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Future antimalarials from *Artemisia*? A rationale for natural product mining against drug-refractory *Plasmodium* stages

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Infusions of the plants *Artemisia annua* and *A. afra* are gaining broad popularity to prevent or treat malaria. There is an urgent need to address this controversial public health question by providing solid scientific evidence in relation to these uses. Infusions of either species were shown to inhibit the asexual blood stages, the liver stages including the hypnozoites, but also the sexual stages, the gametocytes, of *Plasmodium* parasites. Elimination of hypnozoites and sterilization of mature gametocytes remain pivotal elements of the radical cure of *P. vivax*, and the blockage of *P. vivax* and *P. falciparum* transmission, respectively. Drugs active against these stages are restricted to the 8-aminoquinolines primaquine and tafenoquine, a paucity worsened by their double dependence on the host genetic to elicit clinical activity without severe toxicity. Besides artemisinin, these *Artemisia* spp. contain many natural products effective against *Plasmodium* asexual blood stages, but their activity against hypnozoites and gametocytes was never investigated. In the context of important therapeutic issues, we provide a review addressing (i) the role of artemisinin in the bioactivity of these *Artemisia* infusions against specific parasite stages, *i.e.*, alone or in association with other phytochemicals; (ii) the mechanisms of action and biological targets in *Plasmodium* of *ca.* 60 infusion-specific *Artemisia* phytochemicals, with an emphasis on drug-refractory parasite stages (*i.e.*, hypnozoites and gametocytes). Our objective is to guide the strategic prospecting of antiplasmodial natural products from these *Artemisia* spp., paving the way toward novel antimalarial "hit" compounds either naturally occurring or *Artemisia*-inspired.

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1. Introduction

Artemisinin (ART) derivatives remain frontline antimalarial drugs prescribed worldwide but are threatened by the rapid spread of ART-resistant *Plasmodium falciparum* strains.[1,2] These have become dominant in many parts of South-east Asia,[3] and have independently emerged recently in Africa.[4–6] Sweet wormwood (*Artemisia annua*, containing ART) and African wormwood (*A. afra*, containing traces of ART, if any), from the Asteraceae plant family, have a long history in malaria-endemic countries as traditional remedies to prevent or treat symptoms associated with the disease. Although ART-derived drugs show undisputable clinical efficacy, their limited availability, cost and/or frequent counterfeit in some areas have triggered a renewed popularity for self-medication with *Artemisia* infusions particularly in Africa.[7–15] These treatments have become the object of intense controversy regarding their efficacy, safety, and effect on the spread of drug resistance as mere ART monotherapy,[16] which has proven to be unreliable.[16–19] Although the WHO still strongly

discourages the use of such unstandardized remedies against malaria,[16] there is a growing need to address this public health issue by providing solid scientific evidence in relation to these uses. While several clinical trials reported the recrudescence of *P. falciparum* blood stages in patients treated with *A. annua* infusions,[16,20,21] the absence of ART resistance in China, despite the traditional use of *A. annua* in this country for more than 2000 years,[22] suggests that ART-containing plants could be superior to ART monotherapy in optimal settings (*i.e.*, if sufficient contents in active principles, not limited to ART, as well as adequate regimens, were met). The central role of ART in the elimination of *P. falciparum* asexual blood stages by these *Artemisia* spp. is supported by the positive correlation between ART content and *in vitro* parasite growth inhibition by the infusions of diverse specimens of *A. annua*.[23] Indeed, *A. annua* infusions strongly inhibit the growth of these stages,[24–27] whereas *A. afra* infusions yield contradictory results[10–12,23,24,27,28] consistent with their variable but generally negligible ART content.[14,24,29,30] Similarly, infusions of biosynthetically impaired *A. annua* strains lose their growth-repression effects *in vitro* against *P. falciparum* asexual blood stages when specifically deprived of ART, whereas strains deprived of flavonoids, an important component of the infusions, keep their efficacy against the parasite.[31,32] *In vivo* however, oral treatment with dry whole *A. annua* powder exerts stronger antiplasmodial effects and delayed the emergence of ART resistance in *P. chabaudi*-infected mice compared to equivalent amounts of pure ART.[33,34] Overall, these results report the inhibitory effects of *Artemisia* spp. infusions against *Plasmodium* asexual blood stages, known to be very sensitive to ART and derivatives, contrarily to the liver and maturing gametocyte stages, showing ablated and reduced sensitivities to endoperoxides, respectively.[35–41] The effects and mechanisms of *A. annua* and *A. afra* infusions against the liver stages of various murine, simian and human *Plasmodium* species were recently investigated.[27] Dilutions of each infusion exerted strong multi-stage inhibition of every species of parasites studied *in vitro*, preventing sporozoite development in the hepatocyte, impairing schizogony and affecting the notoriously drug-insensitive hypnozoites in relapsing parasite species. These broad-spectrum antiplasmodial effects were associated with mitochondria and apicoplast damage and were ART-independent.[27] Infusions of both *Artemisia* spp. were also capable of decreasing the viability of *P. falciparum* gametocytes *in vitro* more efficiently than equivalent ART amounts.[29] Altogether, these observations suggest that some non-ART phytochemicals could either be active against the hepatic and transmittable *Plasmodium* stages, capable of improving the pharmacokinetics of ART and/or synergizing its action.[26,33,34,42–48] The radical cure of *P. vivax*, mediated by hypnozoite elimination, together with the blockage of *P. falciparum* (especially ART-resistant) and *P. vivax* transmission, mediated by gametocyte sterilization, remain pivotal elements of malaria eradication. Current drug treatments targeting these stages are restricted to the 8-aminoquinolines primaquine and tafenoquine,[49–51] a paucity worsened by their double dependence on the host genetic to elicit clinical activity (CYP2D6-dependent) without severe toxicity (G6PD-dependent).[50–53] Besides ART, both *Artemisia* spp. contain a complex mixture of secondary

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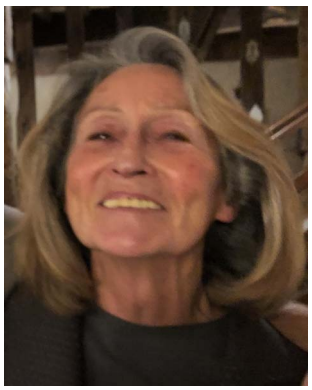

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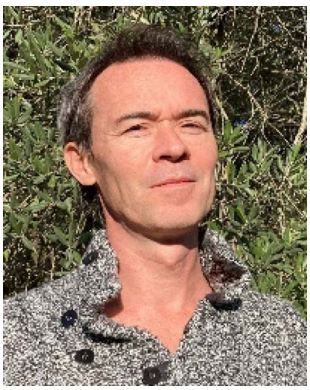

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metabolites eliciting modest to intermediate inhibition of asexual blood-stage parasites, but their activity against the hypnozoite and gametocyte stages was never investigated. The possible occurrence in *A. annua* and *A. afra* of clinically efficient molecules against these drug-refractory *Plasmodium* stages could stimulate antimalarial drug development efforts from natural leads. In the context of important therapeutic issues, we provide a review addressing (i) the role of ART in the bioactivity of these *Artemisia* infusions against specific parasite stages, *i.e.*, alone or in association with other phytochemicals; (ii) the mechanisms of action and biological targets in *Plasmodium* of *ca.* 60 infusion-specific *Artemisia* phytochemicals, with emphasis on drug-refractory parasite stages. Our objective is to guide the strategic prospecting of antiplasmodial natural products from these *Artemisia* spp., paving the way towards novel antimalarial "hit" compounds either naturally occurring or *Artemisia*-inspired.

2. Infusion-specific natural products from *Artemisia annua* and *A. afra*

The dictionary of natural products database (**http://dnp.chemnetbase.com**) shows 1500 records for the *Artemisia* genus and 120 records for the species *A. annua* and *A. afra* altogether. Reviews on the phytochemistry of *A. annua* and *A. afra* can be found elsewhere.[13,14,54,55] The actual content in these phytochemicals (ART included) is reported to be highly variable, depending not only on the species but also on its strain, place of origin, season of harvest and storage,[23,24,56–61] making the identification of compounds or chemical associations responsible for a given bioactivity of the extracts particularly challenging. *A. annua* infusions have already been phytochemically analyzed in detail,[26,62] and those of *A. afra* semi-characterized only recently.[30,63] However, these data are likely not fully representative of the phytochemical content of these *Artemisia* spp. infusions, firstly because of the aforementioned variations, and also because additional compounds to the ones described could be expected upon deepen analysis of the plant aqueous extracts, based on the species exhaustive description in phytochemicals. The many secondary metabolites produced by these *Artemisia* spp. encompass a wide range of physicochemical properties, making some of them readily extracted by water at sub-boiling temperature (*i.e.*, infusions). Yet water solubility relies on many factors (molecular size, log *P*, presence of polar or ionizable functions), and predicting the extent to which a given phytochemical will be extracted by water and found present in the infusion can be very speculative. For instance, ART could logically be considered as water-insoluble ($\log P \sim 3$), yet it is abundant in *A. annua* infusions.[23,26,62,64] In this article, we will review the natural products demonstrated, predicted or likely to occur in *A. annua* and *A. afra* infusions. The rationale followed for this selection of metabolites is based on (i) the production by the two *Artemisia* spp. of many identical phytochemicals, allowing to predict their presence in the infusion of one species whenever identified in the infusion of the other species; (ii) the production by the two *Artemisia* spp. of water-soluble metabolites similar to those identified in their infusions, allowing to suspect their additional presence in the infusions. These phytochemicals belong mainly to the classes of terpenes, flavonoids, phenolic acid esters and coumarins.

2.1. Terpenes

This class encompasses compounds ranging from 10 (*i.e.*, monoterpenes) to 30 carbon atoms (*i.e.*, triterpenes). ART and congeners belong to the sesquiterpene subclass (15 carbon atoms). Of note, several plants from the Asteraceae family, including from the *Artemisia* genus, are known to produce various antiplasmodial terpenes structurally different from ART and congeners.[10,65–69] *A. annua* and *A. afra* infusions remain so far non-investigated for the presence of monoterpenes, which are typical components of plant essential oils (EOs). However, certain monoterpenes present in the EOs of these *Artemisia* spp. are known to be extractable by warm water under the form of hydrosols (syn. hydrolates) despite their hydrophobicity, due to their occurrence as liquids or solids of low melting points. Among these, camphor, eucalyptol (syn. 1,8-cineole) and artemisia ketone are abundant in the hydrosol of *A. annua*,[70] and their typically high concentrations in *A. afra*[58–60,71] allows to predict their presence also in the hydrosol of the latter species. Regarding distinct monoterpenes, *A. afra* EOs generally contains high amounts of thujones[58–60,72] – albeit some cultivars show undetectable levels[73] – and 6,7-epoxylinalool,[74] which are absent in *A. annua*.[75–77] Minor distinct compounds include linalool and limonene present in the EOs of *A. annua*,[75,78,79] but extremely rare or absent in that of *A. afra*[60] (Fig. 1). As for antiplasmodial activity, eucalyptol inhibits the growth of *P. falciparum* asexual blood stages at intermediate micromolar concentration,[59,80] whereas artemisia ketone, thujones, linalool and limonene show weak effects on these parasites up to high micromolar or low millimolar concentrations.[59,81,82] To our knowledge, camphor and the electrophilic 6,7-epoxylinalool were never tested against malarial parasites. Mechanistically, linalool and limonene exert antiplasmodial effects in asexual blood-stage parasites by inhibiting various enzymes (*e. g.*, prenyl synthases and protein prenyltransferases) downstream the apicoplast DOXP/MEP pathway, presumably by competing with their endogenous isoprenoid substrates.[81,82] These inhibitors (as well as similar non-*Artemisia* monoterpenes and sesquiterpenes, *e.g.*, perillyl alcohol and nerolidol) act in the parasite by repressing the biosynthesis of long-chain isoprenoid alcohols (*i.e.*, dolichols), of prenylated proteins[81–85] and of the octaprenyl chain of ubiquinone,[86] thus potentially affecting the mitochondrion.[87] Moreover, the presence of important ART amounts in *A. annua* infusions could also lead to a direct effect on the parasite mitochondrion.[88–91] To our knowledge, no natural terpene has yet been found to repress the DOXP/MEP pathway within the apicoplast, as does the prototypical inhibitor fosmidomycin.[92]

Sesquiterpenes are typically hydrophobic compounds and most of them (*e.g.*, 9-*epi*-ART, deoxy-ART, artemisitene, artemisinic acid) are absent in *A. annua* infusions despite their presence in the plant.[26,62] Exceptions are arteannuin B, dihydroartemisinic

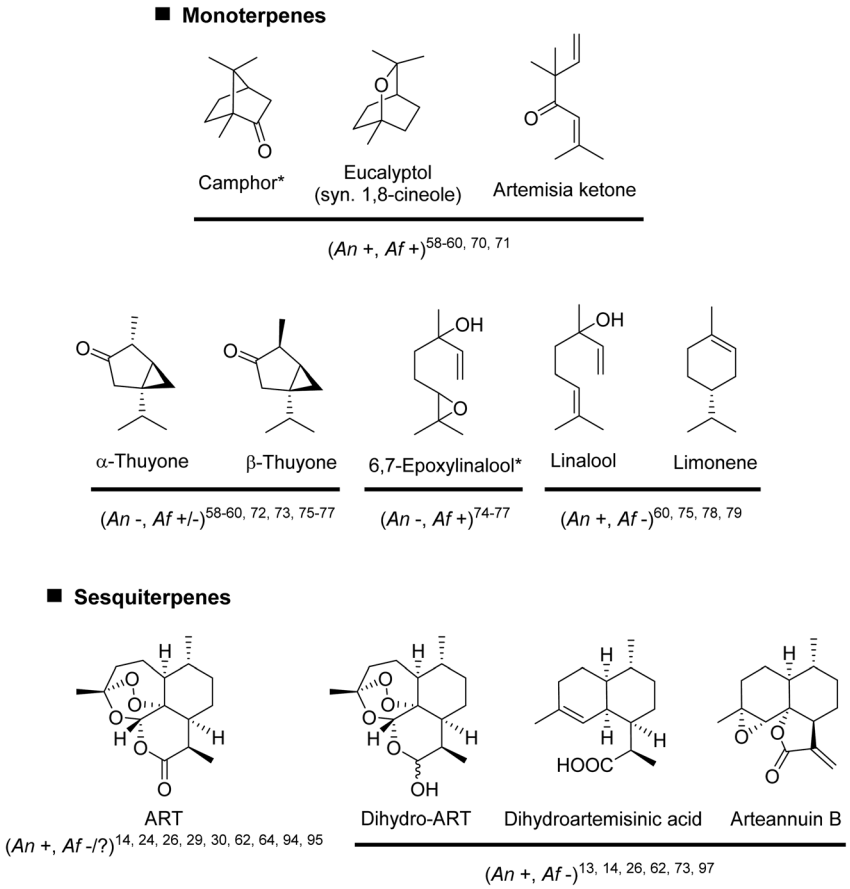


Fig. 1 Terpenes present in *A. annua* (*An*) and/or *A. afra* (*Af*) infusions with established or yet untested (*) antiplasmodial activity.

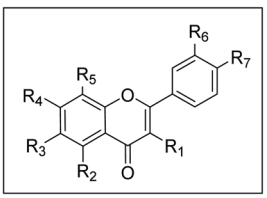
acid (the biosynthetic precursor of ART),[54,93] dihydro-ART and to an important extent, ART itself[25,26,30,62,64,94,95] (Fig. 1). It is of great phytochemical interest that dihydro-ART, the key component of ART-derived semisynthetic antimalarials (*e.g.*, artesunate), was thus detected as a minor compound in the infusion of *A. annua*.[62] This suggests the natural occurrence of dihydro-ART in the *Artemisia* genus, an observation that was confirmed recently.[96] The sesquiterpene content of *A. afra* infusions was never investigated except for the absence or extremely low amount of ART,[14,24,29,30] this plant species seeming also deprived of the infusion-soluble sesquiterpenes found in *A. annua* (*e.g.*, arteannuin B and dihydroartemisinic acid).[13,14,73,97] Since *A. afra* is sometimes grown and harvested in immediate vicinity with *A. annua*, one important question is whether the traces of ART sporadically found in *A. afra* result from a biosynthetic process common to both species but minor in *A. afra*, or from the contamination of *A. afra* by *A. annua* during harvest or storage.[98] When considering a strictly additive effect of phytochemicals of known abundance and potency against *P. falciparum* asexual blood stages *in vitro*,[26,30,43,62,94,99–104] ART as a major and nanomolar-active component of *A. annua* (together with dihydro-ART, a 3- to 10-fold more potent endoperoxide than ART,[35] if present) can be predicted for being almost exclusively (>90%) responsible for the bioactivity of the plant infusion. This observation is supported by the strong correlation between ART concentration and *in vitro* growth inhibition of *P. falciparum* asexual blood stages by 16 different *A. annua* specimens,[23] and by the recent study of *A. annua* strains deficient in either flavanone (Δ*CHI1-1*, impairing the biogenesis of flavonoids) or amorpha-4,11-diene (*Si*AMS or Δ*cyp71av1-1*, impairing the biogenesis of ART and congeners) biosynthetic pathways, showing that the infusion activity against the latter stages was ART-dependent and that flavonoids exerted a negligible contribution.[31,32] In marked contrast, a significant gain (3- to 7-fold, depending on the parasite strain) in growth inhibitory activity against *P. falciparum* asexual blood stages *in vitro* was described for the *A. annua* infusion compared to ART alone at equivalent concentration,[26] suggesting a synergizing effect of ART by other components of the extract (*e.g.*, flavonoids)[26,43,44,105] and echoing results on the dry whole plant.[33,34] Similar effects were observed in *P. falciparum* gametocytes, *Artemisia* infusions exerting a more pronounced inhibition than pure ART at equivalent concentration.[29] Interestingly, the inhibition of replicative as well as dormant hepatic stages of various *Plasmodium* spp. *in vitro* by the infusion of *A. afra* (lacking ART) appeared to be stronger than that of *A. annua* (ART-containing).[27] Both effects were indeed ART-independent, as shown by the weaker action of a 35-fold (for *A. annua*) to a *ca.* 7000-fold (for *A. afra*) superior concentration of dihydro-ART – an even more potent endoperoxide than ART against hepatic stages[35] – than the actual ART amounts present in the infusion assays.[27] In this context, it

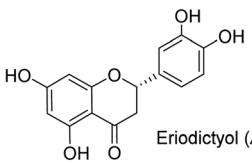
must be kept in mind that the activity of ART and congeners (*e.g.*, dihydro-ART) falls by 1000- to 10 000-fold against *Plasmodium* liver stages relatively to asexual blood stages.[27,35,36] This is correlated with the dependence of endoperoxides on heme (released by the digestion of hemoglobin in the parasite food vacuole) for their bioactivation, triggering the alkylation of multiple targets (heme itself as well as numerous plasmodial proteins) within asexual blood parasites.[90,106–108] This phenomenon is non-existent in hepatic stages where only limited bioactivation (*e.g.*, by cytochromes)[88,109] may occur. The decrease of sensitivity to endoperoxides from young to mature gametocytes comparatively to asexual blood stages[37–41,110] also correlates with a slowdown in hemoglobin proteolysis, although downregulation of active drug transport in the course of gametocytogenesis may participate.[38] Altogether, these observations strongly suggest that phytochemicals distinct from ART are responsible for the effects of *Artemisia* infusions against *Plasmodium* hepatic stages, and to a certain extent, gametocytes. Besides ART and dihydro-ART, arteannuin B and dihydroartemisinic acid seem to be the only other sesquiterpenes detected in *A. annua* infusions (*vide supra*). They inhibit the growth of *P. falciparum* asexual blood stages in the low and intermediate micromolar range, respectively,[26] whilst having unknown biochemical targets in the parasite.

