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Drug Discovery for Antimalarial Agents: An Updated Review

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Abstract:

Background: Malaria, a significant global health challenge, is caused by Plasmodium species and transmitted by mosquitoes. Despite control efforts, malaria remains prevalent, with 247 million cases and 619,000 deaths reported in 2021. Challenges such as drug resistance, climate change, and limited healthcare access hinder eradication efforts. Historical treatments based on natural compounds like quinine and artemisinin have saved millions of lives but face resistance issues.

Aim: This review aims to provide an updated understanding of antimalarial drug discovery, current therapies, emerging resistance mechanisms, and innovative strategies to combat resistance and improve treatment outcomes.

Methods: The review synthesizes recent literature on antimalarial therapies, drug resistance mechanisms, and next-generation drug discovery. It highlights innovative partnerships and strategies addressing the limitations of current treatments.

Results: Current therapies, primarily artemisinin-based combination therapies (ACTs), remain effective but face growing resistance challenges. Resistance mechanisms, including mutations in Plasmodium genes like *kelch13* and *PfCRT*, compromise drug efficacy. Innovations in drug discovery focus on novel compounds with unique mechanisms, long-acting formulations, and better tolerability in vulnerable populations. Public-private partnerships, such as the Medicines for Malaria Venture (MMV), play a pivotal role in advancing accessible and effective treatments.

Conclusion: Despite progress, antimalarial drug resistance poses a persistent threat, necessitating continuous innovation. Collaborative efforts in research and development, integrating next-generation therapies and robust resistance monitoring, are critical for sustainable malaria control. Enhancing accessibility and affordability in endemic regions remains paramount.

Keywords: Malaria, Antimalarial drug discovery, Artemisinin resistance, ACT, Drug resistance mechanisms, Next-generation therapies, Public-private partnerships

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Introduction:

Malaria has significantly impacted human genetics and history, resulting in considerable morbidity and mortality over the millennia. The disease, spread by mosquitoes and caused by protozoan species of the Plasmodium genus, is believed to have resulted in over 300 million fatalities in the twentieth century [1]. The symptoms are generally non-specific, including fever, headache, malaise, gastrointestinal trouble, confusion, or maybe coma. Malaria in sub-Saharan Africa, responsible for 95% of cases and 96% of fatalities, incurs an annual economic burden of over US$12 billion. Its sociocultural consequences affect families, education, workplaces, and communities. Despite prior forecasts indicating that malaria would be eradicated by 2030, recent data reveal a troubling increase in occurrences. In 2021, there were approximately 247 million cases and 619,000 fatalities, indicating a significant rise since 2015 [4]. The increase can be ascribed to factors including resistance in parasites and mosquito vectors to pharmaceuticals and insecticides, climate change, alterations in vector distribution, and operational difficulties such as donor fatigue, counterfeit medications, and healthcare disruptions resulting from the COVID-19 pandemic.

In contrast to numerous viral diseases, malaria infections provide restricted immunity to future infections. This partial immunity may arise from either an inadequate immune response or the significant genetic diversity of Plasmodium variations. Notwithstanding these hurdles, recurrent infections frequently lead to milder disease manifestations. The development of a malaria vaccine has been challenging due to the intricacy of targeting a eukaryotic organism with 5,500 genes and sophisticated immune evasion strategies like antigenic diversity. Significant advancements have been achieved. The 2021 introduction of the WHO-approved Mosquirix (RTS,S/AS01) vaccine was a significant milestone, notwithstanding its inability to confer sterilizing protection [5,6]. The R21/Matrix-M vaccine recently demonstrated 75% efficacy in safeguarding children for 12 months in certain areas affected by seasonal malaria. Significantly, participants in clinical vaccine studies also received traditional malaria control interventions, including insecticide-treated bed nets and seasonal malaria chemoprevention. The integration of pre-erythrocytic stage vaccinations with chemopreventive medicines is becoming a persuasive approach for malaria prevention [8]. Historically, malaria has been treated using chemotherapy. Small compounds aimed at inhibiting parasite proliferation have been utilized long before the introduction of antibiotics. Natural compounds such as the quinoline structure in quinine and the endoperoxide linkage in artemisinin, sourced from cinchona bark and sweet wormwood (Artemisia annua), have been employed for millennia as antipyretics. Contemporary antimalarial pharmaceuticals derived from these chemicals consistently preserve millions of lives each year. Drug resistance continues to pose a substantial issue, requiring ongoing innovation in the development of novel and effective antimalarial medications to combat increasing resistance in Plasmodium parasites.

