Int. J. Pharm. Investigation, 2026; 16(2):476-489.
https://www.jpionline.org

Review Article

Exploiting MMR Pathways in *Plasmodium* as Novel Antimalarial Targets: Opportunities and Challenges

Mohammed Tarique[1,*], Ziaullah Sain[2], Yusuf Ahmad[3]

[1]Almanac Life Science India Private Limited, New Delhi, INDIA.
[2]Department of Microbiology, Faculty of Medicine, King Abdulaziz University, Rabigh, SAUDI ARABIA.
[3]International Pioneer School, Salalah, OMAN.

ABSTRACT

Malaria, which is caused by *Plasmodium* parasites, remains a major international health issue, especially in developing countries. The problem of drug resistance has become a major concern, especially with respect to artemisinin-based combination therapies (ACTs). Another approach that has been suggested but not well explored is the targeting of parasite-specific DNA repair mechanisms, such as the DNA mismatch repair (MMR) pathway. MMR is crucial for genome stability by correcting replication errors, and any defect in MMR has a significant impact on parasite survival, adaptation, and drug resistance. Recent studies have shown that *Plasmodium* has a distinct, possibly divergent MMR system compared to the human host, which could be exploited for therapeutic purposes. Disrupting MMR pathways may make parasites more sensitive to DNA damage, reduce their ability to develop resistance, and increase the effectiveness of current antimalarial drugs. However, there are some challenges, including a poor understanding of *Plasmodium* MMR components, possible functional redundancy with other repair systems, and the potential for off-target effects. In this review, we summarize present knowledge of MMR pathways in *Plasmodium*, discuss their potential as new antimalarial targets, and outline hypothetical models for MMR-based therapeutic approaches. We also discuss the major opportunities and challenges that must be overcome to turn this concept into actual antimalarial interventions. Targeting MMR pathways may provide new ways of combating malaria and help in the fight against the increasing resistance to drugs

Keywords: Biomarkers. Drug Resistance, DNA damage, DNA Repair, Malaria, Mutation, MMR, Parasites.

Correspondence:
Dr. Mohammed Tarique
Almanac Life Science India Private Limited, New Delhi-11025, INDIA.
Email: tariqueaiims@gmail.com

Received: 14-10-2025;
Revised: 21-11-2025;
Accepted: 09-12-2025.

INTRODUCTION

Malaria stands as a major public health problem which continues to affect populations worldwide. The World Health Organization (WHO) World Malaria Report 2023 showed that 249 million cases of malaria and more than 608,000 deaths from malaria occurred worldwide during 2022 (Shin *et al.*, 2024). The highest number of malaria deaths happens in sub-Saharan Africa while children under five and pregnant women bear the majority of the burden. A considerable amount of disease burden exists in Southeast Asia alongside the Eastern Mediterranean and Western Pacific and South American regions.

Malaria control and elimination efforts have achieved notable progress since 2000 because of increased funding along with better diagnostic and treatment access and effective vector control programs but the worldwide malaria burden stays unacceptably high (Dhiman *et al.*, 2019). The malaria landscape becomes more difficult to manage because of climate change together with humanitarian crises and expanding insecticide resistance in mosquito vectors which threaten to undo existing achievements. The disease creates extensive social and economic effects which sustain poverty cycles and block development progress in endemic areas. The clinical treatment of malaria depends on chemotherapy which uses artemisinin-based combination therapies (ACTs) as the standard therapy for treating uncomplicated *Plasmodium falciparum* (*P. falciparum*) infections. The combination of artemisinin derivatives with longer-acting partner drugs in ACTs allows for fast parasite elimination and minimizes the risk of developing drug-resistant parasites. Chloroquine and sulfadoxine-pyrimethamine and mefloquine have previously been crucial for malaria control yet their effectiveness is now limited in various regions because of widespread drug resistance. The success of ACTs as a treatment faces a current threat to its effectiveness. Artemisinin resistance emerged in Southeast Asia's Greater Mekong Subregion as delayed parasite clearance occurs after receiving treatment (Manzoni

OPEN ACCESS

Manuscript TECHNOMEDIA

DOI: 10.5530/ijpi.20260154

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

et al., 2024). The emergence of resistance to piperaquine and lumefantrine partner drugs in ACTs has resulted in rising rates of treatment failures. East African regions have recently shown signs of partial artemisinin resistance which creates widespread worry about a global artemisinin resistance spread.

The antimalarial drug development pipeline exists in a fragile state. The development pipeline for antimalarial drugs remains sparse because several promising compounds are under preclinical and clinical investigation but only few have advanced to late clinical trials or obtained regulatory clearance. The extensive length and high expense of antimalarial drug development along with the parasite's genetic adaptation capabilities makes it difficult to introduce new therapies. The rising issue of drug resistance along with a small number of available therapeutic options creates an immediate need to discover fresh drug targets and treatment methods which will maintain the long-term effectiveness of malaria interventions. The ongoing threat of drug-resistant *Plasmodium* parasites requires immediate attention to discover and validate new molecular targets for antimalarial treatment. The majority of traditional antimalarial drugs target only three key parasite pathways that include hemoglobin digestion, folate metabolism and mitochondrial electron transport (Shibeshi *et al.*, 2020). The well-known targets have become vulnerable to parasite resistance development because of selective pressure which demonstrates why depending on minimal biochemical pathways for therapy poses risks. Research into parasite survival and replication essential pathways which differ from human host biological pathways presents a promising solution to defeat resistance and achieve selectivity. The ability to preserve parasite genome integrity through essential DNA repair processes provides a viable target for treatment as it would block parasite survival under drugs while stopping additional resistance mutations and boost existing therapeutic effects (da Silva *et al.*, 2022).

Targeting biological processes that persist across various parasite life cycle stages allows researchers to create drugs which possess prophylactic, therapeutic and transmission-blocking capabilities. These strategies would deliver maximum value during malaria elimination and eradication programs. Research of new *Plasmodium* molecular weaknesses enables two immediate benefits: it creates innovative therapeutic options and expands antimalarial medication choices while protecting against widespread drug resistance in the future. *Plasmodium* parasites require genomic integrity to survive and propagate between human hosts and mosquito vectors because they face continuous environmental stress. *Plasmodium* completes its complex life cycle by rapidly duplicating DNA during blood stage asexuality and by undergoing sporogony in mosquitoes and gametocyte development. The combination of DNA replication processes with exposure to oxidative stress and immune damage and antimalarial drugs creates substantial DNA damage which the parasite needs to repair efficiently to stay viable.

Plasmodium parasites use multiple DNA repair pathways to manage their challenges but these systems show simpler structures and divergent pathways compared to higher eukaryotic systems. *Plasmodium* possesses four DNA repair pathways which include base excision repair for fixing small non-helix-distorting base lesions from oxidative stress, and alkylation and nucleotide excision repair for removing bulky DNA lesions, and helix-distorting adducts and homologous recombination for repairing double-strand breaks and maintaining genome stability during meiosis (Nastasi *et al.*, 2020). Finally, replication stress and mismatch repair are required for identifying and correcting base-base mismatches and insertion-deletion loops that occur during DNA replication (Goyal *et al.*, 2021). The *Plasmodium* genomes show no clear orthologs for multiple DNA repair genes present in other eukaryotes which indicates the parasite uses either reduced or modified repair protein sets. The parasite maintains its essential genomic functions through this basic repair system which enables enough genetic variation for immune evasion and antigenic diversity and drug resistance. The MMR (mismatch repair) system has become a subject of increased scientific interest because it plays a role in *Plasmodium* genetic diversity and antimalarial drug resistance development. Research into *Plasmodium* DNA repair mechanisms particularly MMR shows promise for discovering new therapeutic targets (Lujan *et al.*, 2021).

An overview of DNA mismatch repair (MMR) pathways

The MMR system represents a fundamental and evolutionarily preserved pathway found in eukaryotic organisms which functions to maintain genome stability through error correction during replication (Lujan *et al.*, 2021). The proofreading mechanism of DNA polymerases fails to detect occasional replication mistakes which result in base-base mismatches and insertion-deletion loops. The accumulation of uncorrected errors leads to genomic instability which results in mutations and eventually causes diseases like cancer. The MMR pathway functions as a backup system which significantly improves DNA replication accuracy through the removal of replication mistakes. The MMR process starts when the newly synthesized DNA strand undergoes mismatch detection (Figure 1). The MutS homolog (MSH) protein complexes perform the essential initial step of mismatch recognition. Eukaryotic cells utilize two main MMR complexes: MutSα which functions as a MSH2-MSH6 heterodimer to detect single-base mismatches and small insertion-deletion loops and MutSβ which consists of MSH2 and MSH3 to detect larger insertion-deletion loops. The MutS complex binds to mismatch sites through an ATP-dependent structural transformation which enables the recruitment of subsequent repair factors. The MutS complex binds to recognized mismatches to recruit MutL homolog (MLH) complex which primarily consists of MLH1 and PMS2 proteins. The MutLα complex functions as

a molecular coordinator that connects mismatch detection to the repair process of excision and resynthesis. The complex possesses endonuclease activity which creates nicks in the newly synthesized strand to guide the repair machinery toward the correct DNA strand (Ortega *et al.*, 2021).

