Computational identification of plant microRNAs targeting *Plasmodium falciparum*: a new strategy to address the challenges of modern malaria treatment

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Abstract

Malaria remains one of the greatest challenges to global health, with *Plasmodium falciparum* responsible for the majority of severe cases and deaths, despite significant progress in diagnosis and treatment. Resistance to antimalarial drugs, particularly associated with *P. falciparum kelch13* (*PfK13*) mutations in Africa, as well as resistance to partner drugs such as piperaquine and lumefantrine, and limited efficacy of vaccines, necessitate the search for new therapeutic approaches. This review analyzes the current challenges in malaria treatment, focusing on the role of microRNAs (miRNAs) as potential regulators of the immune response and potential therapeutic targets. Special attention is paid to the computational screening of plant miRNAs that have promise in suppressing the expression of parasitic genes in *P. falciparum*. We reviewed recent literature on the molecular mechanisms of antimalarial drug resistance and the potential applications of miRNAs in malaria therapy, focusing on host- and parasite-derived miRNAs, their roles in pathogenesis, and experimental therapeutic strategies, including nanoparticle-mediated miRNA delivery. Emerging data indicate that specific host miRNAs (*e.g.*, miR-451, miR-223) can modulate erythrocytic invasion, inflammatory responses, and disease outcomes. In parallel, advances in RNA-based therapeutics demonstrate the feasibility of miRNA mimics and inhibitors as adjunctive tools to complement existing antimalarial regimens. The integration of miRNA-based approaches into malaria therapy represents a promising frontier that could overcome the limitations of conventional drug-based strategies. Future research should prioritize the functional characterization of miRNAs, optimization of delivery systems, and evaluation of combinatorial therapies to enhance clinical translation.

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Introduction

Malaria remains one of the world's most deadly parasitic infections, causing over 600,000 deaths annually, mostly among children under 5 years of age in Sub-Saharan Africa.[1] Despite the availability of effective treatments, the implementation of therapy is hampered by a combination of pharmacological, genetic, and epidemiological factors that limit treatment success and threaten global control efforts.

Drug resistance as a major obstacle

The development of resistance in malaria pathogens to antiparasitic drugs remains one of the most critical barriers to effective treatment of this disease. *Plasmodium falciparum*, the primary causative agent of tropical malaria, has developed widespread resistance to several key antimalarial drugs, including chloroquine,[2] sulfadoxine-pyrimethamine,[3] and, most concerningly, artemisinin and its partner drugs used in artemisinin-based combination therapies.[4] Mutations in the *P. falciparum kelch13* (*PfK13*) gene, which are associated with delayed parasite clearance from the blood, were first identified in the Greater Mekong region, but have now spread to countries in East Africa.[5] Furthermore, *Plasmodium vivax*, although traditionally considered less pathogenic than *P. falciparum*, has also shown resistance to chloroquine in several regions of Asia and South America.[6]

Side effects and limitations of existing drugs

Current antimalarial drugs have a significant toxicity profile, which limits their widespread use and reduces adherence to treatment, especially among vulnerable populations such as pregnant women, children, and immunocompromised patients. The presence of hypnozoite forms of this species requires the use of drugs capable of eliminating the liver stages of the parasite, such as primaquine or tafenoquine. The use of these drugs is complicated by their potential toxicity in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency,[7] which poses additional risks during therapy. Another example is mefloquine, which is often associated with neuropsychiatric side effects, including depression, insomnia, and even psychotic episodes.[8] Quinine can cause serious cardiovascular complications, including cardiotoxicity, and can also cause hypoglycemia and tinnitus.[9] These limitations underscore the urgent need for safer and more effective therapeutic options.

Vaccination challenges: limited efficacy and unavailability

The only malaria vaccine currently approved by the World Health Organization is RTS,S/AS01 (Mosquirix), which provides only a modest level of protection, approximately 30-40% during the initial 12 months following vaccination.[10] The new vaccine candidate R21/Matrix-M has shown promising results in clinical trials, achieving efficacy rates of up to 75%.[11] However, the duration of immune protection and the universality of its effect across age and geographic populations remain poorly understood and require confirmation in large-scale population studies. An additional limiting factor for widespread vaccination in endemic tropical regions is the need to maintain cold chain conditions for vaccine storage and transportation.[12]

Limitations of chemoprevention and mass campaigns

Prophylactic use of antimalarial drugs, particularly among travelers or as part of seasonal malaria chemoprevention programs in children, significantly reduces the risk of *Plasmodium spp.* infection, but if the regimen is not followed, it may contribute to the selection of resistant strains of the parasite.[13] Similar risks arise with the mass use of artemisinin combination drugs in mass drug administration programs, especially if such a strategy is not accompanied by adequate diagnostic monitoring.[14] In these conditions, uncontrolled use of drugs creates additional selection pressure on the pathogen population, which can accelerate the development and spread of drug resistance.

Insufficient access to diagnostics and quality treatment

In many endemic regions, malaria diagnostics, including both conventional microscopy and rapid diagnostic tests, remain underdeveloped, particularly for the detection of asymptomatic infections and cases caused by *P. vivax*.[15] In addition, the proliferation of counterfeit antimalarial drugs is a serious problem: studies show that up to 20% of drugs available on the market in Africa may be counterfeit or not meet regulatory quality standards.[16] This significantly complicates effective treatment and controls the development of resistance.

Given the convergence of these challenges – rising drug resistance, limitations of chemoprevention, diagnostic gaps, and the circulation of substandard medicines – there is a pressing need to explore novel approaches to malaria treatment that go beyond conventional pharmacological interventions. In this context, recent research has highlighted the promising role of microRNAs (miRNAs), small non-coding RNAs that regulate gene expression, in host-parasite interactions. miRNAs have been implicated in modulating immune responses, influencing parasite development, and even serving as potential biomarkers for disease severity. Harnessing these regulatory molecules offers a unique opportunity to develop innovative adjunctive therapies capable of enhancing the efficacy of existing treatments and addressing the growing threat of resistance.

The role of microRNAs in the pathogenesis, immune response, and potential therapy of malaria

miRNAs are small non-coding RNAs of 18-25 nucleotides in length that regulate post-transcriptional gene expression and play a key role in cellular homeostasis, immune response, and anti-inflammatory processes. In recent years, miRNAs have been considered as biomarkers of malaria infection, regulators of acute and chronic responses to parasite load, and potential molecular targets for therapy. Studies have shown that malaria infection causes significant changes in the circulating pool of miRNAs: increased dysregulated levels of miR-451, miR-16, and miR-223 have been found in patients with *P. falciparum*, which correlates with the severity of the disease;[17] miR-150 and miR-146a have an immunomodulatory effect, suppressing the production of pro-inflammatory cytokines and the recruitment of T cells.[18] In experimental models, such as in mice infected with *Plasmodium yoelii*, miRNAs have been shown to affect erythrocyte maturation, macrophage activation, and interferon production.[19] These profiles can be used to distinguish between asymptomatic and severe disease, as well as for early detection of complications, including cerebral malaria.[20]

Stable exosomal miRNAs, which retain a distinct pattern, have been identified in the plasma of infected patients. In particular, miR-150-5p, miR-122, and miR-19b have been proposed as specific biomarkers of malaria, as they do not cross-react with other tropical infections.[21] Elevated levels of miR-451a in erythrocytes have also been associated with hyperparasitemia and anemia.[22] The use of miRNA in diagnostics has several advantages, including: i) the possibility of obtaining samples through minimally invasive procedures (serum or plasma analysis); ii) high sensitivity in the early stages of infection; and iii) the ability to determine the severity of the disease before the appearance of clinical symptoms.

There is also emerging evidence that the *Plasmodium* parasite can modulate the expression of host miRNAs: *P. falciparum* induces global miRNA suppression in erythrocytes, thereby weakening antiparasitic mechanisms.[23] Some parasite proteins interact with components of miRNA-mediated regulation, in

particular with Argonaute complexes.[24] The possibility of the existence of the parasite's own miRNA-like non-coding RNAs, which may act as "molecular traps" in the human immune system, is also discussed.[25]

miRNAs can be used as therapeutic targets, particularly by inhibiting overactivated miRNAs that suppress immunity (*e.g.*, miR-21, miR-146a), thereby enhancing the immune response to infection.[26] In addition, delivery of miRNA mimetics (*e.g.*, miR-150 or miR-451) can restore homeostasis in patients with severe malaria. Combining antimalarial therapy with miRNA modulators that affect cellular responses or interfere with parasite replication has the potential to increase treatment efficacy and reduce the risk of resistance.[27] However, clinical application faces a number of challenges, including the instability of miRNAs in the blood, difficulty in delivering them to infected cells, and possible nonspecific effects.

Materials and Methods

In this study, we conducted a computational analysis of the interactions between miRNAs derived from antimalarial plants and the transcriptome of *P. falciparum* (strain 3D7), focusing on the erythrocytic stage of parasite development. This stage is crucial in malaria pathogenesis and is the most promising for experimental intervention.

An algorithm was developed that performs pairwise sequence alignments between each miRNA (~2200 sequences) and all *P. falciparum* mRNAs (~5500), yielding approximately 12.5 million alignments. Initial evaluation was performed using Smith-Waterman local alignments for both the full sequence and the seed region.[28] The calculation of hybridization energy between miRNA and mRNA was implemented partially due to computational limitations but is planned for full implementation.[29]

It is important to consider not only the best energetic interaction but also the average values of complementarity and energy over all potential binding sites within the mRNA. We also take into account the energy of access to the sites and the possible absence of the canonical RNA interference mechanism in *Plasmodium* (absence of Dicer, Drosha, and Ago2 proteins).[30,31] Despite this, there is evidence that human miRNAs (in particular hsa-miR-451 and hsa-miR-140) are able to enter infected erythrocytes and suppress the expression of parasitic genes, which has been experimentally confirmed.[32,33] As part of our analysis, we compared the complementarity of plant miRNAs with known human miRNAs that exhibit antiparasitic activity. For each plant miRNA, similarity coefficients (seed and full sequence) to human miRNAs, such as hsa-miR-451a, hsa-miR-140-3p, and hsa-miR-140-5p, were calculated.

Results

A number of candidates among plant miRNAs with high similarity values were obtained. Recent evidence supports the concept of cross-kingdom regulation, where plant-derived miRNAs may influence host and pathogen gene expression. Our comparative analysis revealed strong sequence similarities between several plant miRNAs and their human counterparts, which have known roles in malaria pathogenesis. We identified a shortlist of candidates based on high sequence complementarity to vital parasitic genes, notably *P. falciparum* erythrocyte membrane protein 1 (PfEMP1). The selected plant miRNAs, detailed in Table 1, are not random sequences but are evolutionarily honed regulators with functions in plants that suggest a latent potential for targeting parasitic processes.

ppe-miR396a (*Prunus persica*): this miRNA is known to fine-tune growth and development in plants through targeted suppression of growth-regulating factors, thereby regulating cell proliferation and differentiation.[34,35] It is hypothesized that this highly specific targeting mechanism may be leveraged to silence essential proliferative genes in *P. falciparum*, potentially disrupting the parasite's rapid replication cycle within human erythrocytes.

Table 1. Putative cross-kingdom interactions between human and plant miRNAs.

Target human miRNA	Plant miRNA (name)	Plant species	Plant gene (reference)	Plant miRNA Sequence	Seed similarity	Whole sequence similarity	Presence in Chad and usage
hsa-miR-140-3p	ppe-miR396a	*Prunus persica* (peach)	Targets growth-regulating factor genes	UUCCACAGCUUUCUUGAACGG	0.80	0.571	Present in some urban areas; cultivated for fruit consumption
hsa-miR-140-5p	ptc-miRf11655-akr	*Populus trichocarpa* (black poplar)	Putative regulator of auxin response factors	UACCAACGGAAUUACCGACGGA	0.704	0.666	Limited presence; occasionally used in reforestation or as ornamental tree
hsa-miR-140-5p	ath-miRf10951-akr	*Arabidopsis thaliana* (ladies' rock cress)	Related to stress-responsive transcription factors	AAGUGGUGAUGUCUUCUACUCGACC	0.794	0.545	Not present; used only as a laboratory model species
hsa-miR-451a	gar-miR2947	*Gossypium arboreum* (cotton)	Involved in cell differentiation and stress response	UAUACCGUGCCCAUGACUGUAG	0.707	0.681	Widely cultivated in Chad for fiber; key to economy and export
hsa-miR-451a	Han-miRN5702	*Helianthus annuus* (sunflower)	Linked to lipid metabolism and stress tolerance	CAACAGUUAAGAUCCACGGAGC	0.803	0.590	Commonly cultivated for edible oil production and livestock fodder
hsa-miR-451b	aly-miR399f*	*Arabidopsis lyrata* (lyre cress)	Regulates phosphate homeostasis (PHO_2 gene)	GGGCAAGAUCACCAUUGGCAGA	0.812	0.636	Not found in Chad; primarily used in laboratory research

ptc-miRf11655-akr (*Populus trichocarpa*) and ath-miRf10951-akr (*Arabidopsis thaliana*): these miRNAs are typically involved in mediating plant responses to biotic and abiotic stresses, such as pathogen attack or nutrient deprivation.[36] Their expression is often modulated to rewire defense signaling pathways.[37] This suggests an inherent ability to target genes within complex signaling networks, a mechanism that could be directed against *Plasmodium*'s own stress response and virulence pathways.

gar-miR2947 (*Gossypium arboretum*): this miRNA has been implicated in the response to fungal pathogens, regulating genes involved in the plant's immune defense. This plant-derived miRNA could directly interfere with the parasite's ability to evade host immunity, reduce pathological sequestration, and mitigate severe disease outcomes.[38] Its role in combating infection indicates an evolutionary selection for targeting foreign invaders, making it a prime candidate for cross-kingdom activity against a human parasite like *P. falciparum*.

han-miRN5702 (*Helianthus annuus*): identified in the stress-resistant medicinal plant *Hippophae rhamnoides*, han-miRN5702 is characterized as part of regulatory modules controlling seed development and oil biosynthesis processes that require precise metabolic regulation under energy-limited conditions.[39] This suggests that han-miRN5702 evolved to fine-tune genes essential for adaptation and resource allocation in harsh environments. Given the emerging evidence that host miRNAs can influence *P. falciparum* gene expression, we hypothesize that han-miRN5702 may have the potential to target parasite genes critical for survival within the metabolically dynamic environment of the human bloodstream. While direct experimental evidence is not yet available, this hypothesis is consistent with the broader concept of cross-kingdom miRNA regulation and motivates functional studies to test its effects on parasitic metabolic pathways, stress responses, or virulence mechanisms.

aly-miR399f* (*Arabidopsis thaliana*): a passenger strand derived from the miR399 duplex, aly-miR399f* plays a role in maintaining phosphate homeostasis and is now recognized as a stable and functional post-transcriptional regulator.[40] As with its native function, we speculate that aly-miR399f* may target *P. falciparum* mRNAs involved in metabolic adaptation or nutrient sensing to produce cross-kingdom effects. The fact that it was included shows how thorough our computational screening was, as we assessed all possible small RNA regulators that could affect parasitic gene expression in addition to standard guide strands. Table 2 provides examples of plant miRNA candidates for replacing human miRNAs and their potential targets among parasitic genes.

Several human miRNAs, including miR-451a, miR-140-5p, and miR-140-3p, show notable sequence similarity with plant-derived miRNAs, suggesting potential functional overlap. These miRNAs are predicted to target important *P. falciparum* genes such as *PfEMP1* and proteins involved in translation and signaling, which are crucial for parasite survival and immune evasion. In addition, they are linked to host regulatory networks, particularly genes associated with immune responses, apoptosis, and red blood cell function, highlighting their possible dual role in modulating both parasite biology and host defense mechanisms.

Host genetic factors profoundly influence the progression and severity of *P. falciparum* infection. Our bioinformatic analysis of predicted target genes for deregulated hsa-miR-140-3p/5p revealed a significant enrichment for those encoding proteins central to malaria pathogenesis, as summarized in Table 3.[42-47]

Table 2. Interaction of human miRNAs with *P. falciparum* genes and homologous plant miRNAs.

Human miRNA (sequence)	Homologous miRNA (species)	Seed similarity	Whole sequence similarity	Main *P. falciparum* target genes	Other important human target genes
hsa-miR-451a (AAACCGUUA CCAUUACUGAGUU)	Han-miRN5702 (CAACA GUUAAGAUCCACGGAGC)	0.80	0.59	PfEMP1 (*PF11_0008*), Cg1 protein (*PF07_0035*), protein phosphatase putative (*MAL8P1.108*), translation initiation factor SUI1 putative (*PF08_0079*)	-
	gar-miR2947 (UAUACCGUGCCC AUGACUGUAG)	0.71	0.68		
hsa-miR-140-5p (CAGUGGUUUAAC CCUAUGGGUAG)	osa-miRf10067-akr (CAAUGGUCGUAUC CAUAGUAGCCAUG)	0.71	0.68	PfEMP1 (*PF11_0008*)	TNFAIP1, TNFAIP8, TNFAIP8L1, TNFRSF10B, TNFRSF10D, TNFRSF12A, TNFRSF19, TNFSF10, TNFSF11, TNFSF9, CD55, CD59, BSG, ATP2B4, SPTB, ANK1, SOCS1, SOCS3, CD36
	ath-miRf10951-akr (AAGUGGUGAUGUCUU CUACUCGACC)	0.79	0.55		
hsa-miR-140-3p (UACCACAGGGU AGACCACGG)	ppe-miR396a (UUCCACA GCUUUCUUGAACGG)	0.80	0.57	PfEMP1 (*PF11_0008*)	C1QTNF2, C1QTNF3, C1QTNF9, TNFAIP1, TNFAIP3, TNFAIP6, TNFAIP8, TNFAIP8L1, TNFRSF10B, TNFRSF11A, TNFRSF13C, TNFRSF19, TNFRSF21, TNFRSF8, TNFRSF9, TNFSF10, TNFSF11, TNFSF8, CD59, ATP2B4, SOCS3, BACH1, CD36
	ptc-miRf11655-akr (UACCAACGGAAUUA CCGACGGA)	0.70	0.67		

Target genes were calculated taking into account the values that were predicted by the method presented by Kyrollos *et al.*[41] These genes are not merely involved but are essential to key pathological pathways, including: i) cytoadherence and severe disease, notably CD36,[42] the primary endothelial receptor mediating sequestration of infected erythrocytes; ii) inflammatory regulation, including TNFAIP3 (A20), a critical negative regulator of the NF-κB pathway that modulates the cytokine storm, and SOCS3, a key inhibitor of cytokine signaling; and iii) erythrocyte homeostasis and complement evasion, featuring ATP2B4,[43] a major locus of genetic resistance to severe malaria, and the complement inhibitors CD55 and CD59,[44] which protect the parasitized cell from lytic attack. The prediction that hsa-miR-140-3p/5p targets this specific suite of genes is highly significant, suggesting it is not a bystander but a potential master regulator directly influencing critical mechanisms of disease severity and host response.

Discussion

The main advantage of using miRNAs against malaria lies in their ability to act specifically on the genes of *P. falciparum* without interfering with the human genome. Unlike conventional pharmacological drugs, which typically target cellular mechanisms in both the parasite and humans, miRNAs enable a more precise effect. This reduces the risk of side effects, since miRNA activity can potentially be individualized and tailored to a specific patient or parasite strain. Although certain challenges remain, such as the cost of synthesis, instability in the bloodstream, and difficulties with efficient delivery, these limitations are gradually being addressed, particularly with the emerging possibility of using inexpensive plant-derived miRNAs.

tRFs in *P. falciparum* and potential interactions with plant miRNAs

Transfer RNA-derived fragments (tRFs) are increasingly recognized as key regulatory molecules across diverse biological systems, including parasites.[48] In *P. falciparum*, tRFs have been identified primarily during the erythrocytic stage of development.[49] They are generated by specific enzymatic cleavage of mature or precursor tRNAs and are typically 14-35 nucleotides in length. The most common classes are tRF-5 and tRF-3, which originate from the 5′ and 3′ ends of tRNAs, respectively.[50]

These fragments participate in several important regulatory processes. They can interact with ribosomes or translation initiation factors, thereby inhibiting parasite protein synthesis. Similar to miRNAs, tRFs can also bind to target mRNAs, resulting in their degradation or translational inhibition.[51] Furthermore, their expression can increase in response to stress conditions such as oxidative stress, elevated temperature, or drug exposure, where they may play a protective role.[52] Some tRFs can also be secreted in extracellular vesicles and delivered to host cells, where they modulate immune responses.[53]

Given their structural similarity to miRNAs – particularly in size and mRNA interaction – it is plausible that certain plant miRNAs may functionally mimic tRFs or interfere with similar regulatory pathways. For instance, plant miRNAs, such as miR-156 and miR-159, have been shown to cross species barriers and interact with the transcriptomes of other organisms, including pathogens.[54-56] This opens up the possibility of developing therapeutic strategies aimed at modulating parasite gene regulation through exogenous plant miRNAs.