Current Antimalarial Therapies

Malaria is an acute and possibly fatal disease that can advance swiftly, requiring prompt diagnosis and treatment upon suspicion of infection. The predominant treatment for uncomplicated Plasmodium falciparum malaria is artemisinin-based combination therapies (ACTs), with artemether–lumefantrine (AL) commanding a 75% market share in Africa, while artesunate–amodiaquine serves as the second-line option with a 24% share. Infrequently employed combinations comprise dihydroartemisinin–piperaquine (DHA–PPQ), atovaquone–proguanil (Malarone), and quinine in conjunction with doxycycline or clindamycin. Severe malaria patients necessitate injectable therapies, with intravenous artesunate being the preferred choice, while quinine serves as a feasible alternative. Plasmodium vivax infections, common in the Americas, East Africa, and Southeast Asia, are treated with chloroquine alongside either primaquine or tafenoquine for a drastic cure. Preventive interventions are crucial in the management of malaria. Intermittent preventive therapy in pregnancy (IPTp) utilizing sulfadoxine–pyrimethamine (SP) is the established protocol in Africa, provided monthly commencing in the second trimester. Seasonal malaria chemoprevention (SMC) utilizing SP–amodiaquine has been significantly expanded for youngsters aged 6 months to 5 years (and up to 10 years in specific areas), reaching 45 million children in 15 African nations

in 2021, in contrast to only 0.2 million in 2012. These preventative methods, together with medicines providing direct antiparasitic action, are customized according to parameters such as symptom intensity, patient age, pregnant status, and immunological impairment [4].

Next-Generation Antimalarial Therapies

Creating next-generation antimalarial therapeutics necessitates achieving rigorous standards to overcome the shortcomings of current treatments. Central to this initiative are the target candidate profile (TCP), which delineates the requisite attributes of novel chemical compounds, and the target product profile (TPP), which specifies the optimal and minimum standards for new combination medicines. This development is guided by two principal TPP categories: TPP-1 concentrates on therapies for simple malaria, whereas TPP-2 includes chemoprevention and prophylaxis for patients in high-risk regions, including asymptomatic carriers of dormant P. vivax parasites. Chemoprevention is a fundamental strategy in malaria control, particularly in the absence of a comprehensive vaccine. The escalating threat of resistance to SP–amodiaquine necessitates the formulation of alternate pharmaceuticals. Optimal candidates would have two or more effective drugs with unique modes of action, superior safety profiles, and pharmacokinetic compatibility to facilitate monthly administration. Long-acting injectables represent a promising strategy, contingent upon their ability to ensure effective population dispersion and sustained protection. Tropical locations impacted by malaria require therapeutic formulations to maintain stability under elevated temperatures and humidity. Furthermore, given that most malaria cases arise in children under five, new treatments must be well-tolerated in pediatric populations, necessitating creative formulations such as taste-masked and dispersible variants. Pregnant women, including 30 million pregnancies per year in malaria-endemic regions, constitute a vulnerable demographic, highlighting the necessity of reproductive toxicology testing to guarantee drug safety in early pregnancy.

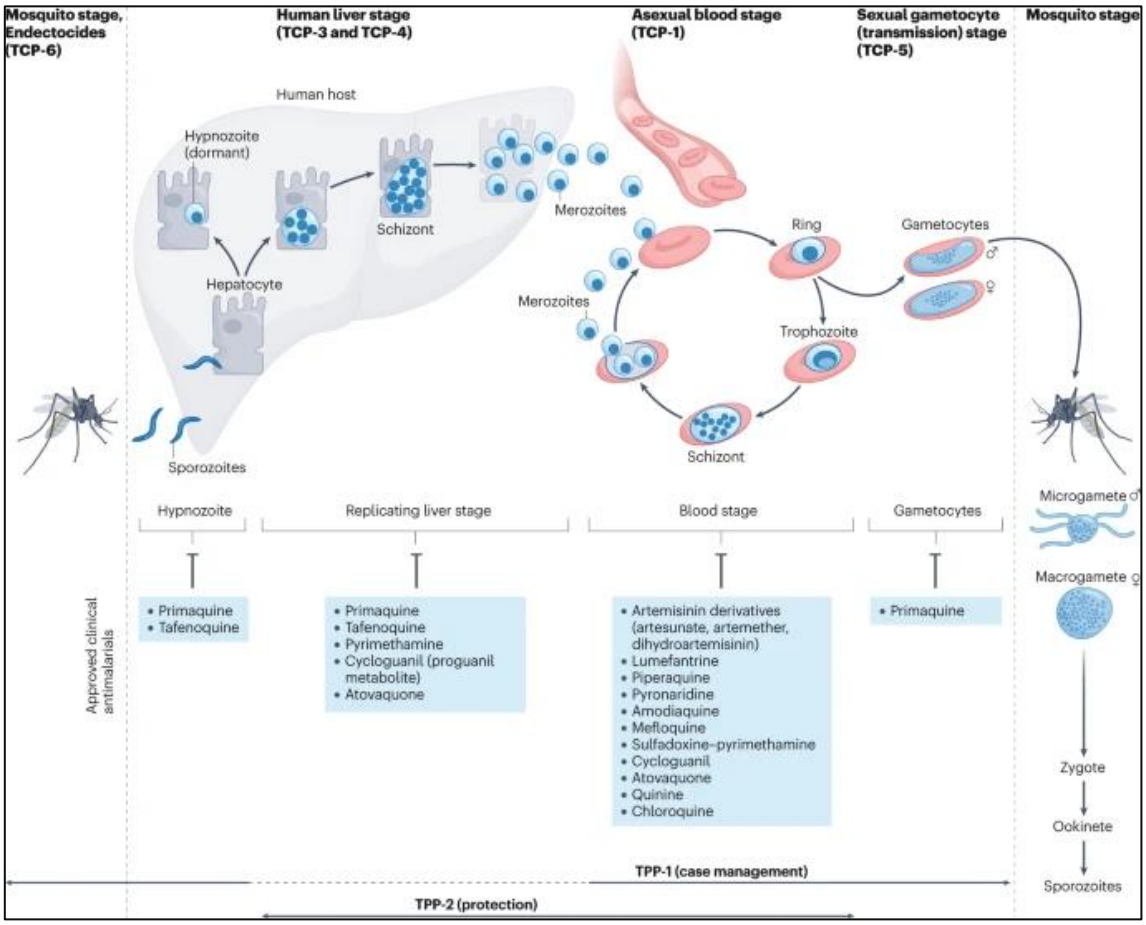

Figure 1: Anti-Malarial Drugs.

Innovations in Antimalarial Drug Discovery

The development of malaria therapeutics poses distinct problems, mostly due to the necessity for fixed-dose combinations of many active compounds to avert resistance and guarantee patient adherence. The discovery method primarily involves discovering individual candidate medications and subsequently assessing optimal combinations based on their modes of action and pharmacological characteristics. In contrast to illnesses common in affluent countries, malaria predominantly impacts impoverished communities in sub-Saharan Africa, frequently requiring complimentary access to medications via public health initiatives and organizations such as the Global Fund. The substantial expenses associated with medication development and restricted financial returns have historically dissuaded pharmaceutical corporations from engaging in malaria research. Innovative partnerships, exemplified by the Medicines for Malaria Venture (MMV), have transformed drug discovery by distributing costs and risks across public and private sectors. Supported by governmental and philanthropic entities, MMV partners with drug development specialists and parasitologists to create and provide effective antimalarial treatments. Its function in enhancing the utilization of existing medicines shapes the goals for subsequent-generation treatments, guaranteeing their availability and efficacy [4].

Antimalarial Drug Resistance

The emergence of *P. falciparum* resistance to antimalarial drugs has posed significant challenges to global malaria control efforts, complicating effective treatment and disease burden reduction [11]. While exceptions like artemether-lumefantrine (AL) and artesunate–pyronaridine demonstrate efficacy, most antimalarial therapies have encountered resistance in various regions [10]. Historical instances include resistance to quinine, which played a pivotal role in eliminating malaria from Europe but saw cases of reduced effectiveness as early as the twentieth century [12]. Resistance to chloroquine and sulfadoxine-pyrimethamine (SP) became widespread in malaria-endemic regions during the 1950s, causing a surge in malaria mortality until the adoption of artemisinin-based combination therapies (ACTs) as first-line treatment in the 2000s [13,14]. The clinical utility of dihydroartemisinin-piperaquine (DHA–PPQ) has been undermined across much of Southeast Asia's Greater Mekong Subregion (GMS), leading to the regional adoption of artesunate–mefloquine despite its previous encounters with resistance [15,16]. Notably, AL, the most widely used ACT, remains effective across Africa. However, partial resistance to artemisinin (ART) has been documented in Rwanda, raising concerns about the evolution of resistance in clinical isolates, as seen in experimental studies in Uganda [17–21]. The combination of artesunate and pyronaridine, though underutilized due to cost, continues to be a viable alternative to AL.

Mechanisms of Drug Resistance and ART

Extensive research has elucidated the mechanisms by which *P. falciparum* develops resistance to antimalarial drugs. For ART derivatives, mutations in the *kelch13* (K13) gene are central to resistance, allowing early ring-stage parasites to survive treatment [21–26]. Clinically, this resistance is characterized by delayed parasite clearance post-treatment without adversely affecting the response rate by day 28, provided the partner drug remains effective. Resistance in vitro is often defined by >1% survival of early ring-stage parasites following a 6-hour exposure to 700 nM DHA. The K13 protein, localized at plasma membrane sites, is involved in hemoglobin endocytosis, a process critical for ART activation through the degradation of hemoglobin into Fe^{2+}–heme [27–29]. Mutations in *kelch13* reduce K13 protein levels, impair hemoglobin uptake, and diminish ART activation, allowing survival of resistant parasites. These mutations also affect other cellular processes, including protein folding, mitochondrial function, and parasite development [30–35]. Interestingly, DHA-treated K13 mutants exhibit heightened susceptibility to mitochondrial inhibitors, suggesting that mitochondria might regulate quiescence and recovery following ART exposure [35]. The impact of specific *kelch13* mutations varies based on parasite genetic background. For instance, the C580Y mutation dominates in the eastern GMS, often co-occurring with secondary genetic factors that facilitate resistance or mitigate its physiological costs [36]. In African strains, *kelch13* mutations impart limited resistance and can negatively impact parasite growth, potentially slowing the spread of resistant strains in these regions [37,38]. Genomic surveillance has identified additional mediators of ART

resistance, including coronin, AP2μ, and ubp1, suggesting the need for expanded genetic screening [28,39–41]. Recent genome analyses have also uncovered shared resistance loci across malaria-endemic regions, with candidate resistance genes identified on chromosome 12 in African samples [42].

ACT Resistance and Emerging Strategies

Resistance to ACTs occurs only when both the ART derivative and its partner drug are compromised [43]. In the GMS, DHA–PPQ resistance resulted from the amplification of tandem genes encoding plasmepsins 2 and 3, enzymes involved in hemoglobin proteolysis and haemozoin formation, coupled with mutations in the chloroquine resistance transporter (*PfCRT*) [44–48]. These mutations enable *PfCRT* to transport PPQ, effectively diverting the drug from its haem target [49–54]. Over time, a few *PfCRT* variants have emerged that confer high-level resistance with minimal fitness costs while also restoring chloroquine susceptibility [51,52,56]. This phenomenon presents opportunities for multidrug regimens that apply opposing selective pressures, thereby suppressing resistance emergence [56]. For example, combining DHA–PPQ with mefloquine or AL with amodiaquine has shown promise in areas with resistance to ART and its partner drugs [57,58]. Additionally, employing multiple first-line therapies, such as AL and artesunate–amodiaquine, could further delay resistance spread by targeting *PfCRT* and the multidrug resistance transporter *PfMDR1* [59]. DHA–PPQ is also being considered as an alternative to SP–amodiaquine for chemoprevention in Africa, given the widespread prevalence of SP-resistant parasites [60,61].

Resistance Studies and Their Implications for Drug Development

Research on resistance often focuses on compounds already in clinical use, yet there remains significant debate over acceptable levels of resistance risk for compounds in the development phase. For instance, in a Phase II dosing study of cipargamin (KAE609) monotherapy, two-thirds of patients with recrudescent malaria (34 of 133 patients) carried the G358S mutation in PfATP4, a concerning resistance marker [62,63]. This study, which tested various dosing regimens, administered cipargamin as a monotherapy, potentially influencing the observed resistance. To address this, stakeholders proposed the use of an *in vitro* minimum inoculum of resistance (MIR) combined with a resistance threshold, expressed as a fold IC50 shift, as a quantitative measure of resistance risk [64]. Emerging evidence, however, suggests that parasite fitness should also be factored into resistance assessments. Measuring MIR is a labor-intensive process but is essential during early development to eliminate chemical scaffolds prone to resistance prior to optimizing compounds. Notably, studies indicate that all compounds targeting specific parasite mechanisms can induce some level of resistance within 60 days in vitro. Consequently, new antimalarial therapies are increasingly being designed as combination treatments to reduce resistance risks.

Strategies for Antimalarial Drug Discovery

The spread of *Plasmodium falciparum* resistance to first-line antimalarials underscores the urgency of developing drugs with novel mechanisms of action. Historically, drug discovery has employed strategies such as isolating and modifying natural products, screening compound libraries, and designing inhibitors targeting known biological pathways [65]. While natural products have provided vital antimalarial drugs, their use is hindered by challenges including variable source composition, unreliable supply chains, and the complexity of isolating active compounds from mixtures [66]. High-throughput screening (HTS) of natural product libraries has yet to yield promising hits of sufficient quality. Although it is theoretically possible to synthesize improved versions of existing natural products like artemisinin (ART), the challenge of overcoming field resistance makes this approach less attractive. As a result, modern antimalarial discovery efforts focus on phenotypic and target-based screening of synthetic small molecules.

Phenotypic Screening for Drug Discovery

Phenotypic screening involves testing large libraries of synthetic compounds against whole-cell parasites at specific lifecycle stages to evaluate *in vitro* activity. This unbiased approach does not rely on predefined targets, allowing researchers to discover active compounds with novel mechanisms of action if such molecules exist in the library. Successful HTS campaigns against *P. falciparum* asexual blood-stage

parasites have been reported [67–70]. This method considers compound properties such as cell permeability and interaction specificity, making it effective for identifying potent candidates [71]. Notable examples of drugs discovered through phenotypic screening include ganaplacide (KAF156), cipargamin (KAE609), cabamiquine (M5717), and ZY-19489. Recently, phenotypic screens have expanded to include liver and gametocyte stages [72,73], as well as modifications to detect slow-acting inhibitors missed in conventional short-term assays [74]. However, phenotypic screening has limitations, particularly the challenge of improving compound potency without knowing the target [75]. A solution involves using focused libraries of compounds targeting known mammalian classes, which may also inhibit *Plasmodium* orthologs. For example, potent amino-amide boronates were optimized to selectively inhibit the *P. falciparum* 20S proteasome [76], and aspartic protease inhibitors were refined to target Plasmodium-specific enzymes Plasmepsins IX and X [77].

