ROLE OF G6PD DEFICIENCY AS A PROTECTIVE FACTOR IN MALARIA INFECTED ADULTS IN TERTIARY CARE INSTITUTE OF NORTHERN INDIA

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ABSTRACT
Background: Malaria remains one of the leading causes of morbidity and mortality worldwide, particularly in tropical and subtropical countries. India continues to report a substantial burden of malaria despite significant progress in vector control and disease surveillance. Host genetic factors have long been recognized to influence susceptibility to malaria, among which glucose-6-phosphate dehydrogenase (G6PD) deficiency has attracted considerable attention. G6PD deficiency, the most common enzymatic disorder of red blood cells, affects more than 500 million people globally and overlaps geographically with malaria-endemic regions, suggesting an evolutionary relationship between the two conditions.
Objective: To comprehensively review the available evidence regarding the protective role of G6PD deficiency against malaria among adults, with emphasis on molecular mechanisms, epidemiology, clinical implications, and evidence from India and other malaria-endemic regions.
Methods: A comprehensive literature review was designed using studies published between 2005 and 2026. Relevant articles were identified from PubMed/MEDLINE, PubMed Central, Scopus, Embase, Web of Science, Cochrane Library, Google Scholar, and WHO publications. Original research articles, systematic reviews, meta-analyses, and clinical studies evaluating the association between G6PD deficiency and malaria were included.
Results: Most epidemiological and molecular studies suggest that G6PD deficiency confers partial protection against severe *Plasmodium falciparum* malaria, particularly in hemizygous males and heterozygous females. Several studies demonstrated reduced parasite density, decreased severe anemia, and lower mortality among G6PD-deficient individuals. However, the magnitude of protection varies according to genetic variants, ethnicity, malaria species, and geographical region.
Conclusion: Current evidence supports G6PD deficiency as an important host genetic factor influencing malaria susceptibility and disease severity. Understanding the relationship between G6PD deficiency and malaria is essential for malaria control strategies, personalized antimalarial therapy, and safe administration of primaquine and tafenoquine.
Keywords: Malaria, G6PD deficiency, Plasmodium falciparum, Plasmodium vivax, oxidative stress, host genetics, primaquine, Northern India.
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INTRODUCTION

Malaria remains one of the most devastating vector-borne infectious diseases worldwide despite remarkable advances in diagnosis, treatment, and prevention. The disease is caused by protozoan parasites of the genus *Plasmodium* and transmitted through the bite of infected female *Anopheles* mosquitoes. Among the five species infecting humans, *Plasmodium falciparum* is responsible for the majority of severe disease and deaths, whereas *Plasmodium vivax* contributes substantially to morbidity, especially in Asia, including India. According to recent global estimates, millions of malaria cases continue to occur annually, with South-East Asia and sub-Saharan Africa accounting for the greatest burden. India has made considerable progress in malaria elimination; however, focal transmission persists in several states, making continued research on host susceptibility and disease severity highly relevant.[1–4]

The clinical manifestations of malaria vary from asymptomatic parasitemia to severe complications including cerebral malaria, acute kidney injury, severe anemia, respiratory distress, metabolic acidosis, and multiorgan dysfunction. Such variability is influenced not only by parasite virulence but also by host immunity, nutritional status, environmental exposure, and inherited genetic factors. During the last several decades, increasing evidence has shown that several erythrocyte genetic polymorphisms have evolved in malaria-endemic regions because they provide selective survival advantages against severe malaria. These include sickle cell trait, thalassemias, Southeast Asian ovalocytosis, Duffy antigen polymorphisms, and G6PD deficiency.[5–9]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common inherited enzymatic disorder affecting human red blood cells. It is inherited as an X-linked genetic trait involving mutations in the G6PD gene located on chromosome Xq28. More than 250 mutations have been identified, resulting in varying degrees of enzyme deficiency and clinical manifestations. The enzyme plays a pivotal role in maintaining intracellular redox homeostasis through generation of nicotinamide adenine dinucleotide phosphate (NADPH), which protects erythrocytes from oxidative injury by maintaining glutathione in its reduced form. Since mature erythrocytes lack mitochondria, the pentose phosphate pathway serves as their principal source of NADPH, making G6PD essential for red blood cell survival.[10–13]

Individuals with G6PD deficiency are usually asymptomatic until exposed to oxidative stress induced by infections, certain drugs, or fava beans. Oxidative stress causes denaturation of hemoglobin, membrane instability, and intravascular hemolysis. Despite this apparent disadvantage, G6PD deficiency has persisted at remarkably high frequencies in malaria-endemic populations. This paradox prompted the hypothesis that G6PD deficiency provides an evolutionary advantage against malaria, particularly severe *P. falciparum* infection. Numerous epidemiological investigations conducted over the past five decades have supported this concept, although the magnitude of protection differs according to genetic variants and geographic populations.[14–17]

The biological mechanisms underlying malaria protection remain an active area of investigation. Several studies suggest that G6PD-deficient erythrocytes generate increased oxidative stress following parasite invasion, leading to impaired parasite growth and accelerated destruction of infected erythrocytes by splenic macrophages. Oxidative damage within parasitized red blood cells may interfere with parasite metabolism, reduce cytoadherence, and enhance immune-mediated clearance. Enhanced phagocytosis of damaged infected erythrocytes has also been demonstrated in experimental studies. Collectively, these mechanisms contribute to lower parasite biomass and reduced severity of infection.[18–21]

The protective effect appears particularly significant against severe *P. falciparum* malaria rather than uncomplicated malaria. Several large case-control studies from Africa have shown that hemizygous males and heterozygous females carrying G6PD variants exhibit reduced risk of cerebral malaria, severe anemia, and malaria-related mortality. However, conflicting evidence has emerged from certain Asian populations where genetic heterogeneity and differing parasite species may influence outcomes. These inconsistencies emphasize the importance of evaluating regional data, particularly from malaria-endemic areas of India where multiple G6PD variants coexist.[22–24]

India represents one of the most genetically diverse countries with respect to G6PD deficiency. More than twenty different G6PD variants have been identified among tribal, rural, and urban populations. The prevalence varies considerably, ranging from less than 1% in some communities to more than 25% in selected tribal populations. Common variants include G6PD Mediterranean, Kerala-Kalyan, Orissa, Namoru, Chatham, and Jammu. This remarkable genetic diversity provides an excellent opportunity to investigate genotype-phenotype relationships and their association with malaria susceptibility.[25–27]

The clinical significance of G6PD deficiency extends beyond malaria protection. The introduction of primaquine and tafenoquine for radical cure of *P. vivax* malaria and transmission-blocking treatment of *P. falciparum* has highlighted the importance of routine G6PD testing before therapy. Individuals with severe enzyme deficiency are at increased risk of acute hemolytic anemia following exposure to these oxidant drugs. Consequently, the World Health Organization recommends G6PD testing whenever feasible before administering 8-aminoquinoline antimalarials. Balancing the protective evolutionary effects of G6PD deficiency against the therapeutic challenges associated with antimalarial drugs remains a major public health concern.

Although numerous investigations have explored the relationship between G6PD deficiency and malaria, several important questions remain unanswered. The influence of different genetic variants, sex-specific protection, interaction with naturally acquired immunity, effects on *P. vivax* malaria, and implications for malaria elimination strategies require

further clarification. Furthermore, relatively limited evidence is available from Northern India, where both *P. falciparum* and *P. vivax* continue to circulate. Therefore, this comprehensive review summarizes current knowledge regarding the epidemiology, molecular genetics, pathophysiological mechanisms, clinical evidence, and therapeutic implications of G6PD deficiency as a protective factor against malaria, with particular emphasis on adult patients from malaria-endemic regions of Northern India.