2.2. Flavonoids

A. annua and *A. afra* infusions contain a variable concentration of the flavonoid aglycone luteolin together with one derived heteroside, luteolin-7-*O*-β-D-glucoside (syn. cynaroside).[30,62,63,111–114] Infusions of *A. annua* show an important proportion of distinctive flavonoids, minor as aglycones (*e.g.*, eriodictyol, chrysosplenol D) and predominant as water-soluble heterosides (*e.g.*, apigenin-6-*C*-β-D-glucoside, syn. isovitexin, quercetin-7-*O*-β-D-glucoside, syn. quercimeritrin).[26,61,62,94,115] *A. afra* infusion specifically contains the aglycone quercetin although its presence seems cultivar-dependent.[30,63] This suggests that other flavonoid aglycones present in *A. afra* (*e.g.*, kaempferol and tamarixetin, being close in structure to quercetin), as well as water-soluble heterosides other than cynaroside, might also be detected in its infusion upon deeper analysis (Table 1). The flavonoids from *A. annua* and *A. afra* exert growth inhibition of *P. falciparum* asexual blood stages *in vitro* across the micromolar range.[10,26,43,99–103,116] Considering the collapse of ART activity against *Plasmodium* hepatic stages and, to a lesser extent, maturing gametocytes, the flavonoid content of *A. annua* and especially *A. afra* infusions can be expected to significantly contribute to the inhibition of these stages, whereas this might

Table 1 Flavonoids present in *A. annua* (*An*) and/or *A. afra* (*Af*) infusions with established or yet untested (*) antiplasmodial activity. Glc: β-D-glucose; Ara: β-D-arabinose; Rut: β-D-rutinose





Eriodictyol (*An* +, *Af* ?)[62]

Flavonoid aglycones	R_1	R_2	R_3	R_4	R_5	R_6	R_7	*An*	*Af*	Ref.
Casticin (syn. vitexcarpin)	OMe	OH	OMe	OMe	H	OH	OMe	+	?	26, 61
Chrysosplenol D	OMe	OH	OMe	OMe	H	OH	OH	+	?	115
Cirsilineol	H	OH	OMe	OMe	H	OMe	OH	+	?	62
Jaceidin*	OMe	OH	OMe	OH	H	OMe	OH	+	?	62
Luteolin	H	OH	H	OH	H	OH	OH	±	±	30, 63, 112 and 113
Quercetin	OH	OH	H	OH	H	OH	OH	?	±	30 and 63

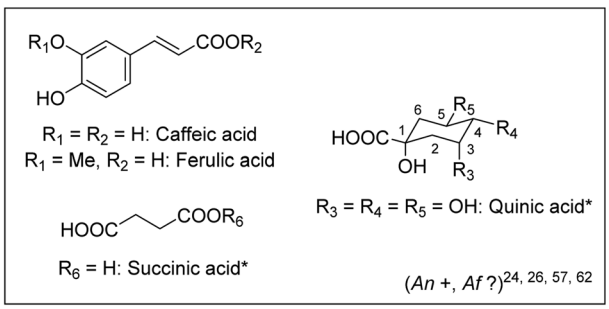
Flavonoid heterosides	R_1	R_2	R_3	R_4	R_5	R_6	R_7	*An*	*Af*	Ref.
Apigenin-6-*C*-β-D-glucoside (syn. isovitexin)	H	OH	Glc	OH	H	H	OH	+	?	26 and 62
Apigenin-8-*C*-β-D-glucoside (syn. vitexin)	H	OH	H	OH	Glc	H	OH	+	?	62
Apigenin-6-*C*-β-D-arabinosyl-8-*C*-β-D-glucoside (syn. isoschaftoside)*	H	OH	Ara	OH	Glc	H	OH	+	?	115
Apigenin-6,8-di-*C*-β-D-glucoside	H	OH	Glc	OH	Glc	H	OH	+	?	115
Apigenin-8-*C*-β-D-arabinoside-6-*C*-β-D-glucoside (syn. schaftoside, vicenin III)*	H	OH	Glc	OH	Ara	H	OH	+	?	62
Chrysoeriol-7-*O*-β-D-rutinoside	H	OH	H	O-Rut	H	OMe	OH	+	?	62
Luteolin-7-*O*-β-D-glucoside (syn. cynaroside)	H	OH	H	O-Glc	H	OH	OH	+	+	62 and 112
Patuletin-3-*O*-β-D-glucoside* and/or Patuletin-7-*O*-β-D-glucoside* (syn. patulitrin)	O-Glc / OH	OH	OMe	OH / O-Glc	H	OH	OH	+	?	62 and 115
Quercetin-3-*O*-β-D-glucoside (syn. isoquercitrin)	O-Glc	OH	H	OH	H	OH	OH	+	?	94
Quercetin-7-*O*-β-D-glucoside (syn. quercimeritrin)	OH	OH	H	O-Glc	H	OH	OH	+	?	115
Quercetin-3-*O*-β-D-rutinoside (syn. rutin, rutoside, sophorin)	O-Rut	OH	H	OH	H	OH	OH	+	?	115

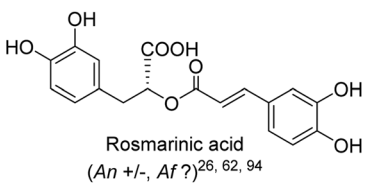
not be the case in asexual blood parasites (*vide supra*). Mechanistically, antiplasmodial flavonoids are believed to exert inhibition by binding to the free heme present in the food vacuole, thereby preventing its detoxification into hemozoin.[117–119] While such a scenario may apply to the actively digesting asexual blood stages (*e.g.*, trophozoites) and immature gametocytes,[120] mimicking the action of heme-binding antimalarials (*e.g.*, chloroquine, lumefantrine) against these parasite stages,[37,41] it is irrelevant in liver stages. Several antiplasmodial flavonoids present (*e.g.*, quercetin, luteolin, cynaroside) or suspected (*e.g.*, kaempferol, tamarixetin) in the infusions of *A. annua* and/or *A. afra* could target the *Plasmodium* apicoplast, as they inhibit FabG, FabZ and/or FabI *in vitro* at micromolar concentrations.[102,116] Fabs are enzyme components of the type II fatty acid synthase (FASII) machinery in the apicoplast,[92,121] and are essential for the development of *Plasmodium* hepatic stages.[122–124] Regarding anti-mitochondrion effects, many of the antiplasmodial flavonoids present in the infusion of *A. annua* (*e.g.*, casticin, isovitexin), or suspected in that of *A. afra* (*e.g.*, kaempferol, tamarixetin), disrupt the mitochondrial inner membrane potential in cancer cells, generating reactive oxygen species (ROS) and inducing apoptosis.[125–132] In plants, isovitexin impairs the mitochondrial respiratory chain by interacting with ubiquinone-binding sites.[133] In *Leishmania* parasites, quercetin is responsible for ROS generation, mitochondrion depolarization and swelling.[134,135] Similar pro-oxidative mechanisms at the mitochondrial level could underpin the action of these flavonoids in *Plasmodium*. To the contrary, certain antiplasmodial flavonoids present in the infusions of either *Artemisia* spp. (*e.g.*, cynaroside) possess ROS-scavenging capability, with mitoprotective and antiapoptotic effects in human cells,[136,137] suggesting that mitochondrion-impairing mechanisms are unlikely to explain parasite inhibition by these compounds.

2.3. Phenolic acid esters

A. annua and *A. afra* infusions contain important concentrations of various caffeic, ferulic and succinic esters of quinic acid (syn. chlorogenic acids, CGAs[138]), associated in *A. annua* to a variable proportion of rosmarinic acid.[10,13,14,24,26,30,62,63,94] These esters are accompanied in the infusion of *A. annua* by their free carboxylic acid precursors (*i.e.*, caffeic and quinic acids) although ferulic and succinic acids are generally not detected.[24,26,57,62] These free acids were never characterized in *A. afra* infusions, where they can be expected considering the common CGA metabolism of the two plant species (Table 2). These various CGAs, but also rosmarinic and caffeic acids, exert modest growth inhibition of *Plasmodium* asexual blood stages with *in vitro* activities in the high micromolar range.[24,26,101–104] As for flavonoids, the lack of ART in *A. afra*, together with the weak activity of ART against the

Table 2 Phenolic acid esters present in *A. annua* (*An*) and/or *A. afra* (*Af*) infusions with established or yet untested (*) antiplasmodial activity. **Substitution modes are depicted using R_2/R_6-(R_3, R_4, R_5) connectivity where R_2/R_6-R_x equals to a direct chemical bond; NA, not applicable





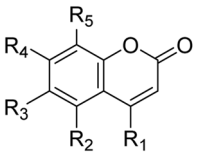
CGAs	R_1	R_2**	R_3	R_4	R_5	R_6**	*An*	*Af*	Ref.
3-*O*-Caffeoylquinic acid (syn. neochlorogenic acid)	H	R_3	R_2	OH	OH	NA	+	+	26, 30 and 62
4-*O*-Caffeoylquinic acid (syn. cryptochlorogenic acid)	H	R_4	OH	R_2	OH	NA	+	+	26, 30 and 62
5-*O*-Caffeoylquinic acid (*syn.* CGA)	H	R_5	OH	OH	R_2	NA	+	+	26, 30, 62, 63 and 94
3,4-Di-*O*-caffeoylquinic acid (syn. isochlorogenic acid A)	H	R_3, R_4	R_2	R_2	OH	NA	+	+	26, 30 and 62
3,5-Di-*O*-caffeoylquinic acid (syn. isochlorogenic acid C)	H	R_3, R_5	R_2	OH	R_2	NA	+	+	26, 30 and 62
4,5-Di-*O*-caffeoylquinic acid (syn. isochlorogenic acid B)	H	R_4, R_5	OH	R_2	R_2	NA	+	+	26, 30, 62 and 63
3,4,5-Tri-*O*-caffeoylquinic acid	H	R_3, R_4, R_5	R_2	R_2	R_2	NA	+	?	26
3-*O*-Feruloylquinic acid*	Me	R_3	R_2	OH	OH	NA	+	?	62
4-*O*-Feruloylquinic acid*	Me	R_4	OH	R_2	OH	NA	+	?	62
5-*O*-Feruloylquinic acid*	Me	R_5	OH	OH	R_2	NA	+	?	62
3,4-Di-*O*-feruloylquinic acid*	Me	R_3, R_4	R_2	R_2	OH	NA	+	?	62
3,5-Di-*O*-feruloylquinic acid*	Me	R_3, R_5	R_2	OH	R_2	NA	+	?	62
4,5-Di-*O*-feruloylquinic acid*	Me	R_4, R_5	OH	R_2	R_2	NA	+	?	62
3-*O*-Caffeoyl-5-*O*-feruloylquinic acid	H (for R_3)/ Me (for R_5)	R_3, R_5	R_2	OH	R_2	NA	+	?	62
4-*O*-Caffeoyl-3,5-di-*O*-succinoylquinic acid*	H	NA	R_6	R_2	R_6	R_3, R_5	+	?	62

parasite hepatic stages and mature gametocytes, might give the phenolic acid esters present in these *Artemisia* spp. infusions a significant contribution to the observed inhibitory effects.[27,29] Mechanistically, the fact that 5-*O*-caffeoylquinic acid (syn. CGA) inhibits bacterial FabG[139] (keeping in mind the general sensitivity of apicoplast enzymes, including Fabs, towards antibacterials)[121,140,141] and is also predicted to bind plasmodial FabI *in silico*,[142] suggests FASII inhibition and possible anti-apicoplast effects for CGAs in *Plasmodium*. Regarding a possible mitochondrial inhibition, CGAs induce mitochondrion-dependent apoptosis in cancer cells *via* the disruption of its inner membrane potential and production of ROS, in addition to other cytotoxic effects (*e.g.*, inhibition of the PI3K/AKT/mTOR pathway)[143–146] which could be relevant in host cells and *Plasmodium* parasites altogether.[147,148]

2.4. Coumarins

A. annua and *A. afra* infusions contain significant amounts of scopoletin and its heteroside, scopoletin-7-*O*-β-D-glucoside (syn. scopolin).[30,63,94,115] Specific coumarins in the infusion of *A. annua* are esculetin and eleutheroside B1,[115] which are not described in *A. afra*.[149] A putative trimethoxycoumarin was detected in *A. annua* infusion while being previously undescribed in this species, but remains unidentified regarding its substitution pattern,[62] which is known to vary between *Artemisia* spp.[150–152] Other hydrophilic coumarins present in *A. annua* and/or *A. afra* may be suspected in their infusions (*e.g.*, 4-methylesculetin from *A. annua* and isofraxidin from either *Artemisia* spp.)[57,153–155] (Table 3). Other coumarins from the two *Artemisia* spp. are terpene-based and lipophilic (*e.g.*, qinghaocoumarin in *A. annua*),[156] their presence in aqueous extracts thus being unlikely. Regarding antiplasmodial effects, scopoletin and esculetin are very weak growth inhibitors of *P. falciparum* asexual blood stages with *in vitro* potencies in the high micromolar range,[157,158] whereas isofraxidin shows intermediate micromolar activity.[158] To our knowledge, scopolin, eleutheroside B1 and 4-methylesculetin have not been evaluated against *Plasmodium* parasites. Mechanistically, coumarins are general

Table 3 Coumarins present in *A. annua* (*An*) and/or *A. afra* (*Af*) infusions with established or yet untested (*) antiplasmodial activity. Glc: D-glucose



Coumarins	R_1	R_2	R_3	R_4	R_5	*An*	*Af*	Ref.
Esculetin	H	H	OH	OH	H	+	?	115 and 149
Scopoletin	H	H	OMe	OH	H	+	+	30, 63 and 94
Scopolin*	H	H	OMe	*O*-β-Glc	H	+	+	30, 63 and 115
Eleutheroside B1*	H	H	OMe	*O*-α-Glc	OMe	+	?	115 and 149

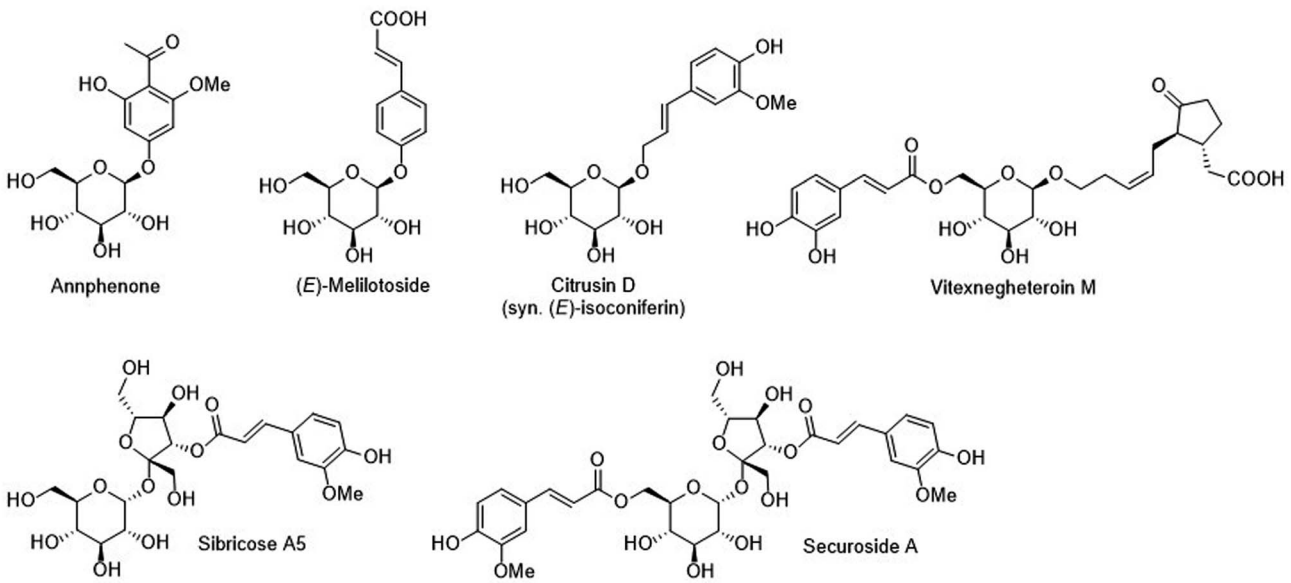


Fig. 2 Miscellaneous glucosides and sucrosides present in the aqueous extract of *A. annua*.[115]

inhibitors of the *P. falciparum* η-carbonic anhydrase,[159] but none of the above-mentioned compounds seems to have been tested yet against this parasite target.

2.5. Miscellaneous compounds

The aqueous extract of *A. annua* contains a number of phenolic heterosides consisting in glucosides (*e.g.*, annphenone) and sucrosides (*e.g.*, sibricose A5) (Fig. 2),[115] in addition to neutral or acidic branched hetero-polysaccharides.[160–162] In the former category, (*E*)-melilotoside possesses very weak growth inhibitory activity against P. falciparum asexual blood stages *in vitro*.[163] The existence of related compounds in *A. afra* remains speculative.

3. Discussion

The aim of this review is to account for the peculiar chemical diversity and associated antiplasmodial activity of infusion-contained *A. annua* and *A. afra* phytochemicals. Exception made of specific sesquiterpenes, flavonoids and coumarins, many natural products described or expected in these infusions are common, often ubiquitous, plant metabolites (*e.g.*, CGAs).[138] However, both empirical and scientific observations suggest to investigate these non-ART metabolites as new drug scaffolds against malaria: (i) *A. annua* has been utilized as an antimalarial remedy for thousands of years in Asia.[22] Its infusions are currently undergoing a quickly-spreading use in malaria-endemic regions, with claimed efficacy to both prevent and treat the disease. *A. afra* is following a similar, although more recent,[13] trend of use in Africa where the plant is indigenous, and where the majority of severe malaria cases and fatalities occur;[164] (ii) a growing body of scientific evidence reports on the important inhibitory activities of the infusions of either *Artemisia* spp. towards *Plasmodium* asexual blood stages, liver stages and gametocytes *in vitro* but also *in vivo* for the former activity. These properties were characterized as partly or entirely ART-dependent for asexual blood-stage parasites, ART-independent for parasite liver stages, and partly ART-dependent for gametocytes; (iii) while a curative action of *Plasmodium* asexual blood stages and young gametocytes could theoretically be attained by a sufficient ART content in *A. annua* infusions taken at a proper regimen, *A. afra* has a very low or even no ART content,[10,13,14,30,95,97,165] which is inconsistent with the antimalarial effects attributed to this species against active infections. Being a much weaker inhibitor of *Plasmodium* liver stages relatively to asexual blood stages, it is also difficult to perceive ART as eliciting clinical prophylactic activity at the concentrations typically found in *A. annua* (and even more in *A. afra*). Similarly, ART is a modest sterilizer of *Plasmodium* gametocytes especially those of stage V, responsible for the spread of malaria *via* parasite transmission to its *Anopheles* vector. Altogether, these observations suggest that non-ART phytochemicals are involved or even mainly responsible for the various antiplasmodial effects of *A. annua* and *A. afra* observed *in vitro*, as well as some of the antimalarial effects claimed in the field.