Target-Based and Virtual Pharmacophore Strategies

Target-based approaches complement phenotypic screening by enabling the rational design of compounds with enhanced potency and selectivity for specific biological targets. This strategy employs techniques such as DNA-encoded library screening, fragment-based hit identification, and virtual docking of compounds to target protein structures [78]. Target-based screening has produced significant advancements, such as optimizing P218, an inhibitor of dihydrofolate reductase–thymidylate synthase (DHFR-TS), through structure-guided assays [79]. Nonetheless, hits from such screens often require substantial refinement to achieve desired *in vitro* profiles. For instance, initial inhibitors of the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) lacked whole-cell efficacy but led to the development of DSM265 following optimization [80,81]. Despite its success in a Phase IIa study, DSM265 faced resistance challenges due to mutations in DHODH [82]. Target-based approaches also face challenges such as high costs, which limit the size of chemical libraries that can be screened. Virtual screening, a cost-effective alternative, predicts active compounds through computational docking, though subsequent experimental validation is required. Recent virtual pharmacophore models have identified new chemical starting points targeting pathways like DHODH, falcipain 2, and β-haematin formation [83–88]. Although these efforts have not yet yielded potent compounds with broad activity, pharmacophore models and machine-learning tools, such as regenerative modeling (JAEGER), have shown promise in optimizing compound design and identifying novel inhibitors [89].

Approaches to Identifying New Druggable Targets

Target-based drug development relies on the identification and validation of critical parasite targets, including proteins or RNA molecules, that possess chemical and clinical significance. An ideal target should be integral to the parasite's life cycle, have low likelihood of existing resistance, and offer a broad chemical landscape for investigation. Clinically recognized malaria targets comprise cytochrome B (CytB), dihydropteroate synthase (DHPS), dihydrofolate reductase–thymidylate synthase (DHFR-TS), and heme. Furthermore, recent targets like ATPase4 (ATP4), elongation factor 2 (eEF2), prolyl tRNA synthetase (PRS), and phosphatidylinositol 4-kinase (PI4K) have demonstrated potential. Inhibition of these targets frequently leads to swift parasite mortality, guaranteeing favorable patient outcomes when parasite susceptibility and sufficient chemical exposure are attained. Novel targets such as phenylalanine tRNA synthetase (FRS) and acetyl-CoA synthetase (AcAS) have shown in vivo validation but lack clinical testing, whereas preliminary targets like cytoplasmic isoleucine–tRNA ligase (cIRS) and farnesyl pyrophosphate–geranylgeranyl diphosphate synthase (FPPS–GGPPS) are substantiated by in vitro studies. The Malaria Drug Accelerator (MalDA) partnership, comprising 18 research groups, has notably advanced the prioritization of antimalarial targets. Their criteria for target selection prioritize intrinsic qualities and the characteristics of inhibitory substances. Effective targets must be linked to tool compounds that demonstrate swift parasite reduction, limited resistance development in minimum inoculum of resistance (MIR) testing, and extensive efficacy throughout the parasite lifecycle. Moreover, these drugs must exhibit uniform potency across various Plasmodium falciparum strains, particularly those with mutations in multidrug resistance genes such as pfcrt and pfmdr1. Given that these features are essential for compound advancement, they are

similarly significant for the assessment of tool compounds. Nonetheless, discrepancies in resistance risk among tool compounds for the identical target—frequently contingent upon the binding mode—underscore the intricacy of target validation. Target identification strategies are classified according to the availability of tool compounds into compound-dependent and compound-independent methods. Each method presents distinct benefits and drawbacks and can be utilized either separately or in conjunction to identify druggable targets. These methodologies offer a systematic framework to improve the identification of new therapeutic targets, facilitating effective antimalarial therapies.