Eukaryotic MMR strand discrimination functions without the need for methylation signals which are essential in prokaryotes (Reyes *et al.*, 2021). The discrimination mechanism in eukaryotic MMR is believed to operate through two different methods - Okazaki fragment nicks in the lagging strand and replication-associated signals in the leading strand (Muthye *et al.*, 2021). The repair machinery needs nicks in DNA to start its process of strand excision for error-containing DNA. The EXO1 exonuclease together with other enzymes then proceeds to excise the erroneous DNA segment beginning from the nick site. After strand discrimination and incision, the repair machinery employs DNA polymerase δ to synthesize new DNA that fills the gap using the undamaged parental strand as a template. The DNA repair process concludes with DNA ligase I which closes the remaining nick to achieve complete DNA duplex restoration. The eukaryotic MMR system functions through multiple specialized proteins that detect replication errors and begin repair and maintain DNA integrity. The MutS and MutL homologs function as the core components which direct the repair process. MS protein family members known as MSH proteins function to detect mismatched bases. The eukaryotic MutS complexes include MutSα which contains MSH2 and MSH6 and MutSβ which consists of MSH2 and MSH3 (Furman *et al.*, 2021). The MutSα complex detects base-base mismatches and short insertion-deletion loops but MutSβ detects only larger insertion-deletion loops. These complexes bind to mismatches in an ATP-dependent manner, triggering conformational changes necessary for the recruitment of downstream repair factors. The MutSα or MutSβ complex structures provide both flexibility and specific DNA recognition capabilities across a wide range of DNA replication errors. The repair process receives MutL homologs (MLH proteins) from mismatch complexes recognized by MutS complexes with MutLα representing the main complex responsible for the repair process. The molecular bridge function of MutLα allows it to connect mismatch detection with excision mechanisms. MutLα contains built-in endonuclease activity which becomes active after interacting with MutS complexes along with replication factors including PCNA (Chabowska *et al.*, 2023). Single-strand breaks at the mismatch location become essential through endonuclease activity because they allow exonucleolytic degradation. MutLβ (MLH1–PMS1) and MutLγ (MLH1–MLH3) represent other MutL homologs but scientists think these proteins have specialized roles in meiotic recombination and possibly backup mismatch repair functions.

Exonuclease 1 (EXO1) is another protein which removes the incorrect DNA strand after nicking; Replication protein A(RPA) is replication protein A which keeps the single-stranded DNA stable during excision; DNA polymerase δ, which synthesizes the excised DNA segment; and DNA ligase I, which forms the nicks to finish the repair (Schöniger *et al.*, 2022). Thus, the MutS and MutL homologs, and their associated factors, constitute a highly dynamic and tightly regulated system that ensures that replication errors are corrected with high efficiency. Their coordinated actions are not only important for maintaining genomic stability, but also for protecting organisms from mutagenesis and genome instability. The MMR pathway is crucial for genome maintenance across all eukaryotic species. During DNA replication, even with high-fidelity polymerases and proofreading mechanisms, a small number of base mismatches and insertion-deletion loops inevitably arise. If these replication errors are not fixed, they may lead to the creation of permanent mutations, which can result in genomic instability, disruption of important genes and the risk of diseases such as cancer. MMR acts as a vital post-replicative mechanism that ensures that these errors are identified and corrected before cell division is completed.

Beyond its conventional function in replication error correction, MMR plays a role in other important cellular processes. It prevents recombination of non-identical sequences, thus ensuring chromosomal stability. MMR proteins are also involved in the response to certain types of DNA damage, and they connect the pathway to other genome surveillance pathways. Importantly, mutations in MMR genes are associated with microsatellite instability (MSI), a condition characterized by the accumulation of mutations in short repetitive DNA sequences (Schöniger *et al.*, 2022). This phenomenon is a hallmark of several types of cancers, notably colorectal, endometrial and gastric cancers associated with Lynch syndrome. Thus, the biological significance of the MMR system goes well beyond simple error correction; it is essential for maintaining genomic stability, preventing mutagenesis and ensuring organismal health. In *Plasmodium*, where genome stability needs to be carefully regulated with adaptive mutations for survival under selective pressure, the MMR system may play a special role in regulating both stability and evolvability. MMR systems in protozoan parasites, such as *Plasmodium* species, show several differences in comparison with their mammalian homologues. While the basic function of error correction is preserved, the protozoan MMR pathways often consist of a simplified or divergent set of proteins. In *P. falciparum*, for example, clear orthologs of key eukaryotic MMR components such as MSH2, MSH6, MLH1 and PMS2 have been identified, but the overall pathway appears less complex, possibly because of adaptation to the parasite's life cycle and environment (Caja *et al.*, 2020). Certain canonical MMR proteins that are found in higher eukaryotes are either absent or highly divergent in sequence and structure in protozoan parasites, which may affect repair efficiency and regulation.

Another notable aspect of protozoan MMR is its capability to control genome stability versus adaptability. In parasites like *Plasmodium*, reduced MMR fidelity may enable antigenic variation, a mechanism that is crucial for immune evasion (Chulanetra *et al.*, 2021). Mutations resulting from imperfect repair mechanisms could contribute to the generation of genetic diversity within surface antigen genes, which would enhance parasite survival in the presence of host immune responses. Also, partial deficiencies or modulations in the MMR pathway have been linked to drug resistance, providing a selective advantage under pharmacological pressure (Molina *et al.*, 2022). Furthermore, studies suggest that MMR in protozoan parasites may be closely linked to specific stages of the life cycle, with differential expression or activity observed between blood stages and mosquito stages (Schwarzer *et al.*, 2024; Dutta *et al.*, 2022). This stage-specific modulation of DNA repair capacity may reflect varying demands for genome maintenance versus adaptability. These unique features of the protozoan MMR pathways not only give insight into parasite biology but also show potential vulnerabilities that could be exploited for therapeutic intervention.

MMR pathways in *Plasmodium*

The MMR systems of *Plasmodium* species show different characteristics compared to human MMR systems (Figure 2). The main purpose of error correction in MMR pathways is conserved although protozoan MMR pathways consist of a reduced or alternative set of proteins (Table 1). The *P. falciparum* genome contains recognizable MSH2, MSH6, MLH1, and PMS2 orthologs that form the basis of its mismatch repair system although its overall complexity appears lower due to adaptations related to its parasite-specific life cycle and environmental pressures. The protozoan parasites show distinct modifications of their MMR proteins which result in sequence and structural differences from typical higher eukaryotic MMR proteins.

Protozoan MMR systems show remarkable features because they support genome stability through adaptive mechanisms. *Plasmodium* parasites achieve their antigenic variation ability through limited MMR fidelity because this mechanism helps them evade host immune responses. The imperfect repair mechanisms result in mutations that generate genetic diversity in surface antigen genes which enhance parasite survival against host immune responses. The MMR pathway shows partial deficiencies or modulations which contribute to drug resistance development that provides benefits when parasites face pharmacological challenges. MMR activity in protozoan parasites shows an association with life cycle phases according to research which demonstrates different levels of expression between blood and mosquito stages. The different life stages of the parasite require distinct DNA repair capacities which affect their genome stability and adaptability needs. These distinctive MMR pathway features in protozoan parasites both reveal parasite biological mechanisms and create targets for therapeutic development. The MMR pathway in *P. falciparum* and its related species has been fully identified through detailed genomic and bioinformatic investigations. The two principal mismatch recognition proteins among *Pf*MutS homologs are *Pf*MSH2 and *Pf*MSH6 (Assisi *et al.*, 2021). The proteins create a heterodimer structure which functions like the MutSα complex of other eukaryotic organisms to detect base-base mismatches and small insertion-deletion loops during DNA replication. Phylogenetic studies show that *Pf*MSH2 and *Pf*MSH6 maintain fundamental domains needed for mismatch binding and ATPase activity while displaying sequence adaptations suited to parasite genomic and life cycle requirements (Tarique *et al.*, 2017). The *Pf*MutL protein represents the functional equivalent of the MLH1-PMS2 complex that exists in higher organisms. The *Pf*MutL protein contains important domains that enable ATP binding as well as endonuclease activity which supports its predicted function in mismatch recognition and subsequent repair excision processes. Research has identified *Pf*MLH which shares homology with MLH1 but further studies are needed to determine its precise activity within the *Plasmodium* MMR system. The survival of *Plasmodium* depends on *Pf*MutL and *Pf*MLH because knockout attempts have produced unsuccessful results indicating any MMR system impairment would severely affect genomic stability (Payero *et al.*, 2024).

Studies have identified MMR homologs in *Plasmodium* but PMS2 remains either highly divergent or missing from *Plasmodium* genomes. This observation points to a streamlined or modified MMR machinery in the parasite, which may influence both the efficiency of repair and the organism's ability to balance genome stability with adaptability. The absence of known accessory factors that bind to MMR proteins in other systems including EXO1 and replication-associated proteins from *P. falciparum* creates uncertainty about DNA repair mechanisms in the parasite. *Pf*MutS, *Pf*MutL, and *Pf*MLH form the core of the MMR system in *Plasmodium* and these findings provide a starting point for studying DNA repair processes in this genus. These proteins show promise as targets for functional studies and antimalarial development strategies to create DNA instability in parasites. Genomic comparison between *Plasmodium* species and humans demonstrates that MMR core functions are preserved yet pathway elements exhibit substantial variations regarding their composition and structure and regulatory mechanisms (Tarique *et al.*, 2017). The two systems maintain essential components which initiate mismatch repair through homologs of MutS and MutL proteins because genome maintenance is essential for eukaryotes. Sequence alignments demonstrate that *Plasmodium* MMR proteins *Pf*MSH2, *Pf*MSH6 and *Pf*MLH present large sequence differences compared to human homologs especially in non-catalytic domains and regulatory regions. The observed variations appear to result from adaptations that match the parasite's small genome size and its high AT-content and

specialized replicative requirements throughout its complex life cycle. The main distinction occurs because *Plasmodium* lacks several essential auxiliary factors which are fundamental to the human MMR pathway. The human MMR pathway contains all accessory proteins including EXO1 and PCNA interactions and strand-discrimination proteins yet these components remain undetected or poorly understood in *Plasmodium* (Obmolova *et al.*, 2000). The parasite's ability to achieve strand specificity during repair remains unclear and its compensatory mechanisms for lost factors could involve parasite-specific mechanisms.