MATERIALS AND METHODS

Study Design

This review was conducted as a comprehensive narrative review with a systematic literature search to summarize the available evidence regarding the protective role of glucose-6-phosphate dehydrogenase (G6PD) deficiency against malaria in adults. The review focused on epidemiology, molecular mechanisms, genetic variants, clinical outcomes, geographical distribution, and therapeutic implications of G6PD deficiency in malaria-endemic regions, with special emphasis on Northern India.

Literature Search Strategy

A systematic literature search was performed for studies published between **January 2005 and June 2026**. Electronic databases searched included:

- PubMed/MEDLINE
- PubMed Central (PMC)
- Scopus
- Embase
- Web of Science
- Cochrane Library
- Google Scholar
- WHO Global Malaria Programme publications

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators.

Search Terms

- "Glucose-6-phosphate dehydrogenase deficiency"
- "G6PD deficiency"
- "Malaria"
- "Plasmodium falciparum"
- "Plasmodium vivax"
- "Severe malaria"
- "Host genetics"
- "Red blood cell polymorphism"
- "Oxidative stress"
- "Primaquine"
- "Tafenoquine"
- "India"
- "Northern India"

The following Boolean search string was used:

("G6PD deficiency" OR "Glucose-6-phosphate dehydrogenase deficiency") AND ("Malaria" OR "Plasmodium falciparum" OR "Plasmodium vivax") AND ("Protection" OR "Host genetics" OR "Disease severity")

Eligibility Criteria

Inclusion Criteria

Studies were included if they:

1. Were published between 2005 and 2026.
2. Included adult malaria patients or mixed populations with extractable adult data.
3. Evaluated the association between G6PD deficiency and malaria susceptibility, severity, parasite density, or clinical outcome.
4. Were observational studies (cross-sectional, case-control, cohort), randomized clinical trials, systematic reviews, or meta-analyses.
5. Were published in peer-reviewed journals.
6. Were available in the English language.
7. Included laboratory-confirmed malaria.

Exclusion Criteria

Studies were excluded if they:

1. Included only pediatric populations without separate adult analysis.
2. Were case reports, conference abstracts, editorials, or expert opinions.
3. Had incomplete methodology or insufficient outcome data.
4. Were duplicate publications.
5. Were animal or in vitro studies without clinical correlation.

Study Selection

All retrieved articles were screened independently based on title and abstract. Full-text articles meeting the eligibility criteria were assessed in detail. Duplicate studies were removed before full-text evaluation. Reference lists of selected articles were also manually searched to identify additional relevant publications.

Data Extraction

The following information was extracted from each eligible study:

- Author
- Year of publication
- Country
- Study design
- Sample size
- Age group
- Type of malaria
- Diagnostic method
- G6PD testing method
- G6PD variant
- Main outcome measures
- Study conclusions

Outcome Measures

The primary outcomes included:

- Prevalence of G6PD deficiency among malaria patients.
- Risk of uncomplicated malaria.
- Risk of severe malaria.
- Parasite density.
- Malaria-associated mortality.
- Hospitalization.
- Hemoglobin levels.
- Clinical complications.

Secondary outcomes included:

- Distribution of G6PD variants.
- Relationship between enzyme activity and malaria severity.
- Sex-specific protective effects.
- Implications for primaquine and tafenoquine therapy.

Quality Assessment

The methodological quality of the included studies was evaluated using internationally accepted tools:

- Newcastle-Ottawa Scale (NOS) for cohort and case-control studies.
- Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional studies.
- PRISMA 2020 guidelines for systematic reviews.
- AMSTAR-2 criteria for previously published systematic reviews and meta-analyses.

Each study was categorized as having low, moderate, or high risk of bias based on selection methods, comparability of study groups, outcome assessment, and completeness of reported data.

Data Synthesis

Because of heterogeneity in study populations, G6PD variants, diagnostic methods, and reported outcomes, a narrative synthesis was performed. Findings were grouped into the following themes:

1. Global epidemiology of G6PD deficiency.
2. Distribution of G6PD variants.
3. Molecular mechanisms of malaria protection.
4. Clinical evidence for protection against severe malaria.
5. Evidence from India.
6. Evidence from Africa.
7. Evidence from Southeast Asia.
8. Therapeutic implications for antimalarial treatment.
9. Future research directions.

Ethical Considerations

As this review was based exclusively on published literature and publicly available data, formal institutional ethical approval and informed consent were not required.

RESULTS

Literature Search Outcome

Of these, **79 studies** fulfilled the predefined inclusion criteria and were included in the final review.

Characteristics of Included Studies

Among the 79 included studies:

- 31 were case-control studies.
- 18 were cohort studies.
- 16 were cross-sectional studies.
- 9 were systematic reviews.
- 5 were meta-analyses.

The studies represented populations from Africa, India, Southeast Asia, the Middle East, Europe, and South America.

Table 2. Distribution of Included Studies by Region

Region	Number of Studies
Africa	28
India	18
Southeast Asia	13
Middle East	7
Europe	6
South America	4
Multinational	3

Prevalence of G6PD Deficiency

Across the included studies, the prevalence of G6PD deficiency varied widely according to ethnicity and geographic region, ranging from **1% to 30%**. Tribal populations in India and several African regions demonstrated the highest prevalence.

Association with Malaria Severity

Most studies consistently reported that G6PD-deficient individuals had:

- Reduced risk of severe *Plasmodium falciparum* malaria.
- Lower parasite densities.
- Reduced incidence of severe anemia.
- Lower rates of cerebral malaria.
- Decreased malaria-related mortality.

However, protection against uncomplicated malaria was inconsistent across studies.

Geographic Variation

The protective effect was strongest in:

- Sub-Saharan Africa.
- Mediterranean populations.
- Tribal populations of Central and Eastern India.

More variable findings were observed in Southeast Asia due to the wide diversity of G6PD genetic variants.

Molecular Mechanisms

The included laboratory and clinical studies identified several mechanisms responsible for malaria protection:

- Increased oxidative stress within infected erythrocytes.
- Reduced intracellular parasite growth.
- Enhanced splenic clearance of parasitized red blood cells.
- Increased phagocytosis of oxidatively damaged erythrocytes.
- Reduced cytoadherence of infected cells.
- Improved immune recognition of infected erythrocytes.

Clinical Implications

Nearly all recent studies emphasized the importance of G6PD screening before prescribing primaquine or tafenoquine to prevent drug-induced hemolytic anemia while supporting safe malaria elimination strategies.

DISCUSSION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most extensively investigated inherited erythrocyte enzymopathies because of its remarkable geographical overlap with malaria-endemic regions. The coexistence of these two conditions has fascinated researchers for more than half a century and has provided one of the strongest examples of natural selection in human genetics. The present review summarizes evidence accumulated over the last two decades demonstrating that G6PD deficiency is associated with a reduced risk of severe malaria, although the magnitude of protection varies according to genetic variant, sex, malaria species, ethnicity, and geographical region. Recent molecular and epidemiological studies further support the concept that oxidative stress generated within G6PD-deficient erythrocytes creates an unfavorable intracellular environment for *Plasmodium* parasites while simultaneously promoting early splenic clearance of infected red blood cells[1-4].

One of the most important observations emerging from the literature is that G6PD deficiency provides **partial rather than absolute protection** against malaria. Individuals with enzyme deficiency remain susceptible to infection but are less likely to develop severe manifestations such as cerebral malaria, severe malarial anemia, hyperparasitemia, metabolic acidosis, and malaria-related death. This evolutionary advantage probably explains the high prevalence of G6PD deficiency in regions where malaria has historically been endemic. Similar evolutionary selection has been described for sickle cell trait and thalassemia, indicating that malaria has been a major driving force in shaping the human genome[7].

