ARTIFICIAL INTELLIGENCE AS A DRUG DISCOVERY TOOL TO OVERCOME DRUG RESISTANCE IN MALARIA

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ABSTRACT

Malaria remains a major global health concern, particularly in low- and middle-income countries, where Plasmodium falciparum causes the most severe and lethal infections. Although significant strides have been made through vector control and artemisinin-based combination therapies (ACTs), the rise of multidrug-resistant strains, especially those harbouring PfKelch13 mutations, has compromised current treatment efficacy. Traditional drug discovery approaches, often slow, costly and linear, struggle to keep pace with rapidly evolving resistance. In this context, artificial intelligence (AI) has emerged as a transformative force in antimalarial drug development. This review explores the diverse roles of AI in accelerating the discovery pipeline, including virtual screening of large chemical libraries, de novo molecular design, prediction of drug–target interactions and in silico ADMET profiling. Notable platforms such as DeepMalaria, LabMol 167, AtomNet®, Aganitha AI and SandboxAQ have demonstrated success in identifying lead compounds active against resistant Plasmodium strains. AI also supports resistance pathway modelling, drug synergy prediction and real-time pharmacovigilance in endemic regions. Despite challenges like data limitations, black-box model interpretability and unequal access to digital infrastructure, AI continues to redefine the antimalarial research paradigm. With growing global investment in computational tools, AI holds substantial promise for delivering next-generation antimalarial agents and strengthening efforts to combat drug-resistant malaria.

KEYWORDS

Antimalarial drug resistance; Artificial intelligence; Deep learning; Plasmodium falciparum; DeepMalaria; Atomwise; LabMol 167; Drug discovery; PfK13 mutation

INTRODUCTION

Malaria remains one of the most formidable global health challenges, disproportionately affecting low- and middle-income countries (LMICs). According to the World Health Organization's (WHO) 2023 Malaria Report, an estimated 249 million cases

and more than 608,000 deaths were reported in 2022, with Sub-Saharan Africa accounting for nearly 95% of this global burden.[1] Children under five years of age and pregnant women continue to represent the most vulnerable populations due to their immunological immaturity and susceptibility to complications.[2] Among the five *Plasmodium* species known to infect humans, *Plasmodium falciparum* is the most virulent, responsible for the majority of severe clinical manifestations and mortality.[3]

Significant progress has been made in malaria control through widespread implementation of vector control measures, such as insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS), as well as the adoption of artemisinin-based combination therapies (ACTs) as the frontline treatment.[4] However, despite these advances, malaria eradication remains elusive. A key barrier to sustained progress is the growing threat of drug resistance, particularly the emergence and spread of multidrug-resistant *P. falciparum* strains.

The declining efficacy of ACTs, which rely on the synergistic action of a fast-acting artemisinin derivative and a longer-lasting partner drug, has raised urgent concerns. Artemisinin resistance has been strongly associated with nonsynonymous mutations in the *PfKelch13* (*PfK13*) gene, especially within its propeller domain. Variants such as C580Y, Y493H and R539T are mechanistically linked to delayed parasite clearance and treatment failure.[5] Initially reported in the Greater Mekong Subregion of Southeast Asia, these resistance-conferring mutations have now been identified in several African countries, including Rwanda and Uganda, regions with high malaria transmission intensity. Their geographic expansion into Africa, the epicentre of global malaria mortality, portends a potential public health crisis.

Compounding the issue is the emergence of resistance to ACT partner drugs such as piperaquine and lumefantrine. Gene amplification of *plasmepsin 2–3* and point mutations in *mdr1* (multidrug resistance 1) and *crt* (chloroquine resistance transporter) have been implicated in reduced drug susceptibility, further narrowing therapeutic options.[6] The convergence of resistance to both artemisinin and its partner drugs threatens to reverse decades of progress in malaria control and underscores the urgent need for novel antimalarial agents with distinct mechanisms of action.

Traditional drug discovery pipelines, however, are inherently ill-equipped to respond to such dynamic challenges. These processes typically involve a linear sequence of high-throughput screening, hit-to-lead optimization, preclinical evaluation and multi-phase clinical trials, a timeline that often spans over a decade and incurs substantial financial investment. The high attrition rates, limited chemical space exploration and modest predictive power of

these conventional workflows further hamper rapid innovation, particularly in diseases such as malaria with complex biology, antigenic variability and multi-stage life cycles.[7]

Against this backdrop, the integration of artificial intelligence (AI) into pharmaceutical research has emerged as a transformative paradigm, particularly in the domain of infectious disease therapeutics. AI encompasses a suite of computational methodologies, including machine learning (ML), deep learning (DL), reinforcement learning (RL) and graph-based neural networks, that can process and learn from vast, multidimensional datasets.[8] These models can extract hidden patterns and predictive features from chemical structures, protein conformations, omics datasets and clinical outcomes to accelerate every phase of the drug discovery process.