Nevertheless, a complete functional replacement of tRFs by miRNAs is unlikely due to differences in their biogenesis, secondary structures, and binding specificities. More plausibly, plant miRNAs may act as partial mimics of tRFs, especially by targeting overlapping mRNAs or signaling cascades during parasite development and host-parasite interactions.

The mechanisms of action of miRNAs can be broadly divided into two areas: i) interference with the parasite's own genetic processes and ii) modulation of the host immune response (Figure 1). In *P. falciparum*, tRFs play a central role in gene regulation. These 14-35 nucleotide fragments (compared to 19-24 nucleotide for miRNAs) can interact with translation initiation proteins such as eIF4G and eIF4A, or directly bind to parasite mRNAs such as *PfEMP1* – a key gene involved in immune evasion. Importantly, *P. falciparum* lacks canonical miRNA-regulatory machinery such as RISC/Ago2, but tRFs appear to act through alternative mechanisms. There is also evidence that parasite-derived tRFs can affect the human immune response, for instance, through direct binding to host mRNAs or interaction with Ago2 proteins. External

Table 3. Key host target genes and their roles in malaria pathogenesis.

Gene symbol	Role/function	Link to *P. falciparum* pathogenesis
CD36	Adhesion receptor expressed on endothelium and some blood cells	Major host receptor mediating cytoadherence of *P. falciparum*-infected erythrocytes to vascular endothelium; this sequestration contributes to microvascular obstruction and cerebral malaria.[42]
ATP2B4	Plasma-membrane Ca2+ATPase (PMCA4), RBC calcium transporter	Genetic variants and regulatory elements in ATP2B4 affect RBC calcium handling and deformability; certain ATP2B4 alleles have been associated with protection from severe malaria.[43]
TNFAIP3 (A20)	Ubiquitin-editing enzyme; negative regulator of NF-κB and inflammatory signaling	As a key brake on NF-κB/TNF signaling, TNFAIP3 modulates the amplitude of host inflammatory responses. Dysregulation of NF-κB/TNF cascades is central to malaria immunopathology (cytokine storm, blood-brain barrier disruption), so TNFAIP3 activity influences disease severity and tissue damage.[45]
TNFRSF10B TNFRSF10D	Death-receptor family members that can trigger apoptosis	Death-receptor signaling contributes to lymphocyte and endothelial cell apoptosis observed in malaria; modulation of extrinsic apoptosis may affect parasite control, immune cell depletion, and tissue pathology. Direct links to malaria are observed in studies of apoptosis and severity.[46]
SOCS3	Suppressor of cytokine signaling 3, inhibitor of JAK/STAT pathways	SOCS3 negatively regulates JAK-STAT downstream of cytokines (*e.g.*, IL-6); altered SOCS3 expression during infection can blunt protective cytokine signaling or fail to restrain damaging inflammation, and OCS3 changes have been reported in cellular responses to *P. falciparum*.[47]
CD55/CD59	Complement regulatory proteins on erythrocytes	CD55 and CD59 inhibit complement activation on RBCs. Their presence on infected erythrocytes protects parasites from complement-mediated lysis; down- or up-regulation of these regulators during infection modifies parasite survival and clearance.[44]

RBC, red blood cell; TNF, tumor necrosis factor; JAK/STAT, Janus kinase/signal transducer and activator of transcription; IL, interleukin.