Structural modeling shows that *Pf*MutS and human MutS proteins have conserved mismatch-binding domains but their protein-protein interaction interface regions demonstrate significant differences (Sina *et al.*, 2023). The structural differences in these regions could impact repair complex stability and dynamics within *Plasmodium* by creating mechanisms not found in human cells. The control mechanisms that regulate MMR gene expression operate through distinct pathways. Human MMR components function as integral components of the DNA damage response network while undergoing complex transcriptional and post-translational regulations. *Plasmodium* exhibits different patterns of MMR gene regulation since it needs to maintain both genetic accuracy and flexibility when moving between human and mosquito hosts. Several differences between *Plasmodium* and human MMR systems exist including protein sequences and accessory components as well as regulatory mechanisms and functional flexibility which suggest therapeutic targeting opportunities without host system interference.

Studies conducted with genetic and molecular biology techniques have revealed important information about how MMR components function in *Plasmodium* species. The elimination of msh2 and msh6 MMR genes in *P. falciparum* through gene knockout experiments resulted in increased spontaneous mutations and microsatellite instability and enhanced genomic variability (Kalamuddin *et al.*, 2024). Mutant parasites exhibit enhanced mutability because MMR functions as a vital mechanism to preserve genome integrity during normal cell growth. Research attempts to knock out core genes including mlh1 have been unsuccessful because they result in severe fitness defects which demonstrate that some MMR components remain vital for parasite survival. Studies on gene expression demonstrate that MMR plays essential roles throughout various phases of parasite development. Research through transcriptomics shows that MMR genes become more active when DNA replication occurs especially during blood stage proliferation since accurate genome maintenance becomes crucial for fast cell growth (Ahmad *et al.*, 2014). Research using proteomic techniques has shown MMR proteins present in *P.* falciparum nuclear extracts which support their involvement in nuclear DNA surveillance. *Plasmodium* parasites display functional mismatch repair capabilities that demonstrate error correction ability in replication processes but exhibit possible different efficiency compared to mammalian cells. Research has demonstrated that MMR activity reduction leads to higher drug tolerance in antimalarial drug-exposed parasites. Experimental evolution studies demonstrate that parasites with defective MMR pathways develop mutations at higher rates which sometimes lead to drug resistance thus linking MMR competency to treatment failure emergence (Ahmad *et al.*, 2014). The MMR system in *Plasmodium* plays a crucial role in genomic stability while its activity changes according to developmental and environmental signals based on gene knockout models and gene expression profiling and functional assays.

Role of MMR in *Plasmodium* biology

The MMR system in *Plasmodium* has a dual role in maintaining genome stability and in antigenic variation, two processes that are important for the parasite's survival and pathogenicity. During the rapid asexual replication cycles in human erythrocytes, *Plasmodium* parasites are under constant pressure to maintain genomic integrity due to the challenges posed by high rates of DNA replication and exposure to oxidative stress. The MMR machinery ensures that replication errors, such as base mismatches and insertion deletion loops, are efficiently corrected, thus preserving genome stability and preventing the accumulation of deleterious mutations that could impair parasite viability. At the same time, it is also advantageous for the parasite to have controlled genomic variability, especially in evading the host immune response. *P. falciparum* employs antigenic variation to persist within the human host, primarily through the var gene family encoding the surface protein *Pf*EMP1 (*Plasmodium falciparum* erythrocyte membrane protein 1) (Hadjimichael *et al.*, 2025). Emerging evidence suggests that the MMR system influences the regulation of antigenic variation, potentially by modulating the rate of recombination and mutation events within hypervariable regions of the genome. Partial defects in MMR, whether naturally occurring or experimentally induced, have been associated with increased rates of var gene switching and enhanced generation of genetic diversity, thereby promoting immune evasion. Thus, the MMR system in *Plasmodium* must carefully balance two opposing demands: enforcing genomic stability to sustain essential biological functions while allowing enough plasticity to adapt to changing environmental pressures, including immune challenges and antimalarial drug exposure. This is the balance that *Plasmodium* has to strike in the MMR system to sustain its life cycle, and this is crucial for our understanding of the parasite's biology and for the identification of new targets for therapy. The modulation of MMR activity by *Plasmodium* to achieve this balance is a key aspect of the parasite's biology and offers new avenues for therapeutic intervention.

The MMR system in *Plasmodium* has a significant impact on the development of drug resistance, a major hurdle in the control and elimination of malaria (Table 2). Under normal conditions, an intact MMR pathway limits the accumulation of spontaneous

mutations by correcting replication errors, thereby maintaining a relatively stable genome. However, when the efficiency of MMR is compromised either through natural polymorphisms, selective pressure, or experimental disruption mutation rates can increase dramatically. This hypermutability provides a fertile ground for the emergence of genetic variants, some of which can confer resistance to antimalarial drugs. Experimental studies have shown that *P. falciparum* parasites with partial defects in MMR genes, such as msh2 and msh6, exhibit accelerated acquisition of resistance to commonly used drugs, including chloroquine, mefloquine, and artemisinin derivatives (Hjelmqvist *et al.*, 2019). Elevated mutation rates enhance the likelihood of alterations in critical drug target genes, such as *Pf*CRT (*Plasmodium falciparum* Chloroquine Resistance Transporter), *Pf*MDR1 (*Plasmodium falciparum* Multidrug Resistance Protein 1), and kelch13, which are central to resistance phenotypes (Ocan *et al.*, 2022; Waweru *et al.*, 2024). Furthermore, MMR-deficient parasites have been observed to display higher tolerance to drug-induced DNA damage, enabling their survival and propagation even under intense pharmacological pressure.

The connection between MMR dysfunction extends to drug resistance development beyond simple point mutations. The MMR system dysfunction leads to larger genomic rearrangements and copy number variations and microsatellite instability which together enhance *Plasmodium*'s adaptive capacity. MMR activity functions as a two-sided weapon that protects genome stability but allows quick evolutionary responses to create multidrug-resistant parasite strains. Research of this relationship provides essential information for developing strategies to maintain drug effectiveness and delay resistance emergence. The biological features of MMR-deficient *Plasmodium* parasites emerge from phenotypic studies which demonstrate the importance of MMR in parasite survival and adaptation. The disruption or downregulation of msh2 and msh6 MMR core genes leads to hypermutator phenotypes that result in faster point mutations as well as unstable microsatellites and greater genomic variability. The unstable genome allows these parasites to adapt through quick evolutionary changes beyond what MMR-proficient parasites can achieve. MMR deficiency leads to elevated antigenic variation rates especially through higher var gene family switching events. The increased genetic variability enables MMR-deficient parasites to evade the host's immune system and survive longer inside the body while establishing long-term infections. MMR-deficient parasites show better resistance to environmental stresses which makes treatment more challenging. The advantages derived from increased mutability lead to various negative biological effects. MMR-deficient *Plasmodium* parasites demonstrate lower fitness outside selection pressure because they replicate at reduced rates while showing flawed replication and sometimes poor transmission capabilities (Lecture., 2023). The observations indicate that MMR deficiency helps parasites survive specific challenges yet damages their health when there are no selective threats. Research into MMR-deficient phenotypes reveals how *Plasmodium* maintains equilibrium between its genetic stability and ability to adapt while establishing strong scientific grounds for MMR as a therapeutic target.

Targeting MMR pathways: Rationale and strategies

The MMR pathway shows great promise as an uncharted antimalarial pathway which scientists can utilize for creating new treatments. MMR function disruption would result in parasite death because it would allow lethal mutations to build up while the parasite attempts to maintain genome integrity during its fast replication periods. The MMR system functions as a fundamental genomic stability protector which differentiates it from traditional drug targets that concentrate on metabolic enzymes or surface proteins. Targeting the MMR pathway provides potential access to error catastrophe by inducing catastrophic mutational burdens which lead to parasite death.

Research demonstrates that targeting the MMR pathway offers dual benefits because it disrupts antigenic variation while hindering drug resistance development. The parasite's ability to change its immune profile might be disrupted by breaking down its MMR machinery. The specific inhibition of adaptive mutations in the parasite would make it harder for resistant strains to develop thus extending the effectiveness of antimalarial drugs. The MMR pathway shares sequence similarity between *Plasmodium* and humans but structural dissimilarities and regulatory divergence enable selective MMR pathway disruption (Ahmad *et al.*, 2014). The parasite shows distinct domain structures in its *Pf*MutS and *Pf*MutL homologs which enable scientists to create inhibitors that target *Plasmodium* without affecting human MMR functions. The MMR system represents a novel approach to parasite killing while simultaneously delivering a mechanism to enhance immune responses and fight antimalarial drug resistance. The maximum therapeutic benefit of MMR pathway targeting in *Plasmodium* parasites can be achieved by implementing synthetic lethality strategies. Synthetic lethality exists when disrupting two unrelated pathways together results in cell death but blocking either pathway independently causes either minor damage or no lethal effect (Subramaniam *et al.*, 2018). The *Plasmodium* parasite faces dual threats because partial MMR inhibition makes it more vulnerable to endogenous and exogenous genotoxic agents while it experiences constant oxidative stress in the bloodstream during its rapid erythrocytic cycles. The parasite becomes highly susceptible to genotoxic agents and endogenous stress when MMR function suffers even slight damage because it faces constant oxidative stress during its bloodstream residence. MMR inhibition paired with ROS (Reactive oxygen species)-producing compounds or DNA strand break-inducing drugs could push the parasite's DNA repair mechanisms beyond capacity leading to fatal genome instability. The approach of synthetic lethality enables the use of reduced MMR-targeting agent dosages in combination with conventional antimalarials which reduces the

risk of human cell off-target effects. The combination treatment method would boost parasite elimination while simultaneously lowering the chances of drug resistance emergence through simultaneous multiple mechanistic assaults on the parasite. Research on synthetic lethal MMR pathway interactions creates a promising route to create enhanced antimalarial treatments.

Although no *Plasmodium* parasite MMR-specific inhibitors exist at present scientists can develop future drug design strategies by studying other biological systems. Research on human MutS and MutL homologs in oncology has led to small molecule inhibitor development which can serve as a model to specifically target *Plasmodium* MMR complexes (Li *et al.*, 2020). Small molecules that target conserved ATPase domains of *Pf*MutS homologs should be developed as potential treatments to prevent mismatch recognition and processing during DNA replication. Research into MMR complex protein-protein interactions presents an effective method for therapeutic intervention (McPherson *et al.*, 2021). Molecules that block *Pf*MutS dimerization or its binding to *Pf*MutL can eliminate downstream repair signaling to disable the MMR response. Structure-guided drug design and virtual screening can identify parasite-specific binding pockets through the analysis of sequence and structural differences between parasite and host proteins. Research into MMR protein conformational instability-inducing compounds and repair factor recruitment-blocking agents shows promise as new therapeutic approaches. The use of DNA-binding small molecules that create mismatches or replication stress in MMR-deficient *Plasmodium* strains presents another approach that benefits from oxidative stress defense-compromising agents (Pálinkás *et al.*, 2020). Inhibitor development requires thorough structural investigations of *Pf*MutS and *Pf*MutL proteins together with high-throughput chemical library screening and parasite model testing for validation. Research-based approaches including structural studies of *Pf*MutS and *Pf*MutL proteins and high-throughput screening of chemical libraries and parasite model validation are needed to develop such inhibitors. Although hypothetical different plausible and innovative strategies can be identified to target the MMR pathway as a novel therapeutic avenue against malaria.

Research conducted in oncology has delivered important lessons about MMR pathway targeting capabilities and challenges which directly help antimalarial drug development. The hypermutated state of MMR-deficient tumors including Lynch syndrome-related tumors makes them more responsive to DNA-damaging agents and immune checkpoint blockade therapies (Nebot-Bral *et al.*, 2021). The interest in developing compounds that either selectively inhibit MMR or exploit MMR deficiency to enhance therapeutic efficacy has been driven by this observation. The human MMR system components MutSα and MutLα complexes are targeted by early-stage inhibitors which prove that MMR activity modulation through pharmacology makes cells more sensitive to chemotherapy and leads to lethal mutational accumulation. Preclinical models demonstrate that inhibitors which block MSH2-MSH6 ATPase activity or

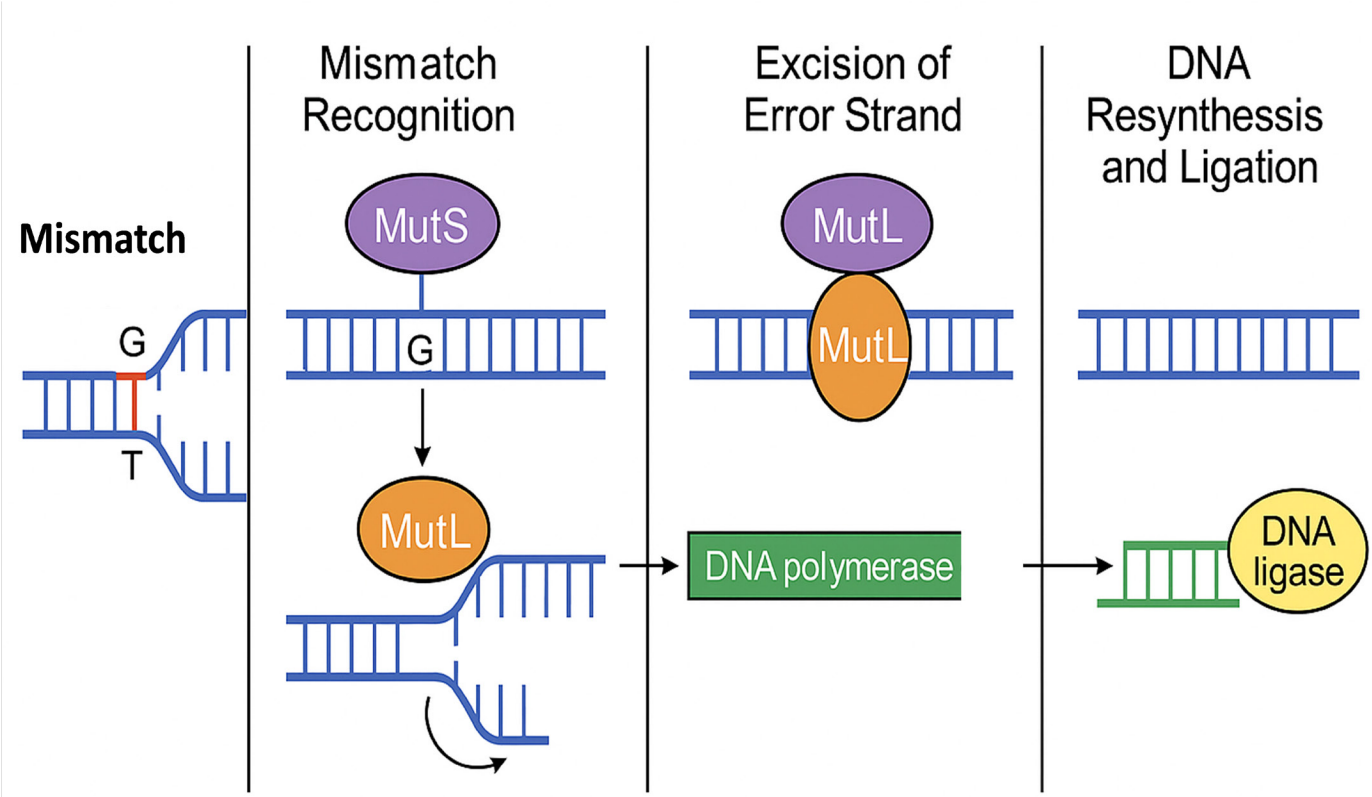

Figure 1: Schematic illustration of the eukaryotic mismatch repair (MMR) pathway. The MutS complex detects mismatched base pairs and recruits MutL homologs to remove the error-containing DNA strand. DNA polymerase creates the correct sequence, and ligase seals the strand to restore continuity.

Table 1:MMR proteins identified in *Plasmodium*.

Protein name	*Plasmodium* Homolog (Eg.)	Function (Putative)	Similarity to human MMR proteins	References
MutSα component	PfMSH2	Recognition of base–base mismatches and small loops	MSH2 homolog	(Hsieh *et al.*, 2017)
MutSα component	PfMSH6	Partner of *Pf*MSH2 in mismatch recognition	MSH6 homolog	(Edelbrock *et al.*, 2013)
MutLα component	PfMLH	Endonuclease activity, recruits downstream repair	MLH1 homolog	(Cannavo *et al.*, 2020)
Additional factors	unknown	Exonuclease, helicase activities	EXO1, others	(Liu *et al.*, 2017)
DNA polymerase	*Pf*DNA polymerase δ/ε	DNA resynthesis after mismatch excision	Polymerase δ/ε	(Molnár *et al.*, 2020)
DNA ligase	*Pf*DNA ligase I	Seals nicks after repair	DNA ligase I	(Tarique *et al.*, 2017)

disrupt MLH1-PMS2 protein interactions show promising results. The research demonstrates two essential concepts: partial MMR inhibition creates synthetic lethality when paired with DNA-damaging agents and MMR activity needs precise modulation to prevent resistance development from excessive mutagenesis. The concepts learned from these findings indicate that *Plasmodium* MMR protein inhibition with selective targeting could make parasites more vulnerable to oxidative and replication stresses that occur during their life cycle. MMR-targeted strategies combined with current antimalarial treatments could produce similar benefits to cancer therapy combination approaches by boosting treatment effectiveness while minimizing resistance development. The lessons from oncology demonstrate that host genome stability requires precise targeting to prevent unwanted effects which supports the necessity of parasite-specific drug development.

Opportunities in targeting MMR pathways

The *Plasmodium* MMR components *Pf*MutS and *Pf*MutL homologs show substantial structural and functional divergence from human MMR components. The distinct genetic and regulatory patterns of *Plasmodium* MMR components enable researchers to develop targeted inhibitors which would target the parasite instead of the host. The parasite MutS homologs display unique structural characteristics through their sequence variations and domain patterns which differ from human MSH protein structures. The distinctive structural elements of the *Plasmodium* MMR components enable drug developers to create specific binding sites that do not exist in human MMR machinery. *Plasmodium* MMR components show distinct post-translational modification patterns and regulatory networks which provide novel pathways for selective inhibition (Rashidi *et al.*, 2021). During the erythrocyte stage of their life cycle *Plasmodium* parasites require their MMR system because they need to replicate rapidly. The parasite's specific need for MMR to maintain genome stability during particular developmental phases creates an improved therapeutic window to target these pathways. The parasite's MMR system operates most intensely during particular developmental stages whereas the host MMR system maintains continuous activity across different cell types thus enabling targeted treatment timing for maximal parasite impairment with minimal host toxicity.

The distinct properties of *Plasmodium* MMR components create both an ideal drug development target and reduce the probability of unwanted side effects which would result in safer malaria treatments. The development of drug resistance in *Plasmodium* typically occurs through multiple drug target gene mutations which MMR repair mechanisms are expected to correct. The inhibition of MMR pathway function leads to elevated mutational errors in the parasite population which creates error catastrophe and impairs its ability to survive under drug pressure. Furthermore, the high genomic instability that arises from MMR deficiency could result in a form of genetic overload where the parasite becomes unable to thrive even under selective pressure due to the accumulation of deleterious mutations. Therapeutic approaches that target MMR could potentially reduce the speed at which resistance develops when compared to current treatment approaches. This strategy would increase the effectiveness of current antimalarial drugs and provide a sustained approach to resistance management. When MMR inhibition is combined with other drug classes such as drugs targeting parasite metabolic pathways or immune evasion mechanisms, it could lead to a synergistic effect that prevents the parasite from developing resistance.

The ability to develop combination therapies represents a significant benefit when the MMR pathway in *Plasmodium* is targeted. The standard treatment for malaria currently depends on ACTs that combine artemisinin derivatives with partner drugs to prevent resistance development. Because MMR plays a critical role in genome stability and drug resistance, inhibiting MMR while using existing or novel antimalarial drugs represents an effective method to improve treatment outcomes while slowing the emergence of resistance. The MMR inhibitors show the potential to produce synergistic effects with diverse antimalarial medications (Blasco *et al.*, 2022). MMR-targeting drugs paired with

DNA-damaging agents such as DNA alkylators or topoisomerase inhibitors would create a double-struck effect that would push the parasite beyond its survival threshold and block its ability to adapt to treatment. The combination of MMR inhibitors with immunomodulatory drugs or host-targeted therapies would lead to a complex treatment method that disrupts parasite genomic integrity and strengthens host immune responses against infected cells. This strategy presents the potential to improve malaria treatment while stopping resistance development through the application of multiple therapeutic pressures on the parasite. The different life cycle phases of *Plasmodium* parasites operate with separate repair systems including both erythrocytic and gametocytic phases. By choosing specific combination therapies that target particular stages of the parasite life cycle it should be possible to develop treatment regimens that increase effectiveness while minimizing the development of targeted resistance.

Thus, MMR inhibition when paired with additional antimalarial drugs becomes a crucial weapon for fighting malaria because it both improves treatment success and creates an effective method to defeat drug resistance. Research into biomarkers which track *Plasmodium* parasite MMR status shows great potential to improve individual antimalarial treatment approaches (Obeagu *et al.*, 2024). The main objective of personalized medicine involves creating individualized treatment plans which use patient genetic and molecular information to optimize outcomes while reducing side effects. Malaria biomarkers would help medical practitioners measure the MMR status of existing parasite populations to choose optimal therapeutic approaches. A potential biomarker-based system would track *Pf*MutS and *Pf*MutL expression levels and activity within parasite samples. The functional state of these proteins as well as their presence or absence helps researchers determine how well parasites can repair DNA and their sensitivity to MMR-targeting drugs. Such information would enable better clinical decision-making for patients whose parasites do not consistently respond to standard treatments and those at risk for drug-resistant strains. The measurement of mutational accumulation in *Plasmodium* genomes through sequencing or microsatellite instability monitoring serves as an indicator for MMR efficiency. When parasites display higher mutational rates due to MMR deficiencies it indicates they will likely develop resistance or undergo antigenic variation which requires treatment approaches that target their defective repair systems. Medical professionals using MMR status as a biomarker in their diagnostic and therapeutic procedures will enhance their ability to forecast treatment responses while enhancing drug combinations and tracking resistant strain development. The use of personalized treatment methods will boost current antimalarial drug efficacy alongside improved patient outcomes through reduced treatment failures and limited resistance development.

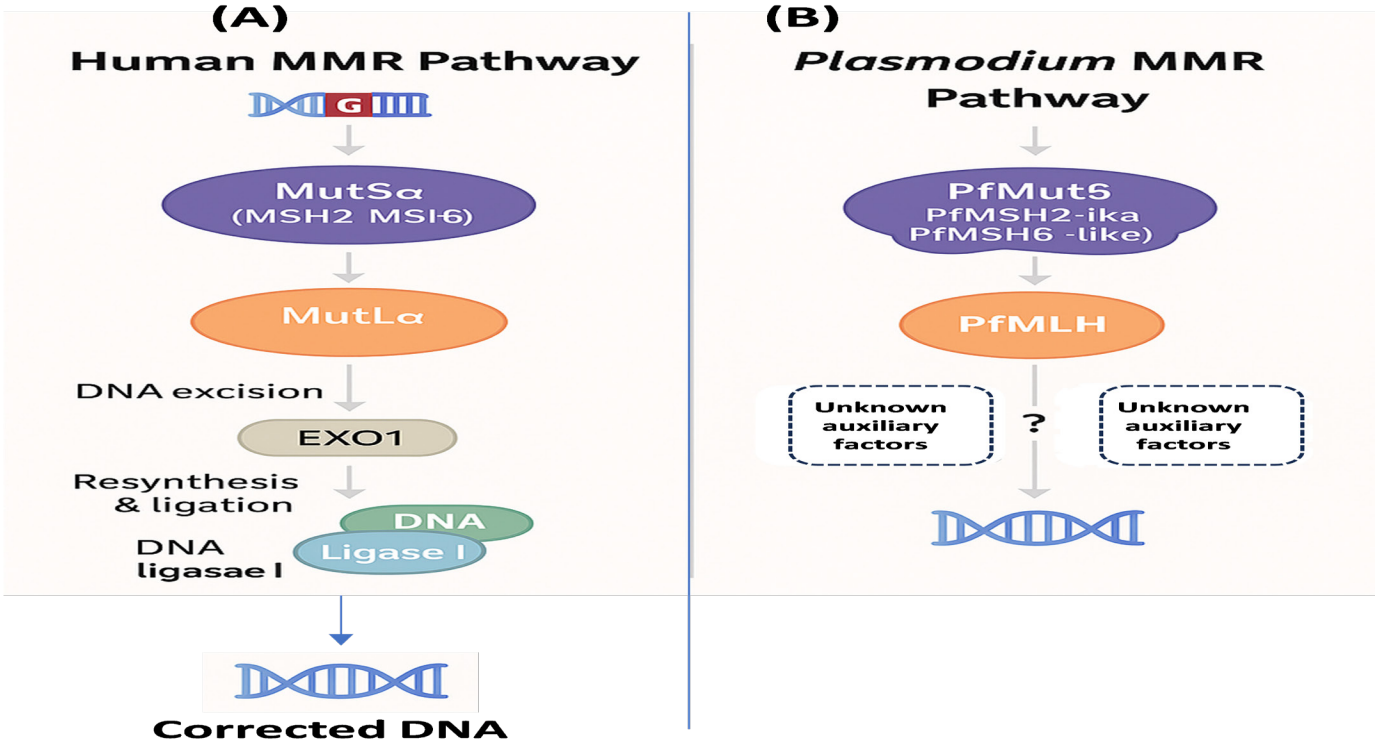

Figure 2: MMR pathways differ between Homo sapiens and *Plasmodium* species. (A) In humans, MutSα & MutSβ complexes detect DNA mismatches. MutLα then starts repair, which includes excision by exonuclease 1, resynthesis by DNA polymerase delta or epsilon, and sealing by DNA ligase I. (B) In Plasmodium, similar proteins PfMSH2, PfMSH6, and PfMLH exist, but several accessory factors, such as known exonucleases and DNA polymerase partners, have not been found. Thus, the steps for excision, resynthesis, and ligation, as shown by dashed lines, remain unclear. Both conserved and species-specific features could be targets for antimalarial drug development.

Table 2: Relationship between MMR status and resultant drug resistance in *Plasmodium* species.

MMR Status	Observed effect	Impact on drug resistance	Example /study	References
MMR-proficient	Efficient genome repair; low mutation rate	Delayed emergence of resistance	Wild-type *P. falciparum* strains	(Palinkas *et al.*, 2020)
MMR-deficient (*Pf*MSH2 loss or mutation)	Increased mutation frequency; genomic instability	Accelerated development of resistance	Mutations linked to resistance to chloroquine, antifolates	(Guillotin *et al.*, 2015; Gupta *et al.*, 2016)
Partial MMR dysfunction	Intermediate genome stability	Gradual resistance development	Laboratory-adapted *P. falciparum* strains	(Claessens *et al.*, 2023)
Overexpression of MMR genes	Enhanced repair capacity	Potential resistance suppression	Experimental gene expression studies	(Sarasin *et al.*, 2008)

Challenges and pitfalls

The main difficulty in targeting *Plasmodium*'s MMR pathway stems from the similarity between parasite and host repair mechanisms which increases the risk of off-target effects. *Plasmodium* MMR proteins possess some distinctive features when compared to human counterparts but they show substantial structural and functional homology in their core mismatch recognition and repair domains. The high similarity between parasite and host MMR mechanisms makes it probable for inhibitors targeting parasite MMR components to also affect the host MMR machinery which results in genomic instability together with an elevated cancer risk in human cells. Off-target inhibition creates significant consequences because it targets tissues with rapid cell turnover which depend on DNA fidelity for proper function. Host cells would lose their capability to fix replication mistakes when MutSα or MutLα human enzymes are inhibited because this could lead to mutagenesis and tumorigenesis alongside immune dysfunction. The lack of precise cell discrimination during MMR inhibitor delivery through systemic routes would escalate the probability of unwanted effects.

The application of MMR pathway as an antimalarial target faces major challenges due to insufficient structural and mechanistic data about *Plasmodium* MMR proteins. Scientists have discovered functional homologs *Pf*MutS and *Pf*MLH but structural information from crystal structures and cryo-EM models remains unavailable. The current lack of structural understanding prevents rational drug development because scientists need to understand protein structures and active sites and protein interactions for making specific inhibitors. The absence of precise structural models prevents scientists from predicting small molecule binding sites to parasite-specific regions while distinguishing between parasite and host proteins. MMR proteins function as multi-subunit complexes through which small structural modifications control their ability to detect and process mismatched bases. The incomplete knowledge of *Plasmodium* protein interactions makes it impossible to identify targetable weak points in the system. A complete structural analysis of the parasite would reveal special features including unique loop insertions and surface charge patterns and post-translational modifications which scientists need to detect drug-binding sites selectively.

Plasmodium's MMR pathway presents additional complexities because different DNA repair mechanisms could substitute for each other (Figure 3). DNA repair mechanisms in *Plasmodium* parasites are diverse and include Base Excision Repair (BER), Nucleotide Excision Repair (NER), Homologous Recombination (HR), and Non-Homologous End Joining (NHEJ) (López-Camarillo *et al.*, 2009). The other DNA repair pathways might replace MMR to help the parasite survive drug treatment. Research on other protozoan parasites along with model organisms indicates that destroying one DNA repair pathway leads to increased activity of backup systems. The parasite's expected lethal mutation accumulation following MMR inhibition might not reach sufficient levels to kill the parasite because *Plasmodium* adapts by relying more on BER or HR. The adaptable nature of *Plasmodium* might produce different outcomes based on parasite developmental stages and species which would make treatment predictions challenging. Targeting the MMR pathway in *Plasmodium* becomes problematic due to the high probability that parasites will quickly develop survival strategies that do not depend on MMR. Parasites have shown exceptional flexibility in their responses to selective pressures which leads them to develop compensatory mechanisms that help them survive when MMR is inhibited. Survival strategies might depend on either strengthened alternative DNA repair systems or stress response network adjustments and genetic and epigenetic adaptations that reduce mutation-related harm. Impaired MMR function can lead to the development of "hypermutator" phenotypes through which parasites generate mutations at extraordinary rates. The increased rate of mutagenesis at first causes harm but under certain conditions it speeds up the production of beneficial mutations that could lead to drug resistance or higher virulence. The selection process will preferentially choose parasites that either endure high genomic instability or develop new survival mechanisms which reduce MMR-targeted therapy effectiveness. *Plasmodium* has the ability to adapt by modifying metabolic functions alongside cell cycle management and stage-dependent gene expression which

creates additional challenges for treatment. The development of drug-resistant populations through MMR-targeted monotherapy interventions may reduce the long-term effectiveness of these therapeutic approaches.

The MMR pathway represents a challenging antimalarial therapeutic target because researchers face difficulties in creating specific *Plasmodium* MMR protein inhibitors that do not impact human MMR pathways. Although comparative genomics has shown sequence and structural differences between parasite and human MMR components, the fundamental functional domains for mismatch recognition and repair coordination as well as ATP binding remain highly conserved. The preservation of these essential protein domains restricts researchers' opportunities to develop selective drugs that target *Plasmodium* enzymes without affecting human MMR components. The required specificity needs extensive knowledge of small differences between *Plasmodium* and human MMR proteins such as accessory domain variations, allosteric regulatory sites and specific protein-protein interfaces. The identification of exploitable differences between *Plasmodium* MMR proteins becomes more complex because researchers lack detailed structural information about these proteins. Small errors during drug design could result in off-target inhibition of human MMR systems that creates both genotoxicity concerns and additional complexity for the drug development process (Lin *et al.*, 2009). MMR proteins operate within dynamic multi-protein complexes which makes it difficult to forecast how inhibitors behave in the body where protein interactions and conformational changes determine their activity. Scientists need advanced methods such as fragment-based drug discovery together with structure-guided design and novel chemical scaffolds to develop small molecules which can recognize slightly different binding sites or conformational states.

Future directions

Developing MMR-targeted antimalarial strategies requires extensive functional research of *Plasmodium* MMR pathways as a key advancement. The critical components *Pf*MutS and *Pf*MLH have been discovered but scientists know very little about their specific functions and regulatory processes and interactions inside the parasite. The use of CRISPR/Cas9 conditional knockdowns and inducible expression systems in functional genomics studies could reveal parasite survival mechanisms at different developmental stages through MMR protein analysis (Dong *et al.*, 2018). The effects of *Pf*MutL disruption on sporozoite development and gametocyte viability should be evaluated to identify stage-specific vulnerabilities. DNA repair regulatory networks that coordinate cellular responses to genotoxic stress can be discovered through transcriptomic and proteomic profiling to identify potential co-targets for combination therapies.

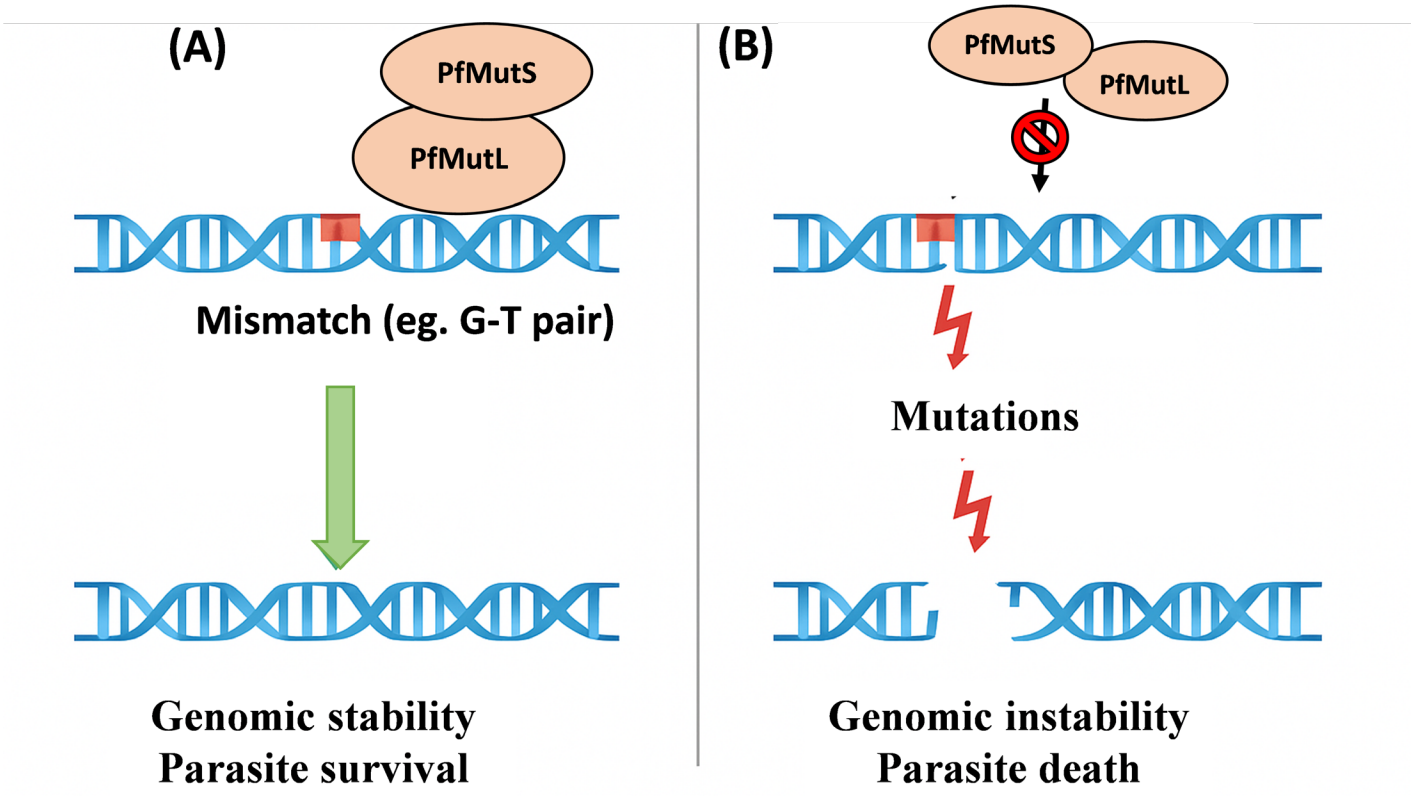

Figure 3: This model reveals how the DNA-MMR pathway works in Plasmodium. In part A, the normal MMR pathway uses Plasmodium-specific proteins PfMutS and PfMutL to recognize and repair errors introduced during DNA replication, thereby maintaining genome stability. In part B, blocking these MMR proteins leads to more DNA mismatches, unstable genomes, and parasite death. This suggests that targeting the MMR pathway could be a promising way to fight malaria, especially under stress.

The development of structural biology approaches must proceed urgently to create rational drugs that target *Plasmodium* MMR components. The combination of cryo-electron microscopy (cryo-EM) and X-ray crystallography allows researchers to create atomic-level models of MMR proteins which can help scientists identify parasite-specific structural elements that drugs can target specifically (Johnson *et al.*, 2018). Research of *Pf*MutS allosteric sites together with parasite-specific conformational states could establish new drug-binding pockets for therapeutic applications. The success in solving structures of challenging *Plasmodium* targets including *Pf*Hsp70x and proteasome components demonstrates the possibility of using these approaches (Barth *et al.*, 2022). AlphaFold represents a new AI-based prediction system which helps scientists create preliminary models of *Plasmodium* MMR proteins to guide experimental verification (Ghosh *et al.*, 2021). MMR inhibitor development requires High-Throughput Screening (HTS) platforms to achieve potent and selective compounds. The use of recombinant *Pf*MutS or *Pf*MLH proteins in assay systems with fluorescence-based mismatch binding assays and ATPase activity measurements enables fast chemical library screening (Fang *et al.*, 2018). The same method used in bacterial MMR system inhibitor discovery and human MutSα complex inhibitor development in oncology research can be applied to *Plasmodium* MMR system. The screening of parasite-specific chemical libraries that contain natural product-derived antiplasmodial compounds will generate lead molecules which are optimal for *Plasmodium* MMR targeting. The results from HTS can be enhanced through Structure-Activity Relationship (SAR) analysis to develop more potent and selective compounds with better pharmacokinetic profiles.