AI-driven technologies are now increasingly deployed throughout the antimalarial discovery pipeline.[9] Key applications include virtual screening of extensive chemical libraries, drug–target interaction (DTI) prediction, in silico absorption, distribution, metabolism, excretion and toxicity (ADMET) profiling and de novo molecular design as illustrated in Fig.1. Notable AI platforms have demonstrated promising results in identifying and optimizing novel antimalarial candidates. For example, DeepMalaria, which utilizes graph neural networks, identifies active compounds across multiple *P. falciparum* life cycle stages. LabMol 167, discovered through AI-enabled shape-based screening, targets kinases PK5 and PK7 and exhibits dual-stage inhibition with minimal cytotoxicity.[10,11] AtomNet®, developed by Atomwise with support from the Bill & Melinda Gates Foundation, employs deep convolutional neural networks for structure-based virtual screening.[12] Similarly, Aganitha AI, in collaboration with India's Centre for Cellular and Molecular Biology (CCMB), utilizes fragment-based generative modelling to design novel scaffolds against parasite-specific targets.[13] SandboxAQ has also contributed a quantum-informed chemical dataset exceeding 5.2 million molecules to aid in open-source screening initiatives.[14]

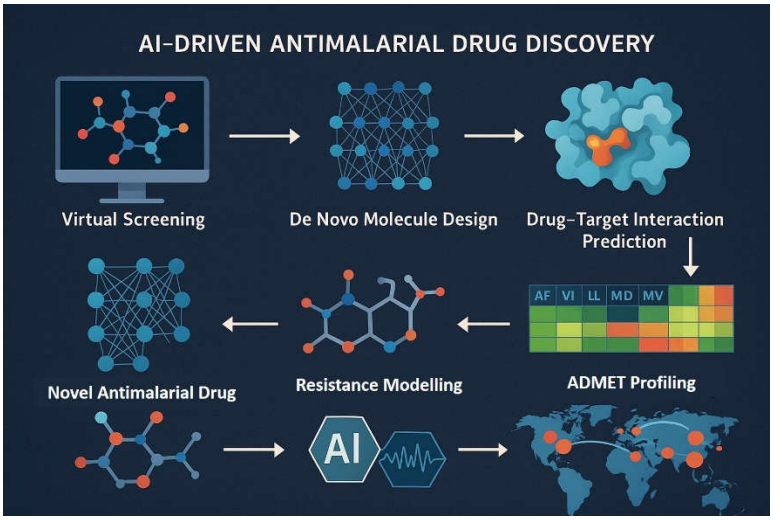

Fig.1. AI-Driven Antimalarial Drug Discovery

Beyond compound discovery, AI tools are revolutionizing system-level insights. These include modelling of host–parasite interactions, prediction of synergistic drug combinations, resistance evolution forecasting and real-time monitoring of molecular surveillance data. Natural language processing (NLP) technologies enable automated mining of clinical literature and adverse event reports, enhancing pharmacovigilance and resistance tracking. Initiatives like Open Source Malaria, Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases initiative (DNDi) are increasingly incorporating AI frameworks to drive innovation, transparency and collaboration. [15–17]

As resistance continues to compromise the efficacy of current treatments, AI offers a critical shift from traditional empirical discovery to data-driven, adaptive and precision-guided therapeutic development. This review explores the expanding role of AI in antimalarial drug discovery and its potential to enable rapid, effective and sustainable responses to the evolving landscape of drug resistance.

MECHANISMS OF RESISTANCE IN MALARIA

The emergence and spread of drug-resistant *Plasmodium falciparum* constitute one of the most critical threats to global infectious disease control. Among the five *Plasmodium* species infecting humans, *P. falciparum* remains the most virulent, contributing disproportionately to malaria morbidity and mortality due to its efficient transmission, high parasitaemia potential and evolving resistance to frontline therapies.[18] For more than two decades, artemisinin-based combination therapies (ACTs) have served as the cornerstone of malaria treatment, combining the rapid action of artemisinin derivatives with longer-acting partner drugs to maximize efficacy and delay resistance. However, declining ACT

effectiveness, initially reported in Southeast Asia and now increasingly observed in sub-Saharan Africa, signals a concerning trend in parasite adaptation. [19,20]

At the molecular level, artemisinin resistance is most strongly linked to mutations in the *Plasmodium falciparum kelch13* (*PfK13*) gene.[21] These mutations, particularly in the propeller domain, are associated with delayed parasite clearance, a clinical hallmark of partial resistance. First identified in western Cambodia, the C580Y variant remains the most widespread and extensively studied. Additional polymorphisms such as Y493H, R539T and I543T have also been implicated.[22] Unlike classic resistance mechanisms that confer full drug insensitivity, *PfK13* mutations allow a subset of parasites to survive artemisinin-induced oxidative stress, likely through interference with the ubiquitin–proteasome system and endocytic pathways that impair cytotoxic accumulation of heme and reactive oxygen species.

A growing concern is the detection of these resistance-associated mutations in *P. falciparum* isolates from African countries such as Rwanda and Uganda. The confirmation of C580Y and R561H variants in sub-Saharan Africa, the region bearing the highest malaria burden, raises the spectre of a continent-wide resistance crisis. The establishment and transmission of these mutations could undermine the therapeutic efficacy of ACTs, eroding decades of progress in malaria control and elimination.[20]

Resistance is not confined to artemisinin alone. ACT success also depends on the sustained effectiveness of partner drugs like piperaquine and lumefantrine.[23] Piperaquine resistance, particularly evident in Cambodia, has been attributed to increased copy numbers of *plasmepsin 2–3*, which encode haemoglobin-degrading proteases in the parasite's food vacuole. This amplification enables continued haemoglobin digestion and nutrient acquisition despite drug exposure. Additionally, mutations in the *crt* (chloroquine resistance transporter) gene, once central to chloroquine resistance, have now been linked to cross-resistance with piperaquine and related quinoline compounds.[24]

Lumefantrine resistance is largely mediated by mutations and overexpression of the *mdr1* gene, which encodes a multidrug transporter responsible for efflux of antimalarial compounds.[25] These genetic changes reduce intracellular drug concentrations and compromise parasite susceptibility. Alarmingly, increasing reports describe *P. falciparum* isolates harbouring combined resistance traits, against artemisinin, piperaquine and lumefantrine, further narrowing therapeutic options and increasing the risk of clinical treatment failure.

In light of this evolving resistance landscape, the development of next-generation antimalarial agents is an urgent priority. Ideal candidates should target novel and essential

parasite pathways, act across multiple life cycle stages, including liver, asexual blood and gametocyte forms, and possess favourable pharmacokinetic and safety profiles. Promising molecular targets include conserved protein kinases, mitochondrial electron transport chain components and epigenetic regulators.

Artificial intelligence (AI) technologies are increasingly being leveraged to address these challenges. AI facilitates the rapid identification of novel chemical scaffolds by enabling predictive screening against resistant *P. falciparum* strains. For instance, LabMol 167, a dual-stage kinase inhibitor targeting PK5 and PK7, was discovered through AI-assisted molecular modelling and has demonstrated potent activity with low cytotoxicity. AI-based genomic tools also enable in silico prediction of resistance-associated mutations, mapping their functional consequences and prioritizing intervention strategies based on gene essentiality and evolutionary conservation.[26]

Furthermore, AI contributes to the modelling of resistance evolution by integrating parasite genomics, epidemiological data and phenotypic screening results. These insights allow for early identification of emerging resistance patterns and inform strategic public health responses. The integration of machine learning algorithms with omics datasets also accelerates the identification of biomarkers for resistance surveillance and treatment efficacy.

The current crisis, defined by *PfK13*-mediated artemisinin resistance and diminishing efficacy of ACT partner drugs, underscores the need for data-driven innovation in drug discovery. A robust understanding of resistance mechanisms is essential for rational therapeutic design and effective clinical deployment. By incorporating AI and computational biology into the antimalarial R&D pipeline, researchers can more effectively discover resistance-resilient compounds, reduce development timelines and improve success rates.

Addressing the challenge of multidrug-resistant *P. falciparum* requires a paradigm shift from traditional discovery models to integrative, adaptive and technology-enabled strategies. AI stands at the forefront of this transformation, offering powerful tools to decode resistance, discover novel leads and safeguard future antimalarial efficacy.

ROLE OF ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY

Artificial intelligence (AI) has emerged as a transformative force in pharmaceutical research, addressing longstanding limitations of traditional drug discovery pipelines. Conventional approaches, characterized by linear workflows, high costs, prolonged timelines and high attrition, struggle to keep pace with urgent therapeutic demands, particularly in diseases like drug-resistant malaria caused by *Plasmodium falciparum*. These limitations are

compounded by the complexity of parasite biology, frequent treatment failures due to resistance and the need for multi-objective optimization encompassing efficacy, safety and accessibility.

AI offers an efficient, predictive and adaptive alternative to conventional methods. Through intelligent automation and data-driven modelling, AI enables high-throughput exploration of chemical space, accurate drug–target interaction (DTI) predictions and rational lead optimization. This shift reduces costs, shortens timelines and increases the likelihood of identifying first-in-class or resistance-resilient compounds.[27]

The power of AI lies in its capacity to learn complex, non-linear relationships from diverse datasets using tools such as machine learning (ML), deep learning (DL), reinforcement learning (RL) and graph neural networks (GNNs). GNNs, for instance, treat molecules as graphs of atoms and bonds, capturing detailed structural features essential for bioactivity prediction. These models generalize well to novel compounds, even with limited experimental data.[28] AI systems leverage a broad range of inputs, including SMILES strings, 3D conformations, protein sequences, omics datasets (e.g., transcriptomics, proteomics) and pharmacokinetic/pharmacodynamic (PK/PD) profiles to develop robust, predictive frameworks.[29]

Advanced AI architectures, such as attention-based models and ensemble learning, integrate these heterogeneous data streams to improve the accuracy and reliability of drug development pipelines.[30] In silico ADMET profiling, toxicity prediction and multi-objective compound optimization are now routinely achieved using AI, streamlining compound triage before costly experimental validation.

AI also supports novel hypothesis generation. Unsupervised learning and clustering techniques uncover hidden molecular patterns linked to efficacy or toxicity, guiding rational drug design.[31] Reinforcement learning further allows adaptive exploration of chemical space, optimizing for potency, selectivity, synthetic feasibility and safety.[32] AI-driven molecular dynamics simulations model protein–ligand interactions and biological processes with high fidelity, revealing conformational dynamics and binding energetics critical for target engagement.[33]

Active learning represents another breakthrough: AI models iteratively propose the most informative experiments, refining predictions with each new data point. This human–AI collaboration minimizes resource use and maximizes discovery speed.[34] Meanwhile, natural language processing (NLP) algorithms mine biomedical literature, patents and clinical trial

databases to extract drug–target–disease associations, facilitating drug repurposing and strategic portfolio expansion.[35]

Collectively, these capabilities enable a shift from trial-and-error methodologies toward a dynamic, integrative and data-centric model of drug discovery. In the context of malaria, where drug resistance continues to erode existing therapies, AI offers an accelerated path to novel, mechanism-informed treatments. By bridging biological complexity with computational insight, AI is redefining the landscape of therapeutic innovation in infectious disease research.

VIRTUAL SCREENING OF LARGE CHEMICAL LIBRARIES

Virtual screening (VS) is one of the most transformative and widely employed applications of artificial intelligence (AI) in modern drug discovery. This computational approach enables the rapid in silico evaluation of vast chemical libraries to identify potential bioactive compounds that interact with specific molecular targets, such as enzymes, receptors or pathogen-specific proteins. By streamlining the hit identification phase, AI-driven VS significantly accelerates the drug discovery timeline, reduces experimental costs and minimizes the consumption of valuable laboratory resources.[36]

Traditional virtual screening approaches, such as molecular docking, pharmacophore modelling and ligand similarity analysis, have historically provided important insights but remain limited by several critical constraints. These include rigid protein conformational assumptions, simplistic scoring functions, inadequate treatment of solvation and induced-fit effects and low sensitivity to complex physicochemical interactions. As a result, they are often associated with high false positive and false negative rates, placing considerable burden on downstream validation.[37]

AI-enhanced virtual screening overcomes many of these limitations by leveraging powerful deep learning architectures capable of learning from complex, high-dimensional molecular data. Convolutional neural networks (CNNs) analyse three-dimensional representations of protein–ligand complexes, capturing spatial and electronic features critical for binding interactions. Meanwhile, graph neural networks (GNNs) represent molecules as graphs, atoms as nodes and bonds as edges, allowing nuanced capture of topological and chemical properties that influence bioactivity. [38]

These models are trained on expansive datasets such as ChEMBL, BindingDB and PubChem BioAssay, which provide experimentally validated ligand–target interaction data. Once trained, AI models can generalize beyond the chemical space encountered in training,

enabling the discovery of novel scaffolds with therapeutic potential. This capacity to extrapolate from learned patterns makes AI particularly well-suited for identifying first-in-class compounds or repurposing existing drugs for new targets.[39]

A major advantage of AI-based virtual screening lies in its superior candidate ranking accuracy. By detecting subtle molecular interaction patterns, AI models can more effectively distinguish active compounds from inactive, thus reducing the false discovery rate and enhancing the quality of hits selected for experimental testing. This precision shortens the iterative cycle of synthesis and screening, ultimately improving the cost-effectiveness and success rate of drug development programs.[40]

Contemporary platforms increasingly integrate hybrid strategies, combining structure-based and ligand-based inputs, including pharmacophore features, docking scores, molecular descriptors and protein–ligand interaction fingerprints, to produce more robust and context-aware models. These multimodal approaches improve scaffold hopping, expand chemical diversity coverage and enable targeting of drug-resistant or previously undruggable proteins.

A particularly impactful innovation is the use of active learning: an iterative process in which AI models identify the most informative compounds for experimental testing, incorporate feedback from results and update predictions in real-time. This closed-loop system enables adaptive chemical space exploration, aligned with therapeutic goals such as enhanced potency, reduced toxicity and multi-target activity.[41]

In antimalarial drug discovery, where resistance continues to undermine current therapies, AI-powered virtual screening provides a strategic advantage. These systems facilitate rapid identification of compounds effective against multiple life stages of *Plasmodium falciparum*, including resistant strains. By enabling deep chemical exploration and intelligent candidate prioritization, AI-based VS is rapidly becoming central to the discovery of next-generation, resistance-resilient antimalarial agents.

DE NOVO MOLECULAR DESIGN

De novo molecular design represents a paradigm shift in drug discovery, offering an innovative alternative to traditional screening and scaffold-hopping approaches. Enabled by artificial intelligence (AI), this strategy allows the generation of entirely novel chemical entities tailored to specific therapeutic goals, without reliance on existing compounds or molecular frameworks.[42] This capacity is particularly significant in the context of antimalarial drug development, where novel scaffolds are urgently needed to overcome emerging resistance in *Plasmodium falciparum*.

The foundation of AI-driven de novo design lies in advanced generative models, such as variational autoencoders (VAEs), generative adversarial networks (GANs), recurrent neural networks (RNNs) and transformer-based architectures.[43] Trained on large chemical datasets encoded as SMILES strings or molecular graphs, these models internalize the grammar and architecture of valid chemical structures. Once trained, they can construct new molecules from scratch, guided by predefined pharmacological and physicochemical parameters.

These models are often coupled with reinforcement learning (RL) algorithms, enabling optimization through reward functions targeting properties such as high binding affinity, selectivity, low toxicity, metabolic stability, synthetic tractability and multi-stage parasitic activity. This allows for iterative refinement of candidate compounds toward molecules with favourable biological and pharmacokinetic profiles.

Unlike conventional medicinal chemistry workflows, which are often slow, linear and constrained by known chemical space, AI-enabled de novo design can explore vast, underrepresented regions of chemical space. This increases the probability of identifying structurally novel and mechanistically distinct scaffolds capable of circumventing established resistance pathways. In malaria research, where resistance to artemisinin and ACT partner drugs continues to rise, such innovation is critical.

De novo molecular design is also being leveraged to develop compounds active across multiple life cycle stages of *P. falciparum*, including asexual blood forms, liver schizonts and gametocytes, thereby contributing to transmission-blocking and prophylactic strategies. AI-generated molecules can be tailored to engage validated or emerging molecular targets such as dihydroorotate dehydrogenase (DHODH), plasmodial kinases (e.g., PK5 and PK7) or PfATP4, a crucial ion homeostasis regulator.[44] Furthermore, integration of pharmacokinetic constraints such as oral bioavailability, half-life and tissue distribution ensures clinical relevance across vulnerable populations, including children and pregnant women in endemic regions.

A critical advancement in this field is the incorporation of synthetic feasibility modules within de novo platforms. These tools assess retrosynthetic accessibility using established chemical reactions, allowing prioritization of candidates that are not only biologically potent but also synthetically viable. This tight coupling between computational design and real-world feasibility significantly reduces downstream attrition.

Several AI platforms have demonstrated substantial success in this domain. Notable examples include Chemistry42 by Insilico Medicine, GENTRL and IBM RXN for Chemistry,

all capable of producing chemically diverse, bioactive and synthesizable molecules.[45] Increasingly, these platforms are being adapted for neglected tropical diseases through collaborations with initiatives like Medicines for Malaria Venture (MMV), ensuring that frontier technologies contribute meaningfully to global health equity.[46]

As generative algorithms evolve and biomedical data becomes more integrative, AI-driven de novo molecular design will become a cornerstone of next-generation antimalarial drug discovery. Its ability to produce structurally innovative, resistance-resilient and pharmacologically optimized compounds positions it as a critical engine for therapeutic innovation in the fight against malaria.

DRUG–TARGET INTERACTION (DTI) PREDICTION

Drug–target interaction (DTI) prediction is a fundamental step in rational drug design, guiding the identification of bioactive compounds with high efficacy and minimal toxicity. Traditional DTI approaches, such as molecular docking or ligand-based screening, often suffer from limited accuracy, poor generalizability and high computational demands. The integration of artificial intelligence (AI) has transformed this landscape, enabling scalable, accurate and data-driven prediction of DTIs.

AI-based DTI models are trained on large datasets containing validated interactions across a broad spectrum of proteins and small molecules. These models leverage diverse data formats, including molecular fingerprints, SMILES strings, 3D ligand conformations and protein sequence or structural features, to predict interaction likelihood and binding affinity. Advanced machine learning architectures, including Siamese networks, attention mechanisms and graph convolutional networks (GCNs), significantly enhance predictive power by learning complex patterns from high-dimensional biochemical data.[47]

In the context of antimalarial research, where many *Plasmodium falciparum* targets remain underexplored, AI facilitates the prioritization of potential drug targets and the identification of novel or repurposed compounds. This approach is especially valuable for overcoming drug resistance, allowing researchers to predict interactions with resistant parasite strains and novel molecular scaffolds.

AI-driven DTI prediction also supports drug repurposing by revealing previously unrecognized interactions between existing therapeutics and essential parasite proteins. Tools like DeepDTI and DeepPurpose are increasingly being tailored for malaria-focused applications using integrated omics and cheminformatic datasets.[48]

When incorporated into broader AI-enabled pipelines, alongside virtual screening, de novo design and ADMET profiling, DTI prediction accelerates the discovery of effective, resistance-resilient antimalarial agents. It reduces experimental burden, enhances target validation and ultimately contributes to more efficient and successful therapeutic development against malaria.

ADMET PROFILING AND SAFETY PREDICTION

A major barrier in drug development is the frequent failure of candidate compounds due to poor pharmacokinetics or unacceptable toxicity, contributing to high attrition rates and escalating costs. Artificial intelligence (AI) has emerged as a transformative tool for early-stage ADMET profiling, predicting Absorption, Distribution, Metabolism, Excretion and Toxicity properties, to prioritize safer and more effective compounds early in the drug discovery pipeline.

AI-driven ADMET models are trained on large datasets from in vitro and in vivo pharmacological studies. These models utilize machine learning algorithms such as support vector machines, random forests and deep neural networks to capture complex relationships between chemical structure and pharmacokinetic behaviour.[49] Advanced techniques like multitask and transfer learning improve generalizability across diverse chemical spaces and endpoints.

AI significantly outperforms traditional QSAR models by accurately predicting risks such as cardiotoxicity (e.g., hERG inhibition), hepatotoxicity, nephrotoxicity and interactions with cytochrome P450 enzymes or drug transporters. Additionally, explainable AI (XAI) methods provide interpretability, enabling researchers to identify and correct structural features responsible for adverse predictions.[50]

In antimalarial drug discovery, early ADMET screening is especially critical due to the need for treatments suitable for vulnerable populations, including children and pregnant women. AI tools can help exclude compounds that cause hematologic toxicity or oxidative stress while optimizing desirable traits like oral bioavailability and metabolic stability. Furthermore, AI models support the prediction of drug–drug interactions, essential in malaria-endemic areas where polypharmacy for co-infections like HIV or tuberculosis is common.

Platforms such as pkCSM, ADMETlab and DeepADMET are increasingly integrated into AI-driven pipelines, ensuring that candidate molecules meet both efficacy and safety standards.[51–53] Looking forward, combining AI with real-world clinical data may further

enhance prediction accuracy, accelerating the development of safe, effective antimalarial therapies.

RESISTANCE PATHWAY MODELLING AND DRUG COMBINATION DESIGN

Artificial intelligence (AI) plays an increasingly vital role in decoding the complex resistance mechanisms of *Plasmodium falciparum* and optimizing drug combination strategies. Artemisinin resistance, largely driven by PfKelch13 mutations (e.g., C580Y) and resistance to ACT partner drugs like piperaquine, lumefantrine and amodiaquine, linked to alterations in *pfcrt*, *pfmdr1* and plasmepsin 2–3, demonstrate the multifactorial, polygenic nature of antimalarial resistance.[54] AI leverages high-throughput omics data (genomics, transcriptomics, proteomics, metabolomics) to model these pathways, predict phenotypic resistance and track the evolutionary dynamics of resistance across endemic regions.

AI models trained on longitudinal datasets can correlate specific mutational patterns with treatment failure, enabling early identification of resistance hotspots and guiding pre-emptive public health responses. Furthermore, AI facilitates the rational design of combination therapies through machine learning models trained on synergy datasets (e.g., DrugComb, SynergyFinder). These tools assess compound structures, target pathways and transcriptomic signatures to predict synergistic or antagonistic drug interactions, identifying combinations that minimize resistance while enhancing efficacy.[55,56] Reinforcement learning (RL) algorithms extend this by simulating dynamic parasite responses to varying drug concentrations and dosing schedules, optimizing regimens that are both effective and resistance-suppressing.[57] This approach is particularly relevant in real-world settings where treatment adherence and resources are inconsistent.

Importantly, AI also supports the repurposing of approved drugs by evaluating synergistic potential with existing antimalarials, thereby accelerating clinical translation and bypassing early-stage development barriers. This is critical in the context of limited investment in neglected tropical diseases like malaria.

By integrating resistance pathway modelling with AI-guided combination design, researchers can systematically counteract drug resistance and develop durable, adaptive treatment strategies, offering a forward-looking framework to sustain malaria control and accelerate eradication efforts.

OVERVIEW OF ADVANCES AND IMPLICATIONS FOR ANTIMALARIAL DISCOVERY

The application of artificial intelligence (AI) in antimalarial drug discovery represents a pivotal advancement in combating *Plasmodium falciparum* resistance. Traditional drug development pipelines, linear, laborious and empirically driven, struggle to keep pace with the rapid emergence of multidrug-resistant parasite strains. In contrast, AI provides a dynamic, data-centric framework that enhances the efficiency, precision and scalability of the discovery process.

AI now underpins critical phases of the antimalarial pipeline, including virtual screening, de novo molecular generation, drug–target interaction prediction, ADMET profiling and resistance pathway modelling. By integrating heterogeneous data, ranging from chemical structures and protein conformations to omics datasets and clinical outcomes, AI enables early identification of high-potential compounds, optimization of safety and pharmacokinetics and pre-emptive adaptation to emerging resistance mechanisms. Notably, AI facilitates the rational design of synergistic drug combinations, addressing polygenic resistance that undermines current artemisinin-based therapies.

Beyond the scientific realm, AI's broader strategic contributions are reshaping the antimalarial research ecosystem. Real-time integration of genomic surveillance data allows for proactive resistance forecasting, while AI-driven drug repurposing accelerates therapeutic development by identifying novel applications for existing compounds. Importantly, AI supports the design of safer therapeutics tailored to vulnerable populations such as children, pregnant women and immunocompromised individuals.

Crucially, the convergence of AI with open-access databases, initiatives like the Medicines for Malaria Venture (MMV) and the expanding availability of computational resources is democratizing innovation. This shift is especially impactful for low- and middle-income countries (LMICs), enabling local research institutions to contribute meaningfully to global malaria control efforts.[58]

As computational capabilities and algorithmic sophistication continue to evolve, AI will transition from a strategic asset to a fundamental necessity in antimalarial R&D. Its power to translate complex biological data into actionable therapeutic insights positions AI as a cornerstone of next-generation malaria drug discovery. Artificial intelligence is redefining the future of antimalarial research, delivering scalable, adaptive and equitable solutions critical to achieving sustainable malaria control and eventual eradication.

AI MODELS AND TECHNOLOGIES APPLIED TO ANTIMALARIAL RESEARCH

The integration of artificial intelligence (AI) into antimalarial research has catalysed the development of innovative strategies to overcome longstanding challenges in drug discovery, resistance mitigation and therapeutic optimization. By leveraging the capacity of machine learning (ML) and deep learning (DL) to identify complex, non-linear relationships within high-dimensional datasets, AI provides a robust framework for accelerating and refining the antimalarial drug development pipeline.

Graph-based neural networks, particularly graph convolutional networks (GCNs), have gained prominence in molecular representation tasks. By modelling molecules as graphs, where atoms serve as nodes and bonds as edges, GCNs capture nuanced structural and chemical properties critical for predicting antiplasmodial activity. Tools like DeepMalaria utilize GCNs to identify potent nanomolar inhibitors against *Plasmodium falciparum*, including resistant strains, demonstrating the utility of these models in lead discovery.[59]

Generative models such as variational autoencoders (VAEs) and generative adversarial networks (GANs) play a central role in de novo molecular design. Trained on chemical structure databases, these models create novel compounds tailored to desired properties like solubility, metabolic stability and target selectivity. The addition of reinforcement learning (RL) allows generative systems to iteratively refine candidates using reward functions optimized for drug-likeness and synthetic feasibility. Transformer-based models, adapted from natural language processing, enhance retrosynthetic prediction and reaction outcome modelling by learning chemical syntax and semantics from SMILES and molecular graph formats.[41]

In structure-based drug design (SBDD), convolutional neural networks (CNNs) are employed to simulate protein–ligand interactions and predict binding affinities with high spatial resolution. Platforms such as AtomNet® utilize deep CNNs to virtually screen large compound libraries against parasite-specific targets. In India, efforts by Aganitha AI in collaboration with the Centre for Cellular and Molecular Biology (CCMB) exemplify the use of AI for fragment-based generative design targeting *Plasmodium* proteins. [12,13]

AI also plays a pivotal role in ADMET profiling, addressing one of the major causes of attrition in drug development. Algorithms such as support vector machines (SVMs), random forests and deep neural networks (DNNs) are trained on curated pharmacokinetic and toxicological datasets to predict key parameters including oral bioavailability, blood–brain barrier permeability, cytochrome P450 interactions and organ-specific toxicity. These

predictions are particularly valuable in optimizing compounds for vulnerable populations, including pregnant women and paediatric patients in malaria-endemic regions.[60]

In the domain of resistance modelling, AI frameworks integrate multi-omics datasets, encompassing genomic, transcriptomic and proteomic data, to identify resistance-associated mutations, model their impact on protein structure and function and simulate their downstream biological consequences. These capabilities enable early detection of emerging resistance patterns and support the rational design of multi-target combination therapies that pre-emptively suppress resistant phenotypes.

The deployment of these AI technologies across antimalarial research is increasingly supported by open-source platforms and collaborative initiatives, including those led by the Medicines for Malaria Venture (MMV). Such efforts are enhancing accessibility, reproducibility and equitable innovation in global health.[58]

With continued advancements in algorithmic performance and data availability, AI systems are becoming integral to the development of next-generation antimalarials, designed to be safe, effective and resilient to resistance, marking a paradigm shift in the global approach to malaria control and elimination.

DeepMalaria: A Graph-Based Deep Learning Model

DeepMalaria is an AI-powered antimalarial discovery tool utilizing graph convolutional neural networks (GCNNs) to predict antiplasmodial activity directly from molecular structure. Trained on ~13,400 compounds from the GSK Tres Cantos Antimalarial Set, the model represents molecules as graphs (atoms as nodes, bonds as edges), enabling it to capture detailed topological and chemical features.[10]

This architecture allows generalization across diverse chemical scaffolds and accurate prediction of bioactivity, including against multidrug-resistant Plasmodium falciparum strains. A key achievement includes identifying nanomolar inhibitors with potent activity against resistant phenotypes. Notably, the model revealed macrocyclic scaffolds with unique binding modes, offering structural novelty and potential to bypass known resistance mechanisms.

DeepMalaria demonstrates strong predictive power across multiple parasite life cycle stages, especially asexual blood stages and gametocytes, making it applicable for both curative and transmission-blocking therapies. By minimizing dependence on traditional in vitro screening, it streamlines early drug discovery, prioritizes leads efficiently and broadens chemical space exploration. DeepMalaria exemplifies the integration of deep learning in

neglected tropical disease research and serves as a scalable model for AI-driven drug discovery pipelines, particularly vital in the fight against drug-resistant malaria.

LabMol 167: A Dual-Stage Inhibitor via AI-Guided Screening

LabMol 167 represents a key outcome of AI-guided antimalarial drug discovery. Identified through a shape-based virtual screening pipeline integrated with machine learning, it targets two essential *Plasmodium falciparum* kinases, PK7 and PK5, involved in parasite proliferation and transmission. The AI system employed molecular shape descriptors, binding site similarity analysis and predictive docking to rank candidates based on spatial fit and interaction potential.[26]

Pharmacological assays showed dual-stage activity, with nanomolar IC_{50} values against both asexual blood stages and ookinete stages, the latter critical for blocking mosquito transmission. LabMol 167 also demonstrated low cytotoxicity in mammalian cells, validating its therapeutic promise. Early-stage AI-driven toxicity filtering helped optimize both potency and safety before experimental testing.

The discovery of LabMol 167 highlights AI's ability to accelerate multi-target lead identification, reduce development attrition and design compounds with broad biological impact. As resistance to single-target drugs grows, dual-stage inhibitors like LabMol 167, enabled by computational screening, offer a strategic path forward for comprehensive malaria control.

Atomwise: Structure-Based Discovery via AtomNet®

AtomNet®, developed by Atomwise, uses deep convolutional neural networks (CNNs) to predict protein–ligand interactions with high speed and accuracy. Funded by a $2.3 million grant from the Bill & Melinda Gates Foundation, it actively supports drug discovery for neglected tropical diseases, including malaria. Unlike traditional docking, AtomNet® treats molecular interactions as 3D spatial grids, enabling CNNs to learn complex binding patterns and predict binding affinity. This allows virtual screening of millions of compounds with superior throughput and precision.[61]

A major advantage is its structural generalizability, critical for Plasmodium falciparum proteins that are conserved or poorly characterized. The platform effectively prioritizes compounds even in the absence of high-resolution experimental data and integrates with medicinal chemistry for faster lead optimization. AtomNet® exemplifies how AI enhances structure-based discovery, enabling scalable, data-driven drug design. In

antimalarial research, it helps uncover novel, resistance-resilient compounds, accelerating progress from in silico prediction to clinical application.

Aganitha AI and CCMB Collaboration: AI-Driven Fragment-Based Antimalarial Design

The partnership between Aganitha AI and India's Centre for Cellular and Molecular Biology (CCMB) merges AI with fragment-based drug design to accelerate discovery of novel Plasmodium falciparum inhibitors. Aganitha's AI platform uses fragment-growing algorithms to expand bioactive cores into potent leads, maintaining pharmacophoric features while optimizing solubility, lipophilicity and metabolic stability. Simultaneously, scaffold hopping explores diverse analogues that retain target affinity and avoid resistance mechanisms.[13]

The approach integrates structure-guided design with AI-driven models trained to assess drug-likeness, synthetic feasibility and bioactivity, streamlining hit-to-lead progression. This significantly reduces experimental load and improves cost-efficiency. Using detailed parasite enzyme structures, the platform applies predictive medicinal chemistry to generate potent, selective and resistance-resilient antimalarial agents. The collaboration reflects a data-centric, interdisciplinary strategy vital for developing next-generation antiplasmodial that are clinically viable and synthetically accessible.

SandboxAQ: Quantum-AI Molecule Dataset for High-Fidelity Antimalarial Modelling

In early 2025, SandboxAQ released a synthetic dataset of 5.2 million quantum-derived 3D molecules, generated via high-fidelity quantum mechanical simulations. Though not malaria-specific, the dataset is proving highly valuable for AI-driven drug discovery targeting *Plasmodium falciparum*. The dataset's quantum-level precision enhances AI model accuracy in predicting structure–activity relationships (SAR) and drug–target interactions (DTI), especially for complex or resistance-linked targets. AI frameworks trained on this data can identify novel scaffolds with antiplasmodial potential, even against drug-resistant strains.[62]

It also supports robust QSAR modelling, enabling efficient virtual screening for bioactivity, ADMET properties and toxicity, streamlining early lead optimization. Multi-objective optimization benefits from the dataset's richness, allowing simultaneous tuning of potency, selectivity and safety. As part of an open-science initiative, the dataset is accessible to academia, non-profits and global health consortia, empowering community-led screening

for neglected diseases like malaria.[63] By uniting quantum chemistry and AI, SandboxAQ advances precision modelling in antimalarial R&D, opening vast, high-resolution chemical space for therapeutic exploration.

