in vitro* antimalarial assessment against chloroquine-sensitive 3D7 strain of *P. falciparum*. According to the reported data and the new findings in our study, plants based phenylpropanoids and phenylethanoids could be a new treasure and promising avenue for developing new antimalarial drugs that can be efficiently used against known drug-resistant *P. falciparum* strains.

Conflicts of interest

The authors declare no conflicts of interest.

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