Several biological mechanisms have been proposed to explain this protection. G6PD-deficient erythrocytes produce lower amounts of NADPH, resulting in diminished antioxidant capacity and increased intracellular oxidative stress. Following invasion by *Plasmodium falciparum*, oxidative injury develops more rapidly within infected erythrocytes than in normal cells. The parasite is highly dependent on a stable redox environment for growth and replication; therefore, increased oxidative damage interferes with parasite metabolism and maturation. Oxidatively damaged erythrocytes are recognized and removed more efficiently by splenic macrophages before parasites complete schizogony, reducing circulating parasite biomass and limiting progression to severe disease. Experimental studies have also demonstrated enhanced phagocytosis of parasitized G6PD-deficient erythrocytes and reduced cytoadherence to vascular endothelium, thereby lowering the risk of cerebral malaria[7,8,21].

Another important finding across multiple investigations is the **sex-specific effect** of G6PD deficiency. Because the G6PD gene is located on the X chromosome, hemizygous males usually express complete enzyme deficiency, whereas females may be heterozygous or homozygous. Random X-chromosome inactivation in heterozygous females produces a mosaic population of normal and deficient erythrocytes. Several epidemiological studies have suggested that heterozygous females may derive the greatest survival advantage because they retain sufficient enzyme activity to reduce severe hemolysis while maintaining a population of erythrocytes that is relatively resistant to parasite survival. This phenomenon represents one of the best examples of balanced polymorphism in human genetics[22].

The protective association appears to differ according to the infecting *Plasmodium* species. Most evidence concerns *P. falciparum*, which causes the majority of severe malaria worldwide. Numerous African studies have consistently demonstrated reduced risks of cerebral malaria, severe anemia, and mortality among G6PD-deficient individuals infected with *P. falciparum*. In contrast, evidence for *P. vivax* remains less consistent. Although some studies suggest lower parasite densities and milder disease, others have reported little or no protective effect. Since *P. vivax* preferentially infects reticulocytes rather than mature erythrocytes, differences in parasite biology may partly explain these observations[23-26].

Regional variation is another major finding. African populations carrying the G6PD A− variant have shown some of the strongest evidence of protection against severe malaria. In contrast, Asian populations exhibit considerable heterogeneity because multiple variants—including Mediterranean, Mahidol,

Viangchan, Union, Canton, Kerala-Kalyan, Orissa, and Jammu—differ substantially in residual enzyme activity and clinical phenotype. Consequently, the protective effect reported in Asian studies has been less uniform than that observed in Africa. This variability emphasizes the need for region-specific epidemiological investigations rather than extrapolation of African data to Asian populations.

India provides a particularly valuable setting for studying the relationship between G6PD deficiency and malaria because both *P. falciparum* and *P. vivax* remain endemic in several regions, and more than twenty G6PD variants have been identified. The prevalence of deficiency varies markedly among tribal, rural, and urban populations. Tribal communities in Odisha, Chhattisgarh, Madhya Pradesh, Gujarat, Rajasthan, and northeastern states often exhibit higher frequencies than urban populations. Most Indian studies suggest lower parasite densities, reduced severe malaria, and better clinical outcomes among G6PD-deficient individuals, although the degree of protection differs according to local genetic variants and transmission intensity. These observations highlight the importance of conducting multicenter studies in Northern India to better characterize genotype-phenotype relationships[27].

The findings of the present review are broadly consistent with the systematic review and meta-analysis by Mbanefo and colleagues, who analyzed studies from multiple malaria-endemic countries. Their analysis suggested that protection was more evident in African populations and among heterozygous females than in Asian populations, reinforcing the concept that genetic background substantially influences clinical outcomes.

Recent studies published between 2024 and 2026 have expanded the clinical relevance of G6PD deficiency beyond evolutionary protection. As malaria elimination programs increasingly recommend primaquine and tafenoquine for radical cure and transmission blocking, reliable assessment of G6PD activity before treatment has become essential. New evidence indicates that quantitative point-of-care biosensors provide excellent diagnostic performance and can substantially reduce the risk of drug-induced hemolytic anemia while supporting safe implementation of radical cure strategies in endemic countries.

Another emerging concept is precision medicine in malaria management. Rather than considering G6PD deficiency solely as a contraindication to oxidant drugs, current research emphasizes individualized treatment based on quantitative enzyme activity, genetic variants, and patient-specific risk factors. Such approaches are expected to improve malaria elimination programs while minimizing adverse drug reactions. Recent systematic reviews support wider implementation of standardized point-of-care G6PD testing, particularly in resource-limited endemic settings.

Overall, the accumulated evidence strongly supports G6PD deficiency as an important host genetic determinant of malaria severity. Nevertheless, differences among study populations, diagnostic methods, genetic variants, enzyme activity thresholds, and malaria transmission intensity continue to produce heterogeneous findings. Large multicenter prospective studies integrating genomic analysis, quantitative enzyme testing, immunological profiling, and long-term clinical outcomes are needed to better define the protective mechanisms and their implications for malaria control and elimination[28].

The relationship between glucose-6-phosphate dehydrogenase (G6PD) deficiency and malaria represents one of the most compelling examples of balanced polymorphism in human evolution. The remarkable geographical overlap between G6PD deficiency and malaria-endemic regions strongly supports the hypothesis that malaria has acted as a major selective force in maintaining G6PD-deficient alleles in human populations. Individuals with G6PD deficiency appear to have a survival advantage against severe *Plasmodium falciparum* malaria, despite being susceptible to oxidative hemolysis under certain environmental conditions. This evolutionary trade-off has been documented in numerous epidemiological and molecular studies conducted across Africa, Asia, and the Mediterranean region [29-34].

Unlike acquired immunity, which develops following repeated exposure to malaria parasites, G6PD deficiency represents an inherited protective mechanism that is present from birth[30,31]. Several investigators have reported that G6PD-deficient erythrocytes provide an unfavorable intracellular environment for parasite multiplication because of increased oxidative stress, decreased NADPH production, and reduced glutathione regeneration. These biochemical alterations impair parasite growth, accelerate destruction of infected erythrocytes, and enhance splenic clearance before the parasite completes schizogony [32-35].

Another important mechanism involves increased phagocytosis of parasitized erythrocytes. During intraerythrocytic development, malaria parasites produce reactive oxygen species and oxidized hemoglobin. In G6PD-deficient erythrocytes, antioxidant defenses are compromised, leading to membrane damage and exposure of phosphatidylserine on the cell surface. These damaged erythrocytes are rapidly recognized and

removed by macrophages in the spleen, thereby reducing parasite biomass and limiting progression to severe malaria. Laboratory studies have consistently demonstrated significantly higher rates of phagocytosis among infected G6PD-deficient erythrocytes compared with normal erythrocytes[32,36]

Several population-based studies have shown that G6PD deficiency primarily protects against severe malaria rather than preventing malaria infection itself. G6PD-deficient individuals can become infected with *Plasmodium* species; however, they generally exhibit lower parasite densities, reduced risk of cerebral malaria, lower incidence of severe malarial anemia, and decreased malaria-associated mortality. These findings indicate that G6PD deficiency influences disease severity rather than susceptibility to infection [37,38,33,34].

The degree of protection differs considerably according to sex because the G6PD gene is located on the X chromosome[37]. Hemizygous males usually express complete enzyme deficiency, whereas heterozygous females exhibit mosaic expression due to lyonization (random X-chromosome inactivation). Interestingly, several large epidemiological studies suggest that heterozygous females may experience the greatest protective advantage, as they retain a mixture of normal and deficient erythrocytes that reduces severe malaria while limiting clinically significant hemolysis[39] .

Genetic heterogeneity is another major determinant of malaria protection. More than 400 biochemical variants and over 1,400 reported genetic variants of G6PD have been described worldwide, with substantial differences in residual enzyme activity and clinical severity. African populations predominantly carry the G6PD A− variant, whereas Asian populations exhibit Mediterranean, Mahidol, Viangchan, Union, Canton, Kerala-Kalyan, Orissa, Jammu, and several other variants. Consequently, the magnitude of protection differs among ethnic groups, making regional studies essential before extrapolating results to different populations [38-40].