The present understanding of MMR in malaria parasites comes mainly from *P. falciparum* but other species like *P. vivax, P. knowlesi*, and *P. malariae* are responsible for substantial malaria cases worldwide. The different *Plasmodium* species have distinct biological characteristics which affect their DNA repair approaches through mechanisms like *P. vivax* hypnozoite formation and host preferences. Research on MMR pathways from other *Plasmodium* species could show therapeutic opportunities through either newly discovered vulnerabilities or species-specific adaptations. MMR inhibitors show promise in treating hypnozoites because the parasite uses MMR more extensively during its dormant liver stage which leads to relapse. The success of MMR-targeted therapy development depends on studying *Plasmodium* species through comparative genomic and functional analyses for developing universal or species-specific therapeutic approaches.

CONCLUSION

The MMR pathway in *Plasmodium* represents a promising yet complex approach for developing new antimalarial therapies. The MMR pathway functions as a crucial element for parasite genome stability and drug resistance development while maintaining parasite-specific features that make it an attractive molecular target. Several major obstacles exist in this approach because of the off-target effects are possible and there may be functional redundancy and limited structural knowledge and adaptive survival mechanisms that do not depend on MMR. A multidisciplinary approach that combines parasite biology with structural biology and medicinal chemistry and genomics and drug delivery systems will be necessary to overcome these hurdles. The complete exploitation of therapeutic potential from the MMR pathway depends on collaborative research between malaria experts and structural biologists and drug discovery specialists. The continued investment and innovation in parasite MMR targeting shows strong potential to deliver substantial contributions to the development of future antimalarial interventions. MMR inhibitors show promise for improved treatment outcomes when used alone or with other medications which could help delay drug resistance development and enhance global malaria control initiatives.

ACKNOWLEDGEMENT

The author expresses sincere gratitude to Almanac Social Welfare for their invaluable support and encouragement. Their commitment to advancing social and humanitarian initiatives is deeply appreciated. By promoting education, healthcare, and community development, they create positive changes in society. This acknowledgment affirms appreciation for their collaboration and dedication to improving lives. Let us all join in supporting their mission and further their progress.

ABBREVIATIONS

WHO: World Health Organization; **MSI:** Microsatellite instability; **PfEMP1:** *Plasmodium falciparum* erythrocyte membrane protein 1; **PfCRT:** *Plasmodium falciparum* Chloroquine Resistance Transporter**;** **PfMDR1:** *Plasmodium falciparum* Multidrug Resistance Protein 1; **ROS:** Reactive oxygen species; ***Plasmodium falciparum*:** *P. falciparum*; **AI:** Artificial Intelligence; **ACTs:** Artemisinin-based combination therapies; **MMR**: Mismatch repair; **MSH:** MutS homolog; **MLH**: MutL homolog; **EXO1**: Exonuclease 1; **RPA**: Replication protein A; **BER**: Base excision repair; **NER**: Nucleotide excision repair; **HR**: Homologous recombination; **NHEJ**: Non-homologous end joining; **cryo-EM**: Cryo-electron microscopy; **SAR:** Structure-activity relationship.

AUTHOR CONTRIBUTIONS

Mohammed Tarique contributed to the conception of the review, conducted the literature search, interpreted the data, and drafted the manuscript. all authors critically revised the work, approved the final version for publication, and agree to be accountable for all aspects of the article.

CONFLICT OF INTEREST

The authors declare no challenging interests

GENERATIVE AI STATEMENT

The author declares that Generative AI (Artificial Intelligence) tools, including, Grammarly, and QuillBot, was used to enhance the language & clarity of this work. I take full responsibility for the accuracy & integrity of the content.

SUMMARY

The mismatch repair (MMR) pathway in *Plasmodium* keeps the parasite's genome stable and plays a role in drug resistance, so it is an important target for new antimalarial drugs. Researchers still face hurdles like off-target effects, overlapping repair systems, limited structural data, and the parasite's ability to adapt. Overcoming these challenges will take close teamwork among experts in molecular biology, medicinal chemistry, genomics, and drug delivery. I encourage malaria researchers, structural biologists, and pharmaceutical scientists to work together to develop MMR pathway inhibitors and move antimalarial treatments forward.

REFERENCES

Ahmad, M., & Tuteja, R. (2014). Emerging importance of mismatch repair components including UvrD helicase and their cross-talk with the development of drug resistance in malaria parasite. Mutation Research, 770, 54–60. https://doi.org/10.1016/j.mrfmmm.2014.09.009

Assisi, C. (2021). Screening and characterization of antimalarial resistance related genetic structural variations in *P. falciparum*.

Barth, J., Schach, T., & Przyborski, J. M. (2022). HSP70 and their co-chaperones in the human malaria parasite *P. falciparum* and their potential as drug targets. Frontiers in Molecular Biosciences, 9, Article 968248. https://doi.org/10.3389/fmolb.2022.968248

Blasco, B., Leroy, D., & Fidock, D. A. (2017). Antimalarial drug resistance: Linking *Plasmodium falciparum* parasite biology to the clinic. Nature Medicine, 23(8), 917–928. https://doi.org/10.1038/nm.4381

Caja, F., Vodickova, L., Kral, J., Vymetalkova, V., Naccarati, A., & Vodicka, P. (2020). DNA mismatch repair gene variants in sporadic solid cancers. International Journal of Molecular Sciences, 21(15), Article 5561. https://doi.org/10.3390/ijms21155561

Cannavo, E., Sanchez, A., Anand, R., Ranjha, L., Hugener, J., Adam, C., Acharya, A., Weyland, N., Aran-Guiu, X., Charbonnier, J.-B., Hoffmann, E. R., Borde, V., Matos, J., & Cejka, P. (2020). Regulation of the MLH1-MLH3 endonuclease in meiosis. Nature, 586(7830), 618–622. https://doi.org/10.1038/s41586-020-2592-2

Chabowska, K. (2023). The structure and mechanism of the EXD2 nuclease in DNA repair.

Chulanetra, M., & Chaicumpa, W. (2021). Revisiting the mechanisms of immune evasion employed by human parasites. Frontiers in Cellular and Infection Microbiology, 11, Article 702125. https://doi.org/10.3389/fcimb.2021.702125

Claessens, A., Stewart, L. B., Drury, E., Ahouidi, A. D., Amambua-Ngwa, A., Diakite, M., Kwiatkowski, D. P., Awandare, G. A., & Conway, D. J. (2023). Genomic variation during culture adaptation of genetically complex Plasmodium falciparum clinical isolates. Microbial Genomics, 9(5), Article mgen001009. https://doi.org/10.1099/mgen.0.001009

da Silva, M. S., McCulloch, R., & Cano, M. I. N. (2022). Editorial: Nuclear genome stability: DNA replication, telomere maintenance, and DNA repair. Frontiers in Cell and Developmental Biology, 10, Article 875749. https://doi.org/10.3389/fcell.2022.875749

Dhiman, S. (2019). Are malaria elimination efforts on right track? An analysis of gains achieved and challenges ahead. Infectious Diseases of Poverty, 8(1), Article 14. https://doi.org/10.1186/s40249-019-0524-x

Dong, Y., Simões, M. L., Marois, E., & Dimopoulos, G. (2018). CRISPR/Cas9 -mediated gene knockout of Anopheles gambiae FREP1 suppresses malaria parasite infection. PLOS Pathogens, 14(3), Article e1006898. https://doi.org/10.1371/journal.ppat.1006898

Dutta, T., Singh, H., Edkins, A. L., & Blatch, G. L. (2022). Hsp90 and associated co-chaperones of the malaria parasite. Biomolecules, 12(8), Article 1018. https://doi.org/10.3390/biom12081018

Edelbrock, M. A., Kaliyaperumal, S., & Williams, K. J. (2013). Structural, molecular and cellular functions of MSH2 and MSH6 during DNA mismatch repair, damage signaling and other noncanonical activities. Mutation Research, 743–744, 53–66. https://doi.org/10.1016/j.mrfmmm.2012.12.008

Fang, X., Zheng, Y., Duan, Y., Liu, Y., & Zhong, W. (2018). Recent advances in design of fluorescence-based assays for high-throughput screening. Analytical Chemistry, 91(1), 482–504. https://doi.org/10.1021/acs.analchem.8b05303

Furman, C. M. (2021). Roles for the intrinsically disordered linker arms of MLH proteins in DNA mismatch repair.

Ghosh, B., & Choudhuri, S. (2021). Drug design for malaria with artificial intelligence (ai). In*Plasmodium* species and drug resistance. IntechOpen.

Goyal, M., Singh, B. K., Simantov, K., Kaufman, Y., Eshar, S., & Dzikowski, R. (2021). An SR protein is essential for activating DNA repair in malaria parasites. Journal of Cell Science, 134(16), Article jcs258572. https://doi.org/10.1242/jcs.258572

Guillotin, D. (2015). Identification of novel therapeutics for the treatment of MMR deficient tumours using high-throughput screens (Doctoral dissertation, Queen Mary University of London).

Gupta, D. K. (2016). Regulation of gene expression during DNA damage response in *Plasmodium falciparum* [Unpublished doctoral dissertation].

Hadjimichael, E., & Deitsch, K. W. (2025). Variable surface antigen expression, virulence, and persistent infection by Plasmodium falciparum malaria parasites. Microbiology and Molecular Biology Reviews, 89(1), Article e0011423. https://doi.org/10.1128/mmbr.00114-23

Hjelmqvist, D. (2019). Effects of DNA damage and vesicular exchange in *P. falciparum* (Doctoral dissertation, Karolinska Institutet (Sweden)).

Honma, H., Takahashi, N., Arisue, N., & Sugishita, T. (2023). Analysis of genome instability and implications for the consequent phenotype in *Plasmodium falciparum* containing mutated MSH2-1 (P513T). Microbial Genomics, 9(4), 9. https://doi.org/10.1099/mgen.0.001003(4), 001003

Hsieh, P., & Zhang, Y. (2017). The devil is in the details for DNA mismatch repair. Proceedings of the National Academy of Sciences of the United States of America, 114(14), 3552–3554. https://doi.org/10.1073/pnas.1702747114

Johnson, R. M., Rawson, S., McPhillie, M. J., Fishwick, C. W. G., & Muench, S. P. (2018). The growing role of electron microscopy in anti-parasitic drug discovery. Current Medicinal Chemistry, 25(39), 5279–5290. https://doi.org/10.2174/0929867324666171109120526

Kalamuddin, M., Shakri, A. R., Wang, C., Min, H., Li, X., Cui, L., & Miao, J. (2024). MYST regulates DNA repair and forms a NuA4-like complex in the malaria parasite *Plasmodium falciparum*. mSphere, 9(4), Article e0014024. https://doi.org/10.1128/msphere.00140-24

Lecture-Opening, F. S. H. K. (2023). Diet, metabolism and cancer progression.

Li, S., Topatana, W., Juengpanich, S., Cao, J., Hu, J., Zhang, B., Ma, D., Cai, X., & Chen, M. (2020). Development of synthetic lethality in cancer: Molecular and cellular classification. Signal Transduction and Targeted Therapy, 5(1), Article 241. https://doi.org/10.1038/s41392-020-00358-6

Lin, A., Giuliano, C. J., Palladino, A., John, K. M., Abramowicz, C., Yuan, M. L., Sausville, E. L., Lukow, D. A., Liu, L., Chait, A. R., Galluzzo, Z. C., Tucker, C., & Sheltzer, J. M. (2019). Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials. Science Translational Medicine, 11(509), Article eaaw8412. https://doi.org/10.1126/scitranslmed.aaw8412

Liu, D., Keijzers, G., & Rasmussen, L. J. (2017). DNA mismatch repair and its many roles in eukaryotic cells. Mutation Research. Reviews in Mutation Research, 773, 174–187. https://doi.org/10.1016/j.mrrev.2017.07.001

López-Camarillo, C., Lopez-Casamichana, M., Weber, C., Guillen, N., Orozco, E., & Marchat, L. A. (2009). DNA repair mechanisms in eukaryotes: Special focus in *Entamoeba histolytica* and related protozoan parasites. Infection, Genetics and Evolution, 9(6), 1051–1056. https://doi.org/10.1016/j.meegid.2009.06.024

Lujan, S. A., & Kunkel, T. A. (2021). Stability across the whole nuclear genome in the presence and absence of DNA mismatch repair. Cells, 10(5), Article 1224. https://doi.org/10.3390/cells10051224

Manzoni, G., Try, R., Guintran, J. O., Christiansen-Jucht, C., Jacoby, E., Sovannaroth, S., Zhang, Z., Banouvong, V., Shortus, M. S., Reyburn, R., Chanthavisouk, C., Linn, N. Y. Y., Thapa, B., Khine, S. K., Sudathip, P., Gopinath, D., Thieu, N. Q., Ngon, M. S., Cong, D. T., Tuseo, L. (2024). Progress towards malaria elimination in the Greater Mekong subregion: Perspectives from the World Health Organization. Malaria Journal, 23(1), Article 64. https://doi.org/10.1186/s12936-024-04851-z

McPherson, K. S., & Korzhnev, D. M. (2021). Targeting protein–protein interactions in the DNA damage response pathways for cancer chemotherapy. RSC Chemical Biology, 2(4), 1167–1195. https://doi.org/10.1039/D1CB00101A

Molina, R. S., Rix, G., Mengiste, A. A., Álvarez, B., Seo, D., Chen, H., Hurtado, J., Zhang, Q., Donato García-García, J., Heins, Z. J., Almhjell, P. J., Arnold, F. H., Khalil, A. S., Hanson, A. D., Dueber, J. E., Schaffer, D. V., Chen, F., Kim, S., Ángel Fernández, L., (2022). *In vivo* hypermutation and continuous evolution. Nature Reviews. Methods Primers, 2(1), Article 37. https://doi.org/10.1038/s43586-022-00130-w

Molnár, P. A. (2020). New approaches to identify and follow key pathways of the malaria parasites (Doctoral dissertation, Budapest University of Technology and Economics (Hungary)).

Muthye, V., & Lavrov, D. V. (2021). Multiple losses of MSH1, gain of mtMutS, and other changes in the MutS family of DNA repair proteins in animals. Genome Biology and Evolution, 13(9), Article evab191. https://doi.org/10.1093/gbe/evab191

Nastasi, C., Mannarino, L., & D'Incalci, M. (2020). DNA damage response and immune defense. International Journal of Molecular Sciences, 21(20), Article 7504. https://doi.org/10.3390/ijms21207504

Nebot-Bral, L. (2021). Characterizing resistance mechanisms to immune checkpoint blockades in mismatch repair-deficient tumors (Doctoral dissertation, Université Paris-Saclay).

Obeagu, E. I., Okoroiwu, G. I. A., Ubosi, N. I., Obeagu, G. U., Onohuean, H., Muhammad, T., & Adias, T. C. (2024). Revolution in malaria detection: Unveiling current breakthroughs and tomorrow's possibilities in biomarker innovation. Annals of Medicine and Surgery, 86(10), 5859–5876. https://doi.org/10.1097/MS9.0000000000002383

Obmolova, G., Ban, C., Hsieh, P., & Yang, W. (2000). Crystal structures of mismatch repair protein MutS and its complex with a substrate DNA. Nature, 407(6805), 703–710. https://doi.org/10.1038/35037509

Ocan, M., Ashaba, F. K., Mwesigwa, S., Edgar, K., Kamya, M. R., & Nsobya, S. L. (2022). Prevalence of arps10, fd, pfmdr-2, pfcrt and pfkelch13 gene mutations in *Plasmodium falciparum* parasite population in Uganda. PLOS One, 17(5), Article e0268095. https://doi.org/10.1371/journal.pone.0268095

Ortega, J., Lee, G. S., Gu, L., Yang, W., & Li, G.-M. (2021). Mispair-bound human MutS–MutL complex triggers DNA incisions and activates mismatch repair. Cell Research, 31(5), 542–553. https://doi.org/10.1038/s41422-021-00468-y

Pálinkás, H. L. (2020). Genomic uracil occurrence and the role of dUTPase in transgenic models (Doctoral dissertation, Szegedi Tudomanyegyetem (Hungary)).

Payero, L., & Alani, E. (2024). Crossover recombination between homologous chromosomes in meiosis: Recent progress and remaining mysteries. Trends in Genetics, 41(1), 47–59. https://doi.org/10.1016/j.tig.2024.09.009

Putnam, C. D. (2021). Strand discrimination in DNA mismatch repair. DNA Repair, 105, Article 103161. https://doi.org/10.1016/j.dnarep.2021.103161

Rashidi, S., Tuteja, R., Mansouri, R., Ali-Hassanzadeh, M., Shafiei, R., Ghani, E., Karimazar, M., Nguewa, P., & Manzano-Román, R. (2021). The main post-translational modifications and related regulatory pathways in the malaria parasite Plasmodium falciparum: An update. Journal of Proteomics, 245, Article 104279. https://doi.org/10.1016/j.jprot.2021.104279

Reyes, G. X., Kolodziejczak, A., Devakumar, L. J. P. S., Kubota, T., Kolodner, R. D., Putnam, C. D., & Hombauer, H. (2021). Ligation of newly replicated DNA controls the timing of DNA mismatch repair. Current Biology, 31(6), 1268–1276.e6. https://doi.org/10.1016/j.cub.2020.12.018

Sarasin, A., & Kauffmann, A. (2008). Overexpression of DNA repair genes is associated with metastasis: A new hypothesis. Mutation Research, 659 (1–2), 49–55. https://doi.org/10.1016/j.mrrev.2007.12.002

Schöniger, S., & Rüschoff, J. (2022). Mismatch repair deficiency and microsatellite instability [Encyclopedia]. Encyclopedia, 2(3), 1559–1576. https://doi.org/10.3390/encyclopedia2030106

Schwarzer, E., & Skorokhod, O. (2024). Post-translational modifications of proteins of malaria parasites during the life cycle. International Journal of Molecular Sciences, 25(11), Article 6145. https://doi.org/10.3390/ijms25116145

Shibeshi, M. A., Kifle, Z. D., & Atnafie, S. A. (2020). Antimalarial drug resistance and novel targets for antimalarial drug discovery. Infection and Drug Resistance, 13, 4047–4060. https://doi.org/10.2147/IDR.S279433

Shin, H. I., Ku, B., Jung, H., Lee, S. D., Lee, S. Y., Ju, J. W. *et al.* (2024). 2023. World malaria report (status of world malaria in 2022).

Sina, M. (2023). Identification and interpretation of pathogenic variants following Next Generation Sequencing (NGS) analysis in human Mendelian disorders.

Subramaniam, S., Schmid, C. D., Guan, X. L., & Mäser, P. (2018). Using yeast synthetic lethality to inform drug combination for malaria. Antimicrobial Agents and Chemotherapy, 62(4), Article e01533-17. https://doi.org/10.1128/AAC.01533-17

Tarique, M., Ahmad, M., Chauhan, M., & Tuteja, R. (2017). Genome wide *in silico* analysis of the mismatch repair components of Plasmodium falciparum and their comparison with human host. Frontiers in Microbiology, 8, Article 130. https://doi.org/10.3389/fmicb.2017.00130

Waweru, H. K. (2024). Prevalence of *Plasmodium falciparum* antimalarial drugs resistance genetic markers in selected Lake Victoria islands, Western Kenya (Doctoral dissertation, JKUAT-COHES).

Cite this article: Tarique M, Sain Z, Ahmad Y. Exploiting MMR Pathways in *Plasmodium* as Novel Antimalarial Targets: Opportunities and Challenge. Int. J. Pharm. Investigation. 2026;16(2):476-89.