The physicochemical features of the various metabolites ocurring in *A. annua* and *A. afra* translate into an established or predicted presence in their infusions (Fig. 1, 2 and Tables 1–3). Species-specific compounds include for *A. annua* infusions some monoterpenes (*e.g.*, linalool, limonene), sesquiterpenes (*e.g.*, arteannuin B, dihydroartemisinic acid, possibly ART), flavonoid aglycones (*e.g.*, casticin, cirsilineol) and coumarins (*e.g.*, esculetin, eleutheroside B1); for *A. afra* infusions only some monoterpenes (*i.e.*, thujones and 6,7-epoxylinalool) as well as the flavonoid aglycone quercetin, keeping in mind that the aqueous extracts of this species remain far less investigated than those of *A. annua*[26,30,61,62,94] and still await extensive analysis.[30,63,111–113] Considering that the two species contain groups of similar metabolites, their infusions are likely to share a larger body of common compounds than the few ones detected up to now (*i.e.*, camphor, eucalyptol, artemisia ketone, luteolin, cynaroside, several CGAs, scopoletin and scopolin). Plants most phytochemically similar to *A. annua* and *A. afra* are, as could be expected, other species within the very large *Artemisia* genus (>300 spp.).[151,154,166,167] Strikingly, significant amounts of ART and dihydro-ART were reported in various *Artemisia* spp., including plants of immense geographic distribution such as mugwort (*A. vulgaris*) or frequent human consumption such as absinth (*A. absinthium*) and tarragon (*A. dracunculus*).[96,168] The exact origin of these endoperoxides in *Artemisia* spp. other than *A. annua* is intriguing, since (i) as the most studied species and prototypical ART producer, *A. annua* itself lacks the final biosynthetic enzymes to produce ART from dihydroartemisinic acid.[169–171] In this species, ART is now admitted to be generated by the sensitized photo-oxidation of dihydroartemisinic acid in the plant glandular trichomes, giving rise to self-assembling allylic hydroperoxides;[54,93,172–174] (ii) to the best of our knowledge, dihydroartemisinic acid was not described in *Artemisia* spp. other than *A. annua*.[96,97] The identification of dihydro-ART as a natural product further broadens these interrogations, being the first example of a lactol congener amongst related lactonized 1,13-dihydrosesquiterpenes (*e.g.*, arteannuins I-M).[54] This suggests that dihydro-ART originates *in planta* from dihydroartemisinic aldehyde, the established precursor of dihydroartemisinic acid,[169,170] rather than from the late-stage reduction of ART itself. Biologically, *Artemisia* spp. often exert pronounced growth inhibitory activities in *Plasmodium* asexual blood stages *in vitro* as well as *in vivo* antimalarial effects in infected mice models, associated with uses in traditional medicine.[166,175–185] However, these properties seem equally found in ART-containing as well as ART-deprived species, a situation reminiscent of that of *A. annua* and *A. afra*. Nevertheless, no *Artemisia* species has reached the repute and development of *A. annua* or *A. afra* as an antimalarial remedy, likely due to an absence in disease-endemic countries despite significant distribution ranges elsewhere. In marked contrast, *A. annua* has an ancient history of human use and is now naturalized in many temperate parts of the planet, with *A. afra* now following the same trend throughout Africa from its originating East- and South-African regions. These aspects are favoring their generalized use against malaria, and underline the necessity and relevance of their in-

depth pharmacochemical, parasitological and biomedical examination. A third species to investigate against drug-refractory *Plasmodium* parasites would be the perennial *A. vulgaris*, due to its strong antiplasmodial activity and abundance in Eurasia.[175,179,180] Common metabolites between most *Artemisia* spp., such as ubiquitous monoterpenes, flavonoids and CGAs,[151,154,166,182,186] are also widely distributed across the plant kingdom with important occurrence in the Asteraceae family, but their presence does not appear to correlate with antiplasmodial or antimalarial activities of the corresponding species.

Plasmodium liver stages are refractory to most antimalarials except antimetabolites (including atovaquone) for replicative stages and 8-aminoquinolines for replicative and dormant stages.[50,187,188] *Plasmodium* gametocytes, particularly at the transmittable stage V, share with the hypnozoites this narrow sensitivity to 8-aminoquinolines but are also inhibited by methylene blue,[37,187,189] which is yet ineffective against hypnozoites.[190] *A. annua* and *A. afra* infusions have a well-documented effect on gametocytes, mediated to a significant extent by ART,[29] but also inhibit *Plasmodium* liver stages independently of ART.[27] These results argue for the investigation of both *Artemisia* spp. infusions regarding antiplasmodial phytochemicals distinct from ART, either known or novel, and targeting these drug-refractory parasite stages. In this respect and compared to that of *A. annua*, the infusion of *A. afra* is poorly investigated while seemingly more active,[27] potentially constituting a distinct source of antiplasmodial metabolites. Except for ART and dihydro-ART, the natural products present in *A. annua* and *A. afra* infusions show modest to intermediate activity against *P. falciparum* asexual blood stages. Evaluating these metabolites against other parasite species or stages critical for drug intervention (*i.e.*, *P. vivax* dormant hepatic stages, the hypnozoites, and to a lesser extent *P. vivax* and *P. falciparum* sexual stages, the gametocytes) is nevertheless important, because their sensitivity to given phytochemicals cannot be anticipated from growth-repression effects in asexual blood stages. This trend is illustrated by primaquine, a potent hepatic schizonticidal, anti-hypnozoite and gametocytocidal drug having less prominence against blood schizonts.[37,191,192]

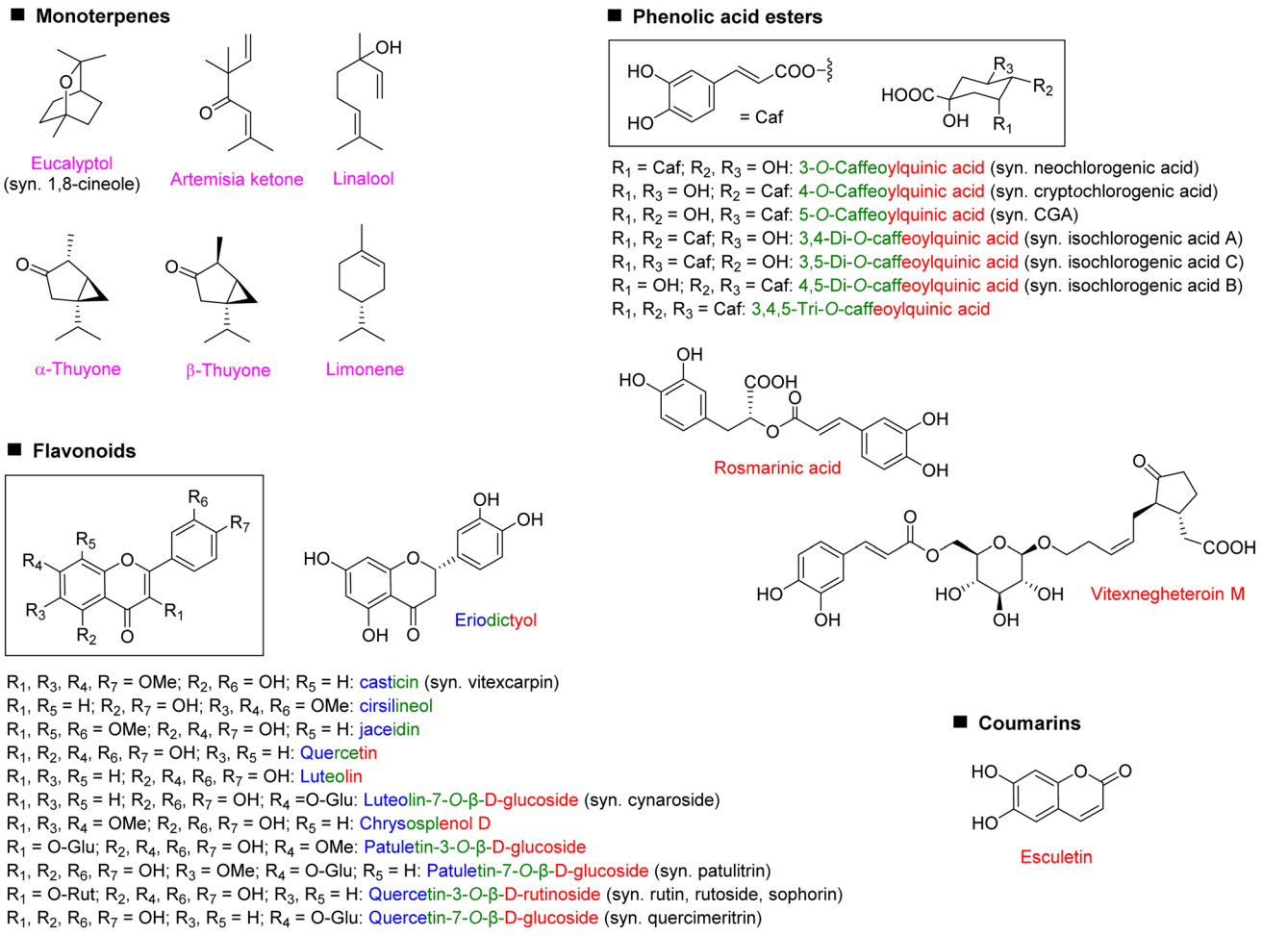


Fig. 3 Non-ART phytochemicals representative of *A. annua* and/or *A. afra* infusions with putative modes of antiplasmodial action, *i.e.*, inhibition of prenyl-associated enzymes (*in pink*), inhibition of heme detoxification (in blue), inhibition of FASII (in green) and/or redox cycling (in red). This selection depicts natural products bearing salient pharmacophores against *Plasmodium*, not considering their possibly active metabolites formed *in vitro* (*i.e.* in primary hepatocyte cultures) or *in vivo*.

Considering the diversity of antiplasmodial natural products present in *A. annua* and *A. afra*, the inhibitory effects of their infusions in *Plasmodium* hypnozoites and gametocytes could be explained by a combined, multi-target action of several moderately potent phytochemicals against weakly ART-sensitive parasite stages. However, one cannot rule out the possibility that only very few metabolites are responsible for these effects of the infusions.

Impairment of specific *Plasmodium* stages *via* the inhibition of putative pharmacological targets (*e.g.*, prenyl-associated enzymes, FASII) by *A. annua* and *A. afra* metabolites has been discussed previously.[80–85,102,116,142] The redox-cycling properties of several phytochemicals present in their infusions could also account for the observed loss of viability of drug-refractory parasite stages, known to be highly vulnerable to ROS-generating inhibitors such as primaquine metabolites[50,51,193,194] and methylene blue.[37,195–199] These inhibitors rely on host or parasite reductases for their continuous reduction into pro-oxidant species in presence of a non-limiting reducing cofactor. Redox cycling constitutes in theory the type of oxidative stress least manageable by the parasite, ROS being stoichiometrically generated by a catalytic concentration of inhibitor.[50,194] Redox-cycling properties are typically carried in natural products by catechol (syn. 1,2-dihydroxyphenyl)[200,201] and quinol (syn. 1,4-dihydroxyphenyl) systems, prone to spontaneous oxidation due to their low mid-reduction potential.[202] Catechol systems are embedded in several flavonoid aglycones (*e.g.*, eriodictyol, chrysosplenol D, Table 1 and Fig. 3) and heterosides (*e.g.*, cynaroside, rutin, Table 1 and Fig. 3), most phenolic acid esters (*e.g.*, rosmarinic acid, all caffeoyl-containing CGAs, Table 2 and Fig. 3), some coumarins (*e.g.*, esculetin, Table 3 and Fig. 3) as well as in recently described caffeoyl-glucosides (*e.g.*, vitexnegheteroin M, Fig. 2 and 3)[115] from either *Artemisia* spp. infusions. Regarding flavonoid *O*-heterosides, their spontaneous or glycosidase-mediated hydrolysis might also generate such redox pharmacophores *in situ* by freeing key hydroxyl functions. This might also be the case for flavonoid aglycones, susceptible of undergoing CYP450-mediated metabolization (*i.e.*, *O*-demethylation and/or *ortho*-hydroxylation) in the liver.[203–206] Strikingly, this latter metabolization is the hallmark of primaquine bioactivation into anti-hypnozoite and gametocytocidal metabolites *in vivo*, though operated by a different CYP.[50–53,193,194] *In vitro* primary human hepatocyte cultures reproduce *in vivo* CYP activity,[207] making these mechanistic hypotheses assessable (*e.g.*, in presence of CYP-specific inhibitors). This global insight on known *A. annua* and *A. afra* phytochemicals with intrinsic targets or redox features (Fig. 3), to be investigated as potential inhibitors of drug-refractory *Plasmodium* stages, does not exclude the discovery of original chemical skeletons (especially from *A. afra*) exerting activity by palpably distinct mechanisms (*e.g.*, covalent inhibition).[67,69]

4. List of abbreviations

AKT:	Serine/threonine protein kinase B
AMS:	Amorpha-4,11-diene synthase
Ara:	β-D-Arabinose
ART:	Artemisinin
CGA:	Chlorogenic acid
CHI1-1:	Chalcone isomerase 1
CYP:	Cytochrome P450
Cyp71av1-1	Amorpha-4,11-diene 12-monooxygenase
DOXP:	1-Deoxy-D-xylulose-5-phosphate
EO:	Essential oil
Fab:	Fatty acid biosynthesis
FAS:	Fatty acid synthase
Glc:	β-D-Glucose
G6PD:	Glucose-6-phosphate dehydrogenase
MEP:	Methylerythritol-4-phosphate
mTOR:	Mammalian target of rapamycin
PI3K:	Phosphatidylinositol 3-kinase
ROS:	Reactive oxygen species
Rut:	β-D-Rutinose

5. Conflicts of interest

There are no conflicts to declare.

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