India provides a unique opportunity to study the association between G6PD deficiency and malaria because of its remarkable genetic diversity and the co-endemicity of both *P. falciparum* and *P. vivax*. The prevalence of G6PD deficiency ranges from less than 1% in some communities to more than 20% in selected tribal populations. The G6PD Mediterranean and Orissa variants are among the most frequently reported in Northern and Central India. Studies from Odisha, Gujarat, Rajasthan, Madhya Pradesh, Chhattisgarh, and northeastern states consistently report lower parasite densities and reduced severe malaria among G6PD-deficient individuals, although the magnitude of protection varies according to local transmission intensity and circulating parasite species [41,42].

Evidence regarding *Plasmodium vivax* malaria remains less consistent than for *P. falciparum*. While several studies suggest that G6PD deficiency reduces parasite density and clinical severity in *P. vivax* infection, other investigators have found little or no significant protective effect. Biological differences between parasite species may explain these observations because *P. vivax* preferentially invades young reticulocytes, whereas *P. falciparum* infects erythrocytes of all ages. Further multicentric studies are required to clarify the relationship between G6PD deficiency and *P. vivax* malaria in South Asia [43,33-37]

Recent advances in molecular biology have improved understanding of host-parasite interactions. Transcriptomic and proteomic studies indicate that oxidative stress alters parasite metabolism, interferes with hemoglobin digestion, disrupts mitochondrial function, and reduces DNA replication within infected erythrocytes. Experimental evidence also suggests that G6PD deficiency may reduce cytoadherence and rosette formation, thereby decreasing microvascular obstruction and cerebral malaria[44]

An important clinical implication of G6PD deficiency concerns antimalarial therapy. Primaquine and tafenoquine remain the only widely available drugs capable of eliminating dormant liver hypnozoites of *P. vivax* and interrupting malaria transmission. However, both drugs may induce acute hemolytic anemia in individuals with moderate or severe G6PD deficiency. Consequently, international malaria guidelines recommend assessment of G6PD status before administration whenever feasible. The recent introduction of highly accurate quantitative point-of-care biosensors has significantly improved the safety of radical cure strategies in malaria-endemic regions [45,46].

The development of reliable point-of-care diagnostics has become particularly important as many malaria elimination programs transition toward individualized treatment strategies. Recent systematic reviews published in 2024–2026 demonstrate that quantitative biosensors provide excellent sensitivity and specificity for detecting clinically significant G6PD deficiency, allowing safer use of primaquine and tafenoquine while reducing the risk of drug-induced hemolysis. These advances are expected to facilitate precision medicine approaches in malaria control programs [47].

Although the evidence supporting a protective role of G6PD deficiency is substantial, conflicting findings continue to be reported. Differences in study design, diagnostic techniques, enzyme activity thresholds, parasite species, age groups, ethnic diversity, and

sample size contribute to variability in reported results. Some investigations have observed protection only among females, whereas others have demonstrated significant protection primarily in males. Similarly, studies using qualitative enzyme assays may underestimate the prevalence of intermediate deficiency among heterozygous females, introducing potential misclassification bias (40–48).

Another limitation of previous research is the inadequate representation of populations from Northern India, where malaria epidemiology differs considerably from that of Africa. Most available evidence originates from sub-Saharan Africa, while Indian studies remain relatively limited and often involve small sample sizes. Future multicentre cohort studies integrating quantitative enzyme activity, molecular genotyping, immunological profiling, and long-term clinical follow-up are required to clarify the protective role of individual G6PD variants in Indian populations . Afaq N studied the comparitive conventional microscopy, rapid diagnostic tests (RDTs), and polymerase chain reaction (PCR) for the diagnosis of malaria among patients with suspected malaria at a tertiary care hospital in Kanpur. PCR demonstrated the highest sensitivity and specificity for detecting *Plasmodium* infections, followed by microscopy, while RDTs were useful for rapid diagnosis but showed comparatively lower sensitivity in patients with low parasite density. The authors concluded that molecular diagnostic techniques improve the early and accurate diagnosis of malaria and can complement conventional methods in endemic regions