Compound-Dependent Approaches to Target Discovery

In the last ten years, phenotypic screening initiatives have produced substantial collections of tool compounds essential for target identification. Among compound-dependent techniques, in vitro evolution combined with whole-genome analysis has proven to be the most effective. This methodology has resulted in the identification of significant targets, including ATP4, eEF2, PI4K, AcAS, and several tRNA synthetase inhibitors, namely KRS, cIRS, PRS, and FRS [91,92]. The procedure entails the selection of resistant parasite genotypes using culture or animal models, succeeded by whole-genome analysis to pinpoint resistance-associated mutations that signify prospective target genes. Challenges emerge when resistance develops via nonspecific mutations in pleiotropic resistance factors such as PfMDR1 or PfCRT, instead of the target gene itself. Supplementary compound-dependent tactics encompass proteomics-based techniques, including affinity chromatography and cellular thermal shift tests, which have found targets such as PI4K and PKG [93–95]. Overexpression libraries, in which parasites are transfected with gene-containing cosmids to assess drug resistance, have demonstrated potential in other parasites and could be applied to Plasmodium studies [96,97]. In silico methodologies, although infrequently utilized, possess significant potential. Structural docking and chemical similarity searches undoubtedly aided in identifying atovaquone's mitochondrial target, CytB, owing to its similarities to naphthoquinone inhibitors. Likewise, chemical profiling methodologies, including metabolomics and transcriptomics, have effectively correlated metabolic inhibitor patterns with established targets, such as CytB, DHODH, and DHFR [67,98]. These targets are frequently corroborated using conditional knockdown, protein overexpression, and direct binding analyses employing biochemical or biophysical techniques like as surface plasmon resonance and crystallography. MMV390048 serves as a significant example, wherein chemoproteomics and in vitro evolution investigations validated PI4K as the principal target throughout lead optimization [99]. A consistently recognized target class via in vitro evolution techniques is the tRNA synthetase enzyme family, crucial for protein synthesis.

These enzymes facilitate the ATP-dependent attachment of amino acids to tRNAs and are situated in the apicoplast, mitochondria, or cytoplasm of Plasmodium falciparum. Numerous tRNA synthetase inhibitors exhibit efficacy against liver-stage parasites, rendering them promising candidates for TCP-1 and TCP-4 class inhibitors. The natural product cladosporin facilitated the identification of KRS as a target, prompting the continued development of inhibitors for FRS, PRS, leucine–tRNA ligase, YRS, and IRS [100–106]. The structural characterisation of these targets highlights their significance, as several exhibit species specificity owing to variations in enzyme accessibility and druggability between humans and infections [105–108]. In vitro evolution has confirmed the on-target efficacy of drugs identified from biochemical screenings, including CLK3 and PNP inhibitors [114,115]. Proteasome inhibitors exemplify a significant case, as evolution-based research validates their efficacy against Plasmodium and other diseases. The whole-genome RNA interference screening in Trypanosoma brucei and resistance investigations in Leishmania donovani have identified the proteasome as the target for compounds such as GSK3494245 and GNF6702, which are currently preclinical candidates for diseases including visceral leishmaniasis, Chagas disease, and sleeping sickness [116]. Likewise, multiomic methodologies identified arylsulfonamides as proteasome inhibitors in Trypanosoma cruzi, underscoring the adaptability of compound-dependent strategies in enhancing drug development.

Conclusion:

Malaria continues to pose a formidable public health challenge, demanding persistent innovation in prevention, treatment, and drug discovery. Despite notable advancements such as the Mosquirix and R21 vaccines, significant hurdles remain, including limited vaccine efficacy and the genetic complexity of *Plasmodium*. Current antimalarial therapies, predominantly ACTs, have saved millions of lives but face increasing resistance. Mechanisms like kelch13 mutations and partner drug failures highlight the need for robust genomic surveillance and innovative therapeutic strategies. The emergence of resistance in *P. falciparum*, especially in high-burden regions like sub-Saharan Africa, necessitates a comprehensive approach to drug development. Fixed-dose combinations, multidrug regimens, and new chemical entities targeting different life stages of the parasite are critical. Partnerships such as the Medicines for Malaria Venture exemplify the power of collaborative efforts in addressing the financial and logistical barriers to drug development. The integration of genomic insights into resistance mechanisms further enhances the potential for targeted interventions. Innovative strategies, such as long-acting injectables and pediatric formulations, are essential for addressing the needs of vulnerable groups, including children and pregnant women. Multidrug approaches that exploit opposing selective pressures offer promising avenues for combating resistance while ensuring sustainability in malaria control efforts. The path forward requires sustained investment in research, development, and public-private collaborations to ensure accessible, effective, and durable malaria interventions. By addressing resistance, enhancing therapeutic efficacy, and improving distribution in resource-limited settings, the global health community can move closer to achieving the long-standing goal of malaria eradication.

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كتشاف الأدوية لعلاج الملاريا: مراجعة محدثة.

الملخص:

الخلفية :تعد الملاريا تحدياً صحياً عالمياً كبيراً، حيث تسببها أنواع *البلازموديوم* وتنتقل عبر البعوض. وعلى الرغم من جهود المكافحة، لا تزال الملاريا منتشرة، حيث تم تسجيل 247 مليون حالة و619,000 حالة وفاة في عام 2021. تعيق تحديات مثل مقاومة الأدوية، وتغير المناخ، وضعف الوصول إلى الرعاية الصحية جهود القضاء على المرض. وقد أنقذت العلاجات التاريخية القائمة على مركبات طبيعية مثل الكينين والأرتيميسينين ملايين الأرواح، لكنها تواجه مشاكل المقاومة.

الهدف :تهدف هذه المراجعة إلى تقديم فهم محدث لاكتشاف أدوية علاج الملاريا، والعلاجات الحالية، وآليات المقاومة الناشئة، والاستراتيجيات المبتكرة لمكافحة المقاومة وتحسين نتائج العلاج.

الطرق :تجمع هذه المراجعة بين الدراسات الحديثة المتعلقة بعلاجات الملاريا، وآليات مقاومة الأدوية، واكتشاف الأدوية من الجيل الجديد. كما تسلط الضوء على الشراكات والاستراتيجيات المبتكرة التي تعالج قيود العلاجات الحالية.

النتائج :لا تزال العلاجات الحالية، وعلى رأسها العلاجات المركبة القائمة على الأرتيميسينين(ACTs) ، فعالة، لكنها تواجه تحديات متزايدة بسبب المقاومة. تشمل آليات المقاومة طفرات في جينات البلازموديوم مثل *PfCRT*و*kelch13*، مما يضعف فعالية الأدوية. تركز الابتكارات في اكتشاف الأدوية على مركبات جديدة ذات آليات فريدة، وصيغ طويلة الأمد، وتحمل أفضل للفئات السكانية الضعيفة. تلعب الشراكات بين القطاعين العام والخاص، مثل مبادرة أدوية الملاريا(MMV) ، دوراً محورياً في تعزيز العلاجات المتاحة والفعالة.

الاستنتاج :على الرغم من التقدم المحرز، لا تزال مقاومة أدوية علاج الملاريا تشكل تهديداً مستمراً، مما يستدعي الابتكار المستمر. الجهود التعاونية في البحث والتطوير، ودمج علاجات الجيل الجديد مع المراقبة الصارمة للمقاومة، ضرورية لتحقيق السيطرة المستدامة على الملاريا. يظل تحسين إمكانية الوصول والقدرة على تحمل التكاليف في المناطق الموبوءة أمراً بالغ الأهمية.

الكلمات المفتاحية :الملاريا، اكتشاف أدوية علاج الملاريا، مقاومة الأرتيميسينين، ACT، آليات مقاومة الأدوية، علاجات الجيل الجديد، الشراكات بين القطاعين العام والخاص.