CHALLENGES AND LIMITATIONS

Despite its promise, artificial intelligence (AI) in antimalarial drug discovery faces several key barriers:

1. Data Scarcity:

AI performance depends on high-quality training data. However, for *Plasmodium falciparum*, curated datasets, molecular, genomic and pharmacological, remain sparse, inconsistent or poorly annotated. This limits model generalizability, especially for novel targets, life cycle stages or chemotypes.

2. Lack of Interpretability:

Many AI models, particularly deep neural networks, function as “black boxes” with limited transparency. In drug discovery, where mechanistic insight is vital, this opacity complicates lead optimization, regulatory acceptance and scientific validation. The absence of explainable AI (XAI) reduces trust and slows adoption in translational research.

3. Infrastructure Inequities:

Low- and middle-income countries (LMICs), most affected by malaria, often lack access to high-performance computing, cloud resources and skilled personnel. These gaps restrict their participation in AI-driven innovation, exacerbating global health disparities.

4. Ethical and Regulatory Barriers:

Concerns over algorithmic bias, data privacy and lack of reproducibility remain unresolved. The absence of standardized protocols for validation, benchmarking and transparent reporting hinders AI integration into regulatory drug development. Ethical oversight is especially critical when applying AI in vulnerable populations.

To unlock AI's full impact in antimalarial R&D, efforts must prioritize: building open-access datasets, developing interpretable models, investing in LMIC infrastructure and establishing global standards for ethical AI use. Only then can AI-driven discovery be truly effective, inclusive and socially responsible.

FUTURE PERSPECTIVES

AI’s future role in antimalarial research is set to expand well beyond traditional small-molecule discovery, unlocking new dimensions of biomedical innovation. A major frontier

lies in the integration of AI with gene-editing technologies like CRISPR-Cas9 to accelerate target validation in *Plasmodium* species. By analysing large-scale genomic, transcriptomic and proteomic datasets, AI algorithms can predict gene–phenotype associations, identify essential parasite genes and prioritize functional targets for knockout, streamlining the identification of novel therapeutic entry points. Another transformative area is quantum machine learning, which merges the capabilities of quantum computing with classical AI. This combination holds immense potential for simulating protein–ligand interactions, predicting reaction mechanisms and performing molecular dynamics at atomic resolution, tasks that are currently limited by classical computational constraints. Such advancements could significantly improve the precision and efficiency of antimalarial drug design.[64]

AI is also expected to make important contributions to vaccine development. Machine learning models trained on epitope data are now being used to predict antigenicity, immunogenicity and HLA-binding affinities across diverse human populations. These predictions can facilitate the rational design of cross-protective or multivalent malaria vaccines that better address challenges like antigenic variation and immune evasion. Additionally, the creation of collaborative, open-source AI platforms will be critical to overcoming the unique challenges posed by tropical infectious diseases. These platforms should support standardized data curation, model validation and broad participation from researchers in endemic regions. By providing equitable access to computational tools, datasets and high-performance infrastructure, such initiatives can democratize innovation and enable region-specific therapeutic solutions.

The long-term impact of AI in malaria research will ultimately depend not only on technological progress but also on ethical oversight, interdisciplinary collaboration and investment in capacity building across low-resource settings. With strategic implementation, AI is positioned to become a central component in malaria eradication efforts, driving the discovery of safe, effective and globally accessible therapeutics and vaccines.

CONCLUSION

The integration of artificial intelligence (AI) into antimalarial drug discovery represents a significant advancement in the fight against malaria, particularly in regions where drug-resistant *Plasmodium falciparum* strains are threatening the efficacy of existing therapies. Mutations such as PfK13 C580Y and associated markers of partner drug resistance have eroded the reliability of artemisinin-based combination therapies (ACTs), demanding innovative and adaptive solutions. AI now plays a central role across all stages of drug

discovery, offering predictive and data-driven tools that enable the rapid identification and optimization of new therapeutic candidates.

AI-powered platforms like DeepMalaria and LabMol 167 illustrate how graph-based models and kinase-targeted designs can uncover novel, potent compounds with activity against resistant parasite strains. Structure-based approaches, including AtomNet®, Aganitha AI's fragment-based design and SandboxAQ's quantum-derived datasets, allow for high-throughput virtual screening with enhanced structural fidelity. These tools support the generation of new chemical scaffolds while also facilitating hit-to-lead progression with greater efficiency.

Beyond compound generation, AI contributes to accurate prediction of drug–target interactions, ADMET profiling and modelling of resistance pathways, improving the prioritization of drug candidates with favourable efficacy and safety profiles. By mining omics data and mapping host–parasite interactions, AI helps uncover novel targets and provides insights into resistance mechanisms that may guide the rational design of drug combinations or dual-stage therapies.[64]

Despite these advances, significant barriers remain. These include limited access to high-quality malaria-specific datasets, the black-box nature of many deep learning models, infrastructural gaps in low-resource settings and the absence of standardized validation and regulatory frameworks. These challenges must be addressed to fully leverage AI's capabilities in a globally equitable and clinically actionable manner.

As the field progresses, the integration of AI with CRISPR-based functional genomics, quantum machine learning and vaccine design is expected to expand the therapeutic arsenal against malaria. Open-access platforms and explainable AI (XAI) will be critical to fostering global collaboration, transparency and regulatory acceptance. Through continued innovation and strategic implementation, AI is reshaping the landscape of antimalarial research, offering scalable, precise and timely solutions to combat a disease that continues to impact millions worldwide.

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