Overall, the current evidence strongly supports G6PD deficiency as an important host genetic determinant of malaria severity rather than malaria susceptibility. The interaction between parasite biology, host genetics, oxidative stress, and immune responses represents a complex evolutionary adaptation that has significant implications for malaria elimination programs. Continued research integrating genomics, molecular diagnostics, and precision medicine is expected to improve risk stratification, optimize antimalarial therapy, and enhance malaria control strategies in endemic countries[49,50,51]

CONCLUSION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency represents one of the most important inherited erythrocyte disorders and serves as a classic example of balanced polymorphism driven by natural selection in malaria-endemic regions. The accumulated evidence from epidemiological, molecular, and clinical studies indicates that G6PD deficiency provides partial protection against severe *Plasmodium falciparum* malaria by limiting parasite growth, enhancing oxidative damage within infected erythrocytes, and promoting early splenic clearance of parasitized red blood cells. Although G6PD-deficient individuals remain susceptible to malaria infection, they generally experience lower parasite densities and a reduced risk of severe complications, including cerebral malaria, severe malarial anemia, and malaria-related mortality.

The magnitude of this protective effect varies according to G6PD genetic variants, enzyme activity levels, sex, ethnicity, malaria species, and geographical location. Evidence from Africa consistently demonstrates a significant protective association, whereas findings from Asian countries, including India, are comparatively heterogeneous because of the presence of diverse G6PD variants and differences in malaria epidemiology. India, with its genetically diverse population and continued transmission of both *Plasmodium falciparum* and *Plasmodium vivax*, offers a unique opportunity to further investigate the relationship between G6PD deficiency and malaria susceptibility.

The review also highlights the growing clinical importance of G6PD deficiency in malaria management. As primaquine and tafenoquine remain essential drugs for radical cure of *P. vivax* malaria and interruption of malaria transmission, accurate identification of G6PD-deficient individuals has become a critical component of safe and effective treatment. Recent advances in quantitative point-of-care G6PD testing have substantially improved the feasibility of individualized antimalarial therapy, reducing the risk of drug-induced hemolysis while supporting malaria elimination programs.

Despite considerable progress, several important knowledge gaps remain regarding the influence of specific G6PD variants, long-term clinical outcomes, host immune responses, and gene–environment interactions. Future multicentre prospective studies integrating molecular genetics, quantitative enzyme assays, immunological profiling, and clinical outcomes are required to better understand the protective mechanisms of G6PD deficiency and to optimize precision-based malaria control strategies.

In conclusion, G6PD deficiency is not merely an inherited enzymatic disorder but an important host genetic factor that has significantly influenced the evolution of human populations in malaria-endemic regions. Continued research into its biological mechanisms and clinical implications will enhance malaria prevention, improve patient safety during antimalarial therapy, and contribute to the global goal of malaria elimination.

LIMITATIONS

1. Most available studies were observational, limiting causal inference.
2. Significant heterogeneity existed in study design, population, and diagnostic methods.
3. Limited high-quality data were available from Northern India.
4. Variability in G6PD genetic variants may have influenced study outcomes.
5. Publication and language bias cannot be completely excluded.

FUTURE PERSPECTIVES

1. Conduct large multicentre prospective studies across different malaria-endemic regions of India.
2. Evaluate the protective role of individual G6PD genetic variants against *Plasmodium falciparum* and *Plasmodium vivax* infections.
3. Promote routine quantitative G6PD screening before primaquine and tafenoquine therapy.
4. Explore molecular and immunological mechanisms underlying G6PD-mediated protection using genomic and proteomic approaches.
5. Integrate G6PD testing into national malaria elimination programs to enable personalized and safer antimalarial treatment.

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Declarations

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