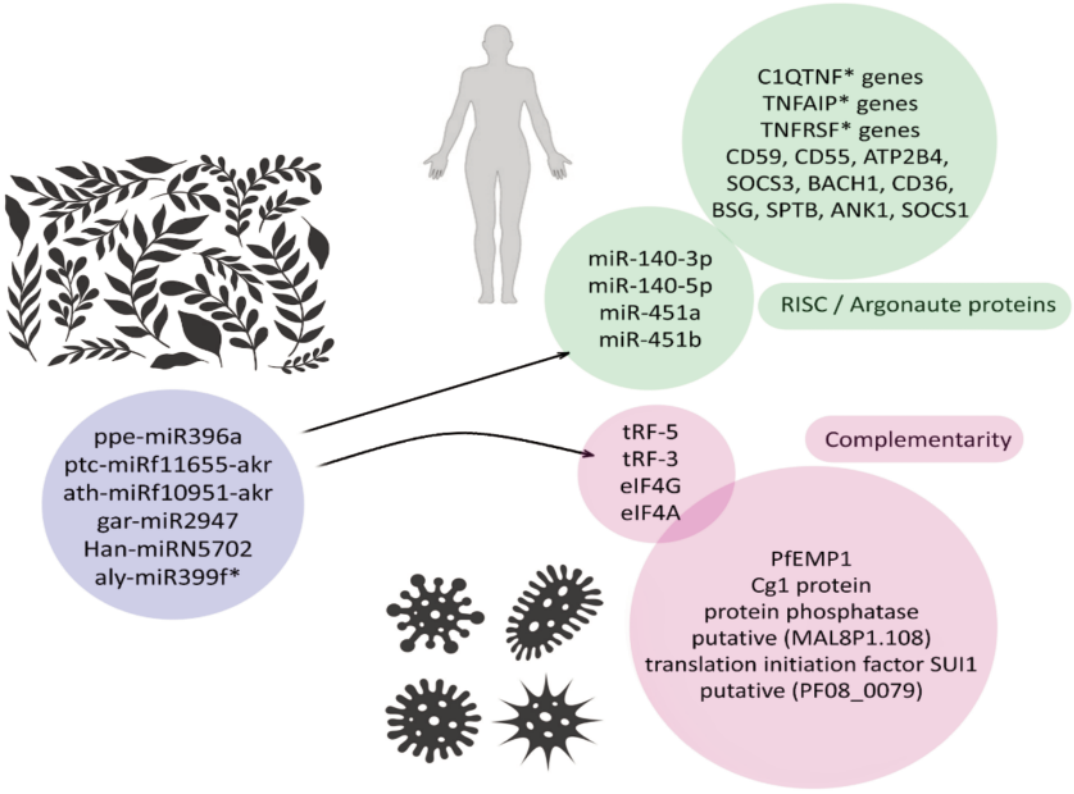

Figure 1. An integrated approach to the use of plant miRNAs in the context of influencing the genetic mechanisms of plasmoids and humans.

miRNAs may therefore disrupt these processes by mimicking or blocking parasite tRFs, ultimately restoring or enhancing host immune defenses. The role of tRFs in stress conditions deserves special attention. They are activated in response to oxidative, temperature, or drug stress. The main antimalarial substance, artemisinin, acts by stimulating the formation of free radicals that destroy parasite cells. In response, the parasite can activate the production of tRFs, which temporarily block cell division or stimulate the synthesis of stress-resistant proteins. This can contribute to the survival of the parasite and the formation of resistance. In this context, the use of miRNAs, in particular of plant origin, is a promising direction in the development of new approaches to malaria therapy. Their mechanism of action not only enables the direct suppression of parasitic mRNAs but also disrupts the immune evasion strategies employed by the parasite through the use of tRFs. This opens up the prospect of creating highly specific, safe, and potentially personalized means of combating malaria, particularly against drug-resistant strains.

Conclusions

Malaria persists as a critical global health challenge, with *P. falciparum* remaining the leading cause of severe morbidity and mortality. The emergence of artemisinin resistance, associated with *PfK13* mutations, reduced efficacy of partner drugs, and limited protection offered by current vaccines, emphasizes the urgent need for alternative therapeutic strategies. Recent findings suggest that miRNAs may play a pivotal role in modulating both host immune responses and parasite survival. In particular, host-derived miRNAs such as miR-451 and miR-223 influence erythrocytic invasion and inflammatory pathways, thereby shaping disease progression. Advances in RNA-based therapeutics, including the development of miRNA mimics, inhibitors, and nanoparticle-mediated delivery systems, highlight the feasibility of this approach. Furthermore, computational studies identifying plant-derived miRNAs capable of downregulating parasite gene expression provide an additional, innovative direction for therapy.

Taken together, these insights support the integration of miRNA-based interventions as complementary strategies alongside conventional antimalarial regimens. Future research should focus on elucidating miRNA functions in malaria pathogenesis, optimizing delivery technologies, and testing combinatorial regimens to accelerate translation into clinical practice.

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