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Reframing Cerebral Malaria Therapy through Blood-Brain Barrier Repair and Neuroprotection: A Systematic Review of Adjunctive Strategies

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ABSTRACT

Introduction: *Cerebral malaria is a severe complication of Plasmodium falciparum infection that can cause coma, death, and persistent neurological impairment despite effective antimalarial treatment. Blood–brain barrier disruption, endothelial dysfunction, inflammation, hypoxia, oxidative stress, and neurovascular injury are central to its pathogenesis. This review evaluated current evidence on adjunctive strategies targeting blood–brain barrier repair and neuroprotection in cerebral malaria. This systematic review aimed to synthesize evidence on adjunctive strategies targeting blood–brain barrier repair and neuroprotection in cerebral malaria.*
Methods: *This systematic review followed PRISMA 2020 guidelines. PubMed, Scopus, Embase, ScienceDirect, and Cochrane Library were searched for studies published between January 1, 2015 and April 30, 2026. Eligible studies included human, animal, and experimental investigations of cerebral malaria reporting adjunctive therapy outcomes related to blood–brain barrier integrity, endothelial activation, neurovascular injury, neurological outcomes, or survival. Data were extracted using a standardized approach and synthesized narratively because of substantial heterogeneity; meta-analysis was not performed.*
Results: *Twenty-two studies met the inclusion criteria. Blood–brain barrier disruption was linked to interacting mechanisms involving parasite sequestration, cytoadherence, endothelial activation, inflammation, hypoxia, oxidative stress, nitric oxide dysregulation, metabolic disturbance, and impaired cerebral microcirculation. Several adjunctive interventions improved blood–brain barrier integrity, reduced vascular leakage, attenuated neuroinflammation, or limited neurovascular injury in experimental models. However, most evidence remained preclinical, and standardized neurovascular endpoints, biomarker-guided stratification, and long-term neurological assessments were rarely used.*
Conclusions: *Blood–brain barrier repair and neuroprotection are important targets for adjunctive therapy in cerebral malaria. Future studies should validate these strategies in clinically relevant models and human trials using standardized endpoints, biomarkers, and long-term neurological outcome measures.*

Introduction

Cerebral malaria remains one of the most severe and life-threatening complications of *Plasmodium falciparum* infection, characterized by acute neurological impairment, coma, high

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mortality, and a substantial risk of long-term neurocognitive sequelae. The urgency of this condition lies not only in its acute fatality but also in its potential to cause persistent neurological disability among survivors. Current evidence increasingly indicates that cerebral malaria is not merely a parasite-driven disease but a complex neurovascular and immunopathological syndrome in which host responses strongly influence disease severity and outcome. Disease outcome in infectious diseases is determined not only by pathogen virulence but also by host immune competence, physiological reserve, and nutritional status, factors that may influence susceptibility to severe complications and recovery (Meilinda et al., 2025).

Although effective antimalarial therapy remains essential for parasite clearance, neurological deterioration may continue despite appropriate antiparasitic treatment. This limitation suggests that conventional antimalarial therapy alone may be insufficient to prevent the downstream consequences of endothelial activation, cerebral microcirculatory impairment, inflammation, and blood–brain barrier (BBB) disruption. Consequently, therapeutic approaches focused exclusively on parasite elimination may not adequately prevent brain edema, neuronal injury, seizures, cognitive impairment, and other long-term neurological sequelae associated with cerebral malaria.

BBB disruption and neurovascular injury are now recognized as central pathological events linking systemic malaria infection to cerebral damage. Infected erythrocytes adhere to the cerebral microvascular endothelium through PfEMP1-mediated cytoadherence, promoting sequestration, vascular obstruction, local hypoxia, and endothelial activation (Gillrie et al., 2016). These processes are associated with increased expression of endothelial adhesion molecules, including ICAM-1, reduced tight-junction integrity, and increased endothelial permeability, as demonstrated in experimental BBB models (Pais & Penha-Gonçalves, 2023). Parasite-derived factors may further amplify endothelial injury, as histidine-rich protein II has been shown to induce endothelial inflammation through inflammasome activation, reactive oxygen species generation, interleukin-1β signaling, and disruption of BBB integrity (Nguyen et al., 2023). Collectively, these findings identify BBB dysfunction as a critical pathway through which parasite sequestration, endothelial activation, inflammation, and microvascular injury converge to produce cerebral pathology.

Inflammation, hypoxia, oxidative stress, metabolic dysregulation, and endothelial dysfunction further aggravate neurovascular injury in cerebral malaria. Elevated lactate levels are strongly associated with disease severity and mortality, reflecting impaired tissue oxygenation and systemic metabolic stress (Brand et al., 2016). Cerebral microvascular dysfunction may also be mediated by endothelin-1-related vasoconstriction, which contributes to impaired cerebral blood flow and long-term cognitive impairment in experimental cerebral malaria (Freeman et al., 2016). Nitric oxide deficiency contributes to cerebrovascular dysfunction, whereas nitric oxide-restorative strategies such as citrulline supplementation and L-arginine administration may reduce vascular leakage or reverse cerebral vasoconstriction (Gramaglia et al., 2019; Ong et al., 2018). Hypoxia-related pathways are also relevant because hyperbaric oxygen therapy has been reported to reduce HIF-1α expression, suppress kynurenine pathway activation, decrease leukocyte accumulation in cerebral vessels, and attenuate BBB injury in experimental cerebral malaria (Bastos et al., 2018). Immune-mediated vascular injury is another important contributor, as activated neutrophils have been associated with cerebral vasculopathy in children with cerebral malaria, while CD8+ T cells have been shown to target the cerebrovasculature in post-mortem human studies (Feintuch et al., 2016;

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Riggle et al., 2020). Together, these observations indicate that cerebral malaria results from the interaction of endothelial, immune, metabolic, oxidative, hypoxic, and parasite-related mechanisms.

Adjunctive therapy has consequently emerged as a strategy to address host-pathology mechanisms that persist beyond parasite clearance. Unlike conventional antimalarial treatment, adjunctive therapy aims to modulate endothelial activation, inflammation, oxidative stress, hypoxia, perfusion failure, immune-mediated injury, and BBB leakage. Similar host-supportive approaches have been explored in other infectious diseases, where natural products and immunomodulatory interventions have been investigated for their ability to support physiological recovery, regulate inflammatory responses, and improve host resilience without necessarily exerting direct antimicrobial effects (Rosanti et al., 2020; Sumartini, 2023). Several experimental interventions have demonstrated BBB-protective or neuroprotective effects in cerebral malaria, including rapamycin, Nrf2 activation, Bacillus Calmette–Guérin vaccination, blood transfusion, atorvastatin–irbesartan therapy, nitric oxide-restorative strategies, hyperbaric oxygen therapy, and herbal–artesunate combination therapy (Bastos et al., 2018; Crowley et al., 2017; Gul et al., 2022; Mejia et al., 2017; Mota et al., 2022; Ong et al., 2018; Plirat et al., 2023; Witschkowski et al., 2020).

However, the available evidence remains fragmented because studies differ substantially in model type, intervention timing, therapeutic targets, comparators, and outcome measurements. Many experimental studies evaluate survival, parasitemia, inflammatory markers, or endothelial activation but do not consistently use BBB integrity or neurological recovery as primary endpoints. Human studies provide important evidence linking endothelial activation, cerebral vasculopathy, hypoxia, CD8+ T-cell infiltration, and hemodynamic abnormalities with disease severity or neurological outcomes, yet most remain observational rather than interventional (Brand et al., 2016; Feintuch et al., 2016; O'Brien et al., 2022; Riggle et al., 2020). In addition, in vitro studies have clarified parasite–endothelial interactions and BBB permeability mechanisms but cannot fully reproduce the systemic complexity of cerebral malaria in vivo (Gillrie et al., 2016; Nguyen et al., 2023; Pais & Penha-Gonçalves, 2023). These limitations create a translational gap between mechanistic plausibility, experimental efficacy, and clinically meaningful benefit in human cerebral malaria.

To address these gaps, this systematic review aimed to synthesize current evidence on adjunctive strategies for cerebral malaria, with particular emphasis on BBB repair and neuroprotection. Specifically, this review evaluated mechanisms underlying BBB disruption and brain injury, including endothelial dysfunction, cytoadherence, inflammation, hypoxia, oxidative stress, metabolic dysregulation, and immune-mediated vascular injury. It also assessed host-directed adjunctive therapies that may improve BBB integrity, reduce neurovascular damage, enhance neuroprotection, or support survival.

The significance of this review lies in its integration of mechanistic evidence, experimental interventions, human observational findings, and translational evidence within a BBB-centered framework. Unlike reviews that discuss cerebral malaria pathogenesis and adjunctive therapy separately, this review directly links pathogenic mechanisms with therapeutic targets and outcome selection. By doing so, it provides a conceptual basis for future adjunctive therapy studies that incorporate standardized BBB-related endpoints, biomarker-guided stratification, and long-term neurological outcomes. Such an approach may strengthen translational relevance, improve patient selection, and support the development of mechanism-based adjunctive therapies for cerebral malaria.

Methods

PROFESIONAL HEALTH JOURNAL
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Study Design

This review adopted selected PRISMA 2020 reporting recommendations to enhance transparency in the literature search, study selection, and reporting processes. A predefined review framework, including the review objectives, eligibility criteria, search strategy, and thematic synthesis approach, was established prior to study selection; however, this framework was not formally registered in PROSPERO or another registry. The completed PRISMA 2020 was provided in Figure1.

Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, Embase, ScienceDirect, and Cochrane Library to identify relevant studies published between January 1, 2015 and April 30, 2026. The final search was conducted on April 30, 2026. Search terms were developed using combinations of Medical Subject Headings and free-text keywords related to cerebral malaria, adjunctive therapy, endothelial dysfunction, BBB injury, and neuroprotection. The primary Boolean search strategy was: ("cerebral malaria") AND ("adjunctive therapy"). Reference lists of eligible articles were also manually screened to identify additional studies.

Eligibility Criteria

Studies were considered eligible if they were original research articles published between January 2015 and April 2026, written in English, and investigated cerebral malaria in humans, animal models, or experimental systems. Eligible studies evaluated adjunctive, host-directed, endothelial-targeted, neuroprotective, vasoprotective, anti-inflammatory, antioxidant, metabolic, or perfusion-restoring interventions and reported outcomes related to BBB integrity, endothelial activation, vascular permeability, neurovascular injury, neurological outcomes, or survival.

Studies were excluded if they were review articles, editorials, commentaries, conference abstracts, or case reports. Additional exclusion criteria included studies that did not specifically address cerebral malaria, lacked outcome measures relevant to BBB dysfunction, endothelial injury, neurovascular pathology, or adjunctive therapy, were published in languages other than English, or did not provide accessible full-text articles.

Study Selection

All retrieved records were exported into a reference management database, and duplicate records were removed prior to screening. Titles and abstracts were independently screened according to the predefined eligibility criteria. Potentially relevant studies underwent full-text assessment. Disagreements regarding study eligibility were resolved through discussion and consensus. The study selection process was documented using a PRISMA flow diagram, including the numbers of records identified, screened, excluded, assessed for eligibility, and included in the final synthesis.

Data Extraction

Data were extracted by a single reviewer using a standardized, predefined extraction form. The extraction framework was piloted on three representative studies encompassing experimental, translational, and clinical designs and refined iteratively prior to full data extraction to ensure consistency and completeness. ChatGPT (OpenAI) was used solely as an assistive tool to facilitate data organization and summarization; however, all extracted information was manually cross-checked against the original articles, and all decisions regarding data inclusion, interpretation, and synthesis were made by the author. As this review was conducted by a single reviewer, independent duplicate extraction was not performed. Consequently, no inter-reviewer disagreements occurred; any uncertainties identified during the extraction process were resolved through repeated

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consultation of the original publications and refinement of the extraction criteria. Information collected from each study included the authors and year of publication, study location, study design and model type (human, animal, or in vitro), adjunctive intervention investigated, pathophysiological target, BBB-related endpoints, neurological outcomes, main findings, study limitations, and the study's contribution to the BBB-centered adjunctive therapy framework. To enhance transparency and reproducibility, the complete extraction form is provided as Supplementary File S2.

Quality Appraisal and Risk of Bias Assessment

Quality appraisal was performed to evaluate the methodological reliability of the included studies. Because the review inclu ded heterogeneous study types, appraisal was conducted using study-design-specific criteria. Human observational studies were assessed for participant selection, comparability of groups or control of confounding, validity of exposure and outcome measurement, completeness of follow-up, and reporting transparency. Animal intervention studies were assessed for randomization, allocation concealment, blinding, baseline comparability, attrition bias, selective outcome reporting, and completeness of intervention and outcome reporting. In vitro studies were assessed for experimental controls, replication, assay validity, exposure conditions, outcome measurement, and transparency of reporting.

The previous evidence classification based on study design was not used as a substitute for methodological quality appraisal. Instead, study design was reported separately as an evidence source category, while methodological quality was assessed independently. Review articles and review-based mechanistic analyses were not included in the formal quality appraisal because they did not meet the eligibility criteria for original research studies; when relevant, they were cited only to support background interpretation in the Introduction or Discussion.

The methodological quality of the included studies varied according to study design. Most animal intervention studies demonstrated low to moderate risk of bias, whereas observational human studies were generally classified as having moderate risk of bias due to potential confounding and limited causal inference. In vitro and mechanistic studies provided valuable mechanistic insights but were inherently limited in translational applicability. The detailed risk-of-bias assessment is presented in Table 2.

Data Synthesis

Due to substantial heterogeneity in study designs, interventions, experimental models, and outcome measures, a meta-analysis was not considered appropriate. Therefore, findings were synthesized narratively using a thematic approach. Studies were grouped into five major domains: endothelial dysfunction and vascular activation; BBB disruption and neurovascular injury; hypoxia and metabolic dysregulation; immune-mediated mechanisms of brain injury; and adjunctive therapeutic strategies targeting BBB repair and neuroprotection. Patterns of convergence and divergence, translational relevance, BBB endpoints, and evidence gaps were identified across studies. Particular emphasis was placed on evaluating whether adjunctive interventions improved BBB integrity, reduced neurovascular injury, or supported neuroprotection. The synthesis was subsequently integrated into a BBB-centered conceptual framework linking pathogenic mechanisms, biomarkers, therapeutic targets, and neurological outcomes in cerebral malaria.

Results

3.1. Study Selection and Characteristics

A total of 18 studies fulfilled the eligibility criteria and were included in the final synthesis. The evidence base comprised 11 animal intervention studies, four human clinical or observational

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studies, and three in vitro studies. Most studies investigated host-directed adjunctive strategies targeting endothelial dysfunction, inflammation, oxidative stress, hypoxia, vascular instability, or metabolic dysregulation rather than direct antiparasitic activity. BBB-related outcomes were evaluated using diverse endpoints, including vascular permeability, Evans Blue extravasation, transendothelial electrical resistance (TEER), endothelial activation biomarkers, cerebral hemodynamics, leukocyte infiltration, and neurological outcomes.

The characteristics of the included studies are summarized in Table 1. Human studies primarily provided evidence linking endothelial activation, cerebral vasculopathy, hypoxia, and hemodynamic abnormalities with disease severity and neurological outcome (Brand et al., 2016; Feintuch et al., 2016; O'Brien et al., 2022; Riggle et al., 2020). In contrast, most intervention studies were conducted in experimental cerebral malaria models and evaluated therapies targeting endothelial activation, BBB permeability, hypoxia, inflammation, oxidative stress, or vascular dysfunction (Bastos et al., 2018; Crowley et al., 2017; Gramagliaid et al., 2019; Gul et al., 2022; Mejia et al., 2017; Mota et al., 2022; Plirat et al., 2023; Witschkowski et al., 2020). In vitro and mechanistic studies further clarified the molecular basis of BBB injury through parasite sequestration, cytoadherence, inflammasome activation, and endothelial dysfunction (Gillrie et al., 2016; Nguyen et al., 2023; Pais & Penha-Gonçalves, 2023).

PROFESIONAL HEALTH JOURNAL
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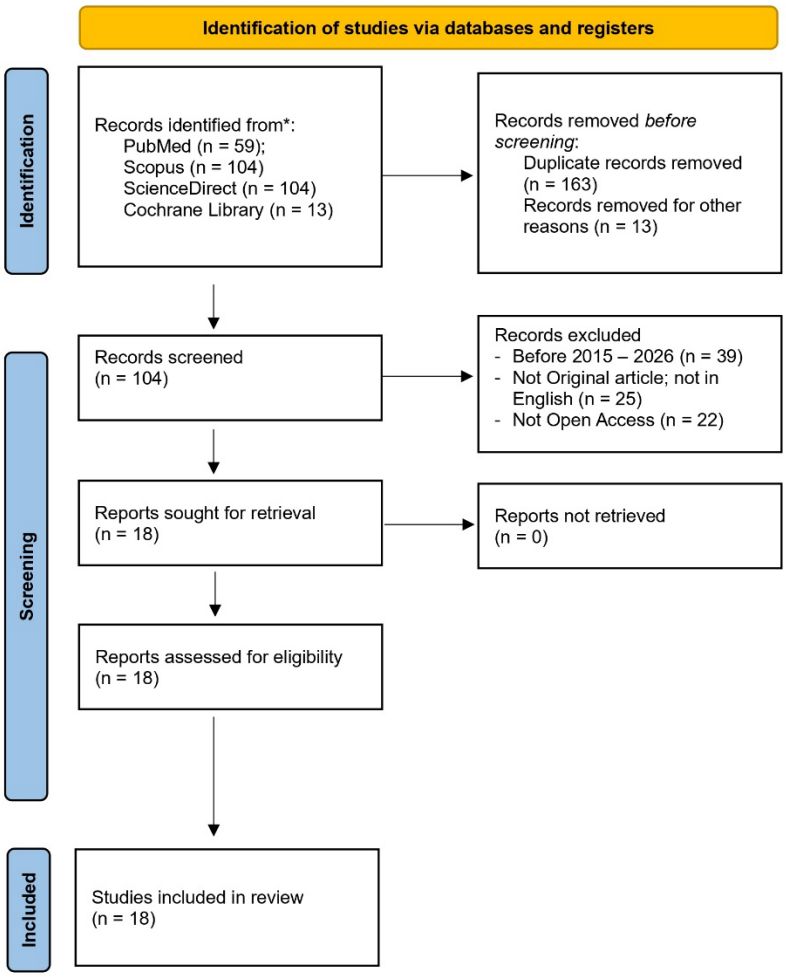

Figure 1. PRISMA 2020 flow diagram

PROFESIONAL HEALTH JOURNAL
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Table 1. Characteristics of Studies Included in the Review and Their Contribution to a BBB-Centered Adjunctive Therapy Framework

No.	Authors (Year)	Therapy/Focus	BBB Endpoint	Main Findings	Contribution to BBB-Centered Framework
1	Freeman et al. (2016)	Endothelin-1 blockade	Cerebral microvascular function, vascular permeability	Improved microvascular function and reduced cognitive impairment	Demonstrates the importance of endothelial stabilization
2	Gillrie et al. (2016)	PfEMP1 cleavage	Cytoadherence reduction (surrogate BBB protection)	Reduced infected erythrocyte adhesion	Supports anti-cytoadherence therapy
3	Gramaglia et al. (2019)	Citrulline	Vascular leak, BBB permeability	Reduced BBB leakage and improved survival	Supports NO-restoration strategies
4	Gul et al. (2022)	Blood transfusion	Vascular integrity recovery	Improved vascular integrity and survival	Supports perfusion-restoration therapy
5	Mota et al. (2022)	Atorvastatin–Irbesartan	Endothelial activation biomarkers	Reduced endothelial activation and mortality	Supports endothelial-targeted therapy
6	Nguyen et al. (2023)	HRPII	Endothelial inflammation, BBB permeability	Increased BBB disruption and inflammasome activation	Identifies molecular targets for BBB protection
7	Feintuch et al. (2016)	Neutrophil activation	Cerebral vasculopathy markers	Activated neutrophils associated with vascular injury	Supports anti-inflammatory approaches
8	Mejia et al. (2017)	Rapamycin	ICAM-1 expression, BBB damage	Reduced endothelial activation and BBB injury	Supports mTOR-targeted immunomodulation
9	Crowley et al. (2017)	Nrf2 activation	BBB integrity, vascular permeability	Improved BBB integrity and survival	Supports antioxidant neuroprotection
10	Brand et al. (2016)	Lactate/hypoxia	Indirect BBB injury through perfusion failure	Lactate associated with mortality	Supports hypoxia-targeted therapy

PROFESIONAL HEALTH JOURNAL
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No.	Authors (Year)	Therapy/Focus	BBB Endpoint	Main Findings	Contribution to BBB-Centered Framework
11	O'Brien et al. (2022)	Cerebral hemodynamics	TCD perfusion phenotypes	Hemodynamic abnormalities associated with outcome	Supports vascular stratification
12	Pais & Penha-Gonçalves (2023)	BBB model	TEER, permeability, ICAM-1	Increased permeability and BBB dysfunction	Provides BBB experimental platform
13	Ong et al. (2018)	L-Arginine	Cerebral vasoconstriction	Reversed cerebrovascular constriction	Supports NO supplementation
14	Plirat et al. (2023)	Herbal + Artesunate	BBB injury markers	Reduced inflammation and BBB damage	Supports multi-target adjunctive therapy
15	Riggle et al. (2020)	CD8+ T cells	Cerebrovascular infiltration	CD8+ T cells associated with vascular injury	Supports immune-targeted therapy
16	Witschkowski et al. (2020)	BCG vaccination	Evans Blue extravasation	Reduced BBB permeability	Supports trained immunity approach
17	Ssentongo et al. (2017)	Epileptogenesis	Long-term neurological injury	Demonstrated post-malaria epilepsy	Supports neuroprotection endpoints
18	Bastos et al. (2018)	Hyperbaric oxygen	HIF-1α, leukocyte accumulation, vascular leak	Reduced hypoxia and BBB injury	Supports hypoxia-targeted neurovascular protection

PROFESIONAL HEALTH JOURNAL
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E-ISSN 2715-6249
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Table 2. Quality Appraisal and Risk-of-Bias Summary of Included Studies

No	Author, Year	Study Design	Appraisal Tool	Key Bias Issues	Overall Quality
1	Freeman et al., 2016	Animal experimental intervention study using an experimental cerebral malaria mouse model; evaluated endothelin receptor antagonism, BBB integrity, microvascular dysfunction, survival, and cognitive outcomes.	SYRCLE Risk of Bias Tool for animal studies	Randomization, allocation concealment, and blinding were not clearly reported. The study used multiple mechanistic and functional endpoints, but sample sizes were relatively small and model-specific. Translation to human cerebral malaria remains limited.	Moderate
2	Gillrie et al., 2016	Mechanistic in vitro and ex vivo study evaluating thrombin-mediated PfEMP1 cleavage, infected erythrocyte cytoadherence, endothelial adhesion under flow, clinical isolates, and autopsy correlation.	Modified ToxRTool / OHAT-based appraisal for in vitro mechanistic studies	Strong mechanistic design with biochemical and functional assays, but limited clinical isolate numbers and incomplete representation of the in vivo neurovascular environment. Randomization and blinding were not clearly applicable or reported. Autopsy correlation was supportive but not causal.	Moderate
3	Gramaglia et al., 2019	Animal experimental intervention study using experimental cerebral malaria; evaluated citrulline/arginine supplementation, nitric oxide bioavailability, vascular leakage, BBB disruption, and survival.	SYRCLE Risk of Bias Tool for animal studies	Randomization, allocation concealment, and blinding were not clearly reported. Several experiments used small animal groups, and some interventions were prophylactic rather than clinically therapeutic. Quinine use may limit direct translation to current artesunate-based treatment contexts.	Moderate

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
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E-ISSN 2715-6249
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4	Gul et al., 2022	Animal experimental intervention study using late-stage experimental cerebral malaria; evaluated intravenous whole blood or plasma transfusion combined with artemether, vascular integrity, BBB permeability, hematological recovery, and survival.	SYRCLE Risk of Bias Tool for animal studies	Random allocation was reported, and clinically relevant late-stage treatment was used. However, blinding and allocation concealment were not clearly reported. Surgical jugular vein transfusion may introduce procedural confounding, and long-term neurological outcomes were not assessed.	Moderate to High
5	Mota et al., 2022	Animal experimental intervention study evaluating atorvastatin–irbesartan as adjunctive therapy with conventional antimalarial drugs in experimental cerebral malaria; outcomes included endothelial activation biomarkers, brain hemorrhage, neurological signs, and survival.	SYRCLE Risk of Bias Tool for animal studies	Random assignment after neurological signs was reported, improving clinical relevance. However, blinding and allocation concealment were unclear. The intervention had possible mild antiparasitic effects in preventive experiments, and direct standardized BBB permeability endpoints were limited.	Moderate
6	Nguyen et al., 2023	Mechanistic in vitro and in vivo experimental study evaluating HRPII:heme nanoparticles, endothelial inflammation, inflammasome activation, BBB leakage, and vascular permeability.	Modified ToxRTool / OHAT-based appraisal for in vitro studies; SYRCLE domains for animal component	Strong mechanistic controls and multiple complementary assays were used. However, patient-derived validation was limited, the animal component used an acute exposure model rather than full experimental cerebral malaria, and randomization/blinding for in vivo leakage assessment were not clearly reported.	Moderate to High for mechanistic evidence; Moderate overall

PROFESIONAL HEALTH JOURNAL
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7	Feintuch et al., 2016	Human observational transcriptomic and biomarker study in Malawian children with retinopathy-positive and retinopathy-negative cerebral malaria; assessed neutrophil activation, vasculopathy, and host-response pathways.	Newcastle–Ottawa Scale / JBI Checklist for analytical cross-sectional or observational studies	Clinically relevant human data and adjustment for peripheral parasitemia were provided. However, the study was observational and cross-sectional, samples were collected after illness onset, prior malaria exposure was unknown, and residual confounding cannot be excluded. Multiple transcriptomic comparisons also increase risk of false discovery despite correction methods.	Moderate
8	Mejia et al., 2017	Animal experimental intervention study using experimental cerebral malaria; evaluated single-dose rapamycin, host immunity, endothelial activation, parasite sequestration, BBB damage, and survival.	SYRCLE Risk of Bias Tool for animal studies	Intervention timing was clinically relevant because rapamycin was tested after infection progression. However, randomization, allocation concealment, and blinded outcome assessment were not clearly reported. The study remained model-specific and did not assess long-term neurological outcomes.	Moderate
9	Crowley et al., 2017	Animal experimental intervention study evaluating synthetic oleanane triterpenoid CDDO-EA alone and as adjunctive therapy with artesunate in experimental cerebral malaria; outcomes included BBB integrity, inflammation, endothelial stability, neurological severity, and survival.	SYRCLE Risk of Bias Tool for animal studies	Clinically relevant adjunctive artesunate comparison and late-treatment design were strengths. However, randomization and blinding were incompletely described. Model-specific limitations, relatively small animal groups, and lack of long-term neurocognitive assessment limit translational certainty.	Moderate

PROFESIONAL HEALTH JOURNAL
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10	Brand et al., 2016	Human observational cohort study comparing cerebral malaria and severe malarial anemia in Ugandan children; assessed lactic acidosis, deep breathing, parasite biomass, hemoglobin, and mortality.	Newcastle–Ottawa Scale / JBI Checklist for observational cohort studies	Large clinical sample and multivariable regression strengthened the analysis. However, the study was observational, not interventional, with potential residual confounding. Some children lacked lactate measurements, and findings were context-specific to hospitalized Ugandan children. Causal inference remains limited.	Moderate to High
11	O'Brien et al., 2022	Prospective human observational study in children with cerebral malaria; evaluated transcranial Doppler phenotypes, clinical variables, and neurological outcome at discharge.	Newcastle–Ottawa Scale / JBI Checklist for cohort or observational studies	Prospective design and relatively large sample strengthened the study. However, it was single-centre, observational, and not designed to infer causality. Some assessments depended on availability of imaging and operator-dependent TCD measurements. Long-term neurological outcomes were not assessed.	Moderate to High
12	Pais and Penha-Gonçalves, 2023	In vitro mechanistic study using primary mouse brain endothelial cell barrier model; assessed TEER, permeability, tight junction proteins, and endothelial activation after exposure to Plasmodium blood-stage factors.	Modified ToxRTool / OHAT-based appraisal for in vitro studies	Strong mechanistic model with multiple barrier-function readouts. However, it lacked systemic immune, vascular, and neuroinflammatory complexity of cerebral malaria in vivo. Randomization and blinding were not clearly applicable or reported.	Moderate
13	Ong et al., 2018	Animal experimental mechanistic study using intravital microscopy to assess L-arginine effects on pial arteriolar vasoconstriction in experimental cerebral malaria.	SYRCLE Risk of Bias Tool for animal studies	Strong physiological endpoint using direct vascular imaging. However, sample sizes were small, vessel responses were variable, and randomization, allocation concealment, and blinding were not clearly reported. Survival benefit was secondary to vascular-function assessment.	Moderate

PROFESIONAL HEALTH JOURNAL
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14	Plirat et al., 2023	Animal experimental intervention study using PbA-induced experimental cerebral malaria; evaluated artesunate combined with *Atractylodes lancea* or Prabchompoothaweep extracts.	SYRCLE Risk of Bias Tool for animal studies	Random group allocation and blinded clinical/histological assessments were reported. However; allocation concealment was not clearly described. Herbal extract composition may vary, only male mice were used, and translation to human CM remains uncertain.	Moderate
15	Riggle et al., 2020	Human post-mortem observational mechanistic study using multiplex immunohistochemistry of brain tissue from children with cerebral malaria and controls.	JBI Checklist for analytical cross-sectional/pathology studies / Newcastle–Ottawa adapted criteria	Strong human tissue relevance and advanced multiplex imaging. However, the study was post-mortem and cross-sectional, with small subgroup sizes, possible autopsy-selection bias, and limited ability to infer causality. HIV status and sequestration level introduced important stratification but also potential confounding.	Moderate
16	Ssentongo et al., 2017	Animal model-development study for post-malarial epilepsy and SUDEP after malaria infection; included multiple mouse–parasite strain combinations and chronic video/EEG monitoring.	SYRCLE Risk of Bias Tool / ARRIVE reporting checklist	Innovative model with extensive chronic monitoring. However, it was primarily a technical/model-development report rather than an adjunctive therapy study. Attrition after infection, small cohort sizes in some strain combinations, and unclear blinding/randomization limit confidence.	Moderate for model development; Low for therapeutic evidence

PROFESIONAL HEALTH JOURNAL
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E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

17	Witschkowski et al., 2020	Animal experimental study evaluating BCG-mediated protection against experimental cerebral malaria, including survival, BBB integrity, parasite burden, cytokines, and brain immune-cell recruitment.	SYRCLE Risk of Bias Tool for animal studies	The study assessed relevant ECM outcomes, including survival and Evans blue BBB leakage. However, BCG was given as a preventive intervention rather than true adjunctive therapy after CM onset. Randomization, allocation concealment, and blinded outcome assessment were not clearly reported.	Moderate
18	Bastos et al., 2018	Animal experimental mechanistic intervention study evaluating hyperbaric oxygen in experimental cerebral malaria, including endothelial activation, leukocyte/parasite accumulation, hypoxia response, kynurenine pathway, and survival.	SYRCLE Risk of Bias Tool for animal studies	Mechanistically strong with molecular, vascular, and genetic approaches. However, sample sizes were relatively small, HBO was applied in an experimental setting that may not fully mirror clinical timing, and randomization/blinding were not clearly described. Clinical feasibility and safety in human CM require validation.	Moderate

Overall, most studies provided moderate-quality mechanistic or translational evidence (Table 2). Human observational and post-mortem studies offered high clinical relevance but remained limited by confounding and lack of causal inference. Animal studies provided the strongest interventional evidence, although incomplete reporting of randomization, allocation concealment, and blinding reduced confidence. In vitro studies clarified BBB-related mechanisms but had limited direct clinical applicability. Opinion or narrative review articles should not be included in the formal quality appraisal if the review eligibility criteria exclude non-original studies.

3.2 Mechanisms Driving BBB Disruption in Cerebral Malaria

3.2.1 Endothelial Activation and Cytoadherence

Endothelial activation and parasite sequestration emerged as central mechanisms underlying BBB dysfunction. Experimental studies demonstrated that endothelin-1-mediated cerebrovascular constriction impaired cerebral microvascular function and contributed to long-term cognitive deficits (Freeman et al., 2016). In vitro evidence showed that thrombin-mediated cleavage of PfEMP1 significantly reduced infected erythrocyte adhesion, highlighting the importance of cytoadherence in vascular obstruction (Gillrie et al., 2016). Additional BBB models demonstrated increased ICAM-1 expression, reduced barrier resistance, and increased endothelial permeability following exposure to infected erythrocytes or parasite-derived products (Pais & Penha-Gonçalves, 2023). Histidine-rich protein II (HRPII) further promoted endothelial inflammation through inflammasome activation and

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
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reactive oxygen species generation, leading to BBB disruption (Nguyen et al., 2023). Collectively, these findings identify endothelial activation and cytoadherence as major contributors to BBB injury.

3.2.2 Hypoxia and Perfusion Failure

Several studies identified hypoxia and impaired perfusion as important drivers of neurovascular injury. Clinical evidence demonstrated a strong association between elevated lactate concentrations and mortality in severe malaria, indicating impaired tissue oxygen delivery (Brand et al., 2016). Hyperbaric oxygen therapy reduced HIF-1α expression, leukocyte accumulation within cerebral vessels, and vascular leakage in experimental cerebral malaria (Bastos et al., 2018). Furthermore, cerebral hemodynamic abnormalities measured using transcranial Doppler ultrasonography were associated with clinical outcomes in pediatric cerebral malaria (O'Brien et al., 2022). Together, these findings suggest that perfusion failure and hypoxia are closely linked to endothelial dysfunction and BBB breakdown.

3.2.3 Immune-Mediated Neurovascular Injury

Immune activation was consistently associated with cerebrovascular pathology. Activated neutrophils were strongly associated with cerebral vasculopathy in children with cerebral malaria (Feintuch et al., 2016), while post-mortem studies demonstrated accumulation of CD8+ T cells within cerebral microvessels, indicating direct participation of adaptive immunity in vascular injury (Riggle et al., 2020). HRPII-mediated inflammasome activation further amplified endothelial injury through IL-1β signaling and oxidative stress (Nguyen et al., 2023). These observations support a major role for immune-mediated vascular injury in BBB disruption.

3.2.4 Metabolic Dysregulation and Oxidative Stress

Metabolic and oxidative pathways represented another major component of cerebral malaria pathogenesis. Hyperbaric oxygen therapy reduced IDO-1 activity and kynurenine production, indicating involvement of kynurenine-mediated neurotoxicity in disease progression (Bastos et al., 2018). Nitric oxide deficiency was implicated in cerebrovascular dysfunction because citrulline supplementation restored nitric oxide bioavailability, reduced vascular leakage, and improved survival (Gramagliaid et al., 2019), while L-arginine reversed cerebrovascular constriction (Ong et al., 2018). Activation of the Nrf2 pathway reduced oxidative stress and preserved BBB integrity (Crowley et al., 2017). These findings indicate that oxidative stress and metabolic dysregulation contribute substantially to BBB injury and neurological damage.

3.3 Effects of Adjunctive Therapies on BBB Integrity

3.3.1 Endothelial-Stabilizing Interventions

Several adjunctive therapies directly targeted endothelial dysfunction. Rapamycin reduced endothelial activation, ICAM-1 expression, parasite sequestration, and BBB injury (Mejia et al., 2017). Atorvastatin–irbesartan therapy reduced endothelial activation biomarkers and mortality (Mota et al., 2022), while blood transfusion accelerated recovery of vascular integrity and improved survival (Gul et al., 2022). These findings support endothelial stabilization as a promising therapeutic strategy for mitigating BBB disruption.

3.3.2 Anti-Inflammatory and Immunomodulatory Strategies

BCG vaccination reduced inflammatory cytokine production, endothelial adhesion molecule expression, and BBB permeability despite lacking direct antiparasitic activity (Witschkowski et al., 2020). Rapamycin reduced neurovascular inflammation by limiting T-cell infiltration (Mejia et al., 2017), while Nrf2 activation reduced oxidative stress and neuroinflammatory responses (Crowley et al., 2017). Collectively, these interventions suggest that modulation of host immune responses can preserve BBB function.

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

3.3.3 Perfusion-Restoring and Hypoxia-Modulating Therapies

Hyperbaric oxygen therapy reduced HIF-1α expression, leukocyte accumulation, and vascular leakage (Bastos et al., 2018). Citrulline supplementation restored nitric oxide bioavailability and reduced BBB permeability (Gramagliaid et al., 2019), whereas L-arginine improved cerebral vascular tone and perfusion (Ong et al., 2018). These findings indicate that restoration of vascular homeostasis and oxygen delivery may play an important role in BBB protection.

3.3.4 Multi-Target Neuroprotective Approaches

Combination therapy consisting of artesunate and herbal extracts reduced inflammation and BBB injury markers (Plirat et al., 2023). Likewise, endothelial-targeted combination therapy attenuated endothelial activation and reduced mortality (Mota et al., 2022). These findings suggest that interventions targeting multiple interconnected mechanisms may provide greater neurovascular protection than single-pathway approaches.

3.4 Translational Evidence and Remaining Gaps

3.4.1 BBB Endpoints

BBB integrity was consistently identified as a biologically relevant therapeutic outcome. However, endpoints varied substantially across studies and included Evans Blue extravasation, vascular permeability, TEER measurements, endothelial activation biomarkers, leukocyte infiltration, and vascular leakage assessments (Bastos et al., 2018; Crowley et al., 2017; Pais & Penha-Gonçalves, 2023; Witschkowski et al., 2020). This heterogeneity limits direct comparison across studies and complicates translation into clinical applications.

3.4.2 Biomarker-Based Stratification

Only a limited number of studies explored biomarker-guided approaches. The one review article was excluded. Experimental endothelial-targeted therapies reduced biomarker expression concurrently with improvements in vascular integrity and survival (Mota et al., 2022), suggesting potential utility for monitoring therapeutic response.

3.4.3 Neurological Outcome Assessment

Neurological outcomes were assessed less frequently than survival, parasitemia, inflammation, or BBB permeability. Long-term cognitive impairment associated with cerebral microvascular dysfunction was reported in experimental models (Freeman et al., 2016), while post-malaria epileptogenesis was demonstrated in murine studies (Ssentongo et al., 2017). Clinical evidence further linked cerebral hemodynamic abnormalities with neurological outcomes (O'Brien et al., 2022). Nevertheless, most intervention studies focused primarily on acute vascular or inflammatory parameters rather than functional neurological recovery.

3.5 Comparative Evidence Matrix of Adjunctive Therapies

To facilitate translational interpretation, the therapeutic evidence was synthesized according to BBB protection, neuroprotection, survival benefit, human evidence, and translational readiness (Table 3). Among the reviewed interventions, rapamycin and Nrf2-targeted therapies demonstrated the strongest BBB-protective effects in experimental models, showing consistent improvements in endothelial activation, vascular permeability, and survival (Crowley et al., 2017; Mejia et al., 2017). Hyperbaric oxygen therapy showed beneficial effects on hypoxia, endothelial activation, and BBB injury, although implementation may be constrained by logistical requirements (Bastos et al., 2018). Citrulline exhibited moderate translational potential because nitric oxide restoration has already been explored in human malaria studies (Gramagliaid et al., 2019). Blood transfusion demonstrated the highest translational readiness owing to its established clinical use, known safety profile, and documented effects on vascular recovery and survival (Gul et al., 2022). Overall, Table 3

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

demonstrates that most adjunctive strategies remain supported primarily by preclinical evidence despite strong mechanistic rationale.

Table 3. Evidence Matrix of Adjunctive Therapies for Blood–Brain Barrier Repair, Neuroprotection, and Translational Development in Cerebral Malaria

Therapy Class	BBB Protection	Neuroprotection	Survival	Human Evidence	Translational Readiness
Rapamycin	+++	++	++	Low	Moderate
Nrf2 activator	+++	++	++	Low	Moderate
Hyperbaric oxygen	++	++	++	Low	Moderate
Citrulline	++	+	++	Moderate	Moderate
Blood transfusion	++	+	++	Moderate	High

Table note: This evidence matrix summarizes the relative strength of reported effects of selected adjunctive therapy classes on blood–brain barrier (BBB) protection, neuroprotection, survival, human evidence, and translational readiness in cerebral malaria. The symbols indicate the consistency and biological relevance of findings across the reviewed literature: +++ indicates strong and consistent evidence of benefit, ++ indicates moderate evidence of benefit, + indicates limited or indirect evidence of benefit, and – indicates no clear evidence or insufficient data. "Human Evidence" refers to the availability of clinical, observational, or human translational data supporting the therapeutic concept, whereas "Translational Readiness" reflects the overall plausibility for further clinical development based on biological rationale, consistency of preclinical findings, feasibility of administration, safety profile, and proximity to current clinical practice. This matrix is intended as an interpretive synthesis of therapeutic potential and should not be interpreted as a formal risk-of-bias assessment or GRADE-based certainty rating.

3.6 Summary of Evidence Synthesis

Across the 18 included studies, BBB disruption emerged as the consequence of interacting pathogenic processes involving cytoadherence, endothelial activation, inflammation, hypoxia, oxidative stress, and metabolic dysregulation. Adjunctive therapies targeting endothelial stabilization, inflammatory control, oxidative stress reduction, vascular restoration, and hypoxia mitigation consistently demonstrated beneficial effects on BBB integrity or neurovascular injury. However, the evidence remains predominantly preclinical, BBB-related endpoints are not standardized, and biomarker-guided stratification has rarely been incorporated into therapeutic studies. Collectively, these findings support BBB repair and neuroprotection as central therapeutic targets for future adjunctive therapy development and provide a rationale for biomarker-guided, BBB-centered translational research in cerebral malaria.

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

Discussion

This section should discuss the implications of the findings in the context of existing research and highlight the limitations of the study.

Blood–Brain Barrier Dysfunction as the Central Convergence Point in Cerebral Malaria

The findings of this systematic review support the interpretation that blood–brain barrier (BBB) dysfunction is a central convergence point in the pathogenesis of cerebral malaria, rather than a late or isolated consequence of parasite sequestration. Across the included experimental, in vitro, mechanistic, and human observational studies, BBB injury was repeatedly associated with interacting processes involving parasite-endothelial adhesion, endothelial activation, inflammatory signaling, hypoxia, oxidative stress, metabolic dysregulation, and cerebral microcirculatory impairment. This pattern supports a shift from a purely parasite-centered model toward a neurovascular-immunological model of cerebral malaria, in which the cerebral endothelium and BBB serve as key interfaces between systemic infection and brain injury.

The reviewed evidence indicates that infected erythrocyte sequestration and PfEMP1-mediated cytoadherence initiate endothelial activation, microvascular obstruction, and impaired perfusion, while parasite-derived factors further amplify vascular injury. Histidine-rich protein II, for example, promotes endothelial inflammation through inflammasome activation, reactive oxygen species generation, interleukin-1β signaling, and BBB disruption (Gillrie et al., 2016; Nguyen et al., 2023). In vitro BBB models also demonstrate increased endothelial permeability, reduced barrier resistance, and altered tight-junction integrity following exposure to infected erythrocytes or parasite-derived products (Pais & Penha-Gonçalves, 2023). These findings indicate that BBB failure is not simply a structural consequence of severe disease, but an active pathogenic process through which parasite burden, immune activation, and endothelial dysfunction are translated into cerebral injury.

This BBB-centered interpretation is strengthened by broader clinical and mechanistic literature showing that cerebral malaria involves endothelial protein C receptor dysregulation, Angiopoietin-1/Angiopoietin-2 imbalance, ICAM-1 activation, von Willebrand factor release, platelet activation, coagulation disturbance, nitric oxide depletion, and inflammatory endothelial injury (Albrecht-Schgoer et al., 2022; Nortey et al., 2022; Song et al., 2022). Together, these processes promote vascular instability, BBB leakage, cerebral edema, neuronal injury, seizures, stroke-like vascular complications, and long-term neurological sequelae. Therefore, BBB dysfunction should be positioned not only as a marker of severe cerebral malaria, but also as a biologically relevant therapeutic target.

Adjunctive Therapies Converge on Shared Neurovascular and BBB-Protective Mechanisms

A major finding of this review is that mechanistically diverse adjunctive therapies converge on a limited number of shared neurovascular targets. Rapamycin, Nrf2 activation, citrulline supplementation, L-arginine, hyperbaric oxygen therapy, blood transfusion, Bacillus Calmette–Guérin vaccination, atorvastatin–irbesartan therapy, and herbal–artesunate combinations differ in their proximal mechanisms, but their reported beneficial effects consistently involve endothelial stabilization, inflammatory control, oxidative stress reduction, perfusion restoration, nitric oxide pathway modulation, or BBB protection (Bastos et al., 2018; Crowley et al., 2017; Gramagliaid et al., 2019; Gul et al., 2022; Mejia et al., 2017; Mota et al., 2022; Ong et al., 2018; Plirat et al., 2023; Witschkowski et al., 2020)

This convergence is important because several adjunctive interventions produced benefit without directly reducing parasitemia. Citrulline improved vascular leakage and survival without

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

acting as a direct antiparasitic intervention, while Bacillus Calmette–Guérin vaccination reduced BBB permeability and inflammatory injury despite no clear reduction in parasite burden (Gramagliaid et al., 2019; Witschkowski et al., 2020). These findings suggest that adjunctive therapy in cerebral malaria should not be conceptualized merely as an enhancement of parasite clearance, but as host-response stabilization and disease-tolerance support. In this context, BBB repair and neuroprotection become legitimate therapeutic objectives alongside antimalarial treatment.

The evidence also supports the potential value of multi-target adjunctive strategies. Combination approaches may be particularly relevant because cerebral malaria pathogenesis involves interconnected vascular, inflammatory, metabolic, and neurological pathways. Experimental evidence showing that dihydroartemisinin combined with rapamycin and atorvastatin improved survival, neurological scores, BBB permeability, parasitemia, cerebrovascular pathology, and histopathological damage illustrates the potential advantage of therapies that combine antiparasitic, immunomodulatory, endothelial-protective, and neuroprotective effects (Song et al., 2023). Similarly, broader therapeutic reviews argue that future adjunctive therapy should address oxidative stress, neuroinflammation, cytoadherence, BBB disruption, and neurological outcomes rather than relying on parasite clearance alone (Das & Prabhu, 2022; Panda & Mahapatra, 2022).

Translational Limitations of the Current Evidence

Despite the promising biological rationale, the current evidence remains predominantly preclinical. Most intervention studies included in this review were conducted in experimental cerebral malaria models, whereas human studies were largely observational or postmortem. This imbalance limits the certainty with which experimental efficacy can be extrapolated to human cerebral malaria. Although animal models are valuable for mechanistic exploration, they do not fully reproduce the clinical heterogeneity, timing of presentation, supportive care context, and age-related pathophysiology of human disease.

This limitation is particularly important because the murine cerebral malaria model has historically shown limited predictive value for human adjunctive therapy. Many murine studies test interventions before or near the onset of disease, whereas patients usually present after neurological manifestations have developed. Moreover, some preclinical studies do not evaluate adjunctive interventions in combination with standard antimalarial therapy, which reduces their clinical relevance. Therefore, positive experimental findings should be interpreted as evidence of biological plausibility rather than definitive proof of clinical efficacy (Weerasekera & White, 2025).

Another major translational limitation is the heterogeneity of BBB-related endpoints. Across the included studies, BBB integrity was assessed using Evans Blue extravasation, vascular permeability, transendothelial electrical resistance, endothelial activation markers, leukocyte accumulation, tight-junction-related changes, cerebral hemodynamics, survival, and neurological outcomes. Although these measures capture different aspects of BBB and neurovascular dysfunction, their variability prevents direct comparison across studies and complicates evidence synthesis. This heterogeneity also limits the ability to identify which intervention class most consistently provides true barrier-protective or neuroprotective benefit.

Need for Standardized BBB-Centered and Neuroprotective Endpoints

The findings of this review support the need to position BBB integrity as a core endpoint in future adjunctive therapy studies. Survival and parasitemia remain essential outcomes, but they are insufficient to determine whether an intervention protects the neurovascular unit, reduces BBB leakage, prevents cerebral edema, or improves long-term neurological recovery. A therapy designed to reduce BBB injury may have meaningful biological and clinical value even when its effect on all-

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

cause mortality is modest, particularly because mortality in cerebral malaria may result from multiple neurological and non-neurological mechanisms.

This issue is reinforced by evidence that pediatric cerebral malaria deaths may result from cerebral herniation, status epilepticus, shock, respiratory failure, renal failure, hepatic failure, or other systemic complications (Wynkoop et al., 2025). Therefore, all-cause mortality may dilute the measurable benefit of BBB-targeted or neuroprotective adjunctive therapy. Future studies should align endpoint selection with the intended biological target of the intervention. For BBB-directed therapy, relevant endpoints should include BBB permeability, tight-junction integrity, endothelial activation, brain swelling, seizure burden, retinal vascular leakage, perfusion indices, neuroinjury biomarkers, and cognitive outcomes (Postels & Katangwe-Chirwa, 2025; Wilson et al., 2023; Wynkoop et al., 2025).

Long-term neurological assessment should also become an integral component of adjunctive therapy evaluation. Cerebral malaria survivors may develop cognitive impairment, epilepsy, behavioral sequelae, and other neurodevelopmental complications (Bangirana et al., 2026; Ssentongo et al., 2017). Thus, acute survival alone does not fully capture treatment success. Neuroprotection should be evaluated through both early markers of brain injury and long-term functional outcomes.

Toward Biomarker-Guided and Precision Adjunctive Therapy

This review also highlights the need for biomarker-guided stratification in future cerebral malaria trials. Cerebral malaria is biologically heterogeneous, and patients may differ in the relative dominance of endothelial activation, inflammatory injury, hypoxia, metabolic stress, vascular obstruction, or neuronal injury. Endothelial biomarkers such as Angiopoietin-2, soluble Tie2, ICAM-1, von Willebrand factor, and CXCL10 may help identify patients with dominant vascular-endothelial pathology, while neuroinjury markers such as tau, UCH-L1, neurofilament light chain, and extracellular vesicles may help characterize neuronal damage and long-term neurological risk (Datta & John, 2025; Nortey et al., 2022; Pikor et al., 2025).

Biomarker-guided stratification could improve trial design by enriching study populations with patients most likely to respond to specific interventions. Patients with dominant endothelial activation may be more appropriate candidates for endothelial-stabilizing or vasoprotective therapy, whereas those with prominent inflammatory or oxidative signatures may be more suitable for immunomodulatory or antioxidant approaches. Patients with perfusion failure, nitric oxide deficiency, or hypoxia-related phenotypes may require vascular or metabolic support. This approach does not imply that adjunctive therapy must immediately become fully individualized, but it does indicate that future trials should avoid treating cerebral malaria as a biologically uniform syndrome.

Retinal imaging may also contribute to this precision framework. Malarial retinopathy, retinal whitening, vascular leakage, capillary non-perfusion, hemorrhage, and vessel discoloration may provide accessible surrogate evidence of cerebral microvascular pathology and barrier dysfunction (Wilson et al., 2023). The integration of blood biomarkers, retinal imaging, transcranial Doppler ultrasound, neuroimaging, electroencephalography, clinical phenotyping, and long-term neurological assessment may improve patient stratification, endpoint selection, and interpretation of therapeutic response.

Implications for Future Research

The findings of this review have several implications for future adjunctive therapy research. First, future preclinical studies should more closely reflect clinical reality by testing interventions after neurological syndrome onset and in combination with standard antimalarial therapy.

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

Preventive or early-intervention designs are useful for mechanistic exploration but provide limited evidence for clinical applicability.

Second, future studies should use standardized BBB-centered endpoints. These should include direct and indirect measures of vascular permeability, tight-junction integrity, endothelial activation, cerebral edema, retinal vascular leakage, cerebral perfusion, neuroinflammation, and neuroinjury. Harmonizing these endpoints would improve comparability across studies and strengthen translational interpretation.

Third, future trials should incorporate biomarker-guided stratification. Multidomain biomarker panels may help define endotypes of cerebral malaria and identify patients most likely to benefit from specific adjunctive strategies. Such stratification may reduce therapeutic heterogeneity and clarify whether a given intervention truly repairs the BBB, stabilizes the endothelium, restores perfusion, suppresses neuroinflammation, or prevents neuronal injury.

Fourth, long-term neurological outcomes should be integrated into therapeutic evaluation. Cognitive impairment, epilepsy, behavioral sequelae, seizure burden, and neurodevelopmental outcomes should be assessed whenever feasible, especially in pediatric cerebral malaria. This approach is essential because the value of adjunctive therapy lies not only in reducing mortality, but also in preventing persistent brain injury and improving quality of life among survivors.

Strengths and Limitations of This Review

This systematic review provides an integrated synthesis of experimental, mechanistic, translational, and human observational evidence on adjunctive therapy for cerebral malaria with specific emphasis on BBB repair and neuroprotection. Its main strength lies in reframing heterogeneous adjunctive strategies within a BBB-centered framework and identifying common therapeutic targets across diverse interventions. This approach helps bridge pathogenic mechanisms, therapeutic effects, and future endpoint development.

Several limitations should be acknowledged. First, the included evidence was dominated by experimental animal studies, while human interventional evidence remains limited. Second, there was substantial heterogeneity in intervention type, timing, comparator, model, and outcome measurement. Third, BBB integrity was not consistently used as a standardized primary endpoint, limiting direct comparison across studies. Fourth, biomarker-guided stratification and long-term neurological outcomes were rarely incorporated into intervention studies. Finally, clinically applicable cut-off values for endothelial, inflammatory, metabolic, retinal, and neuroinjury biomarkers remain insufficiently validated across endemic settings, age groups, and disease severities.

Despite these limitations, the reviewed evidence consistently supports BBB repair and neuroprotection as biologically relevant targets for adjunctive therapy in cerebral malaria. The central challenge for the field is no longer merely identifying additional adjunctive candidates, but designing translational studies that align mechanism, patient phenotype, intervention target, and clinically meaningful endpoint.

Conclusion

This systematic review concludes that cerebral malaria is a complex neurovascular and immunopathological syndrome in which blood–brain barrier (BBB) dysfunction plays a central role in linking parasite sequestration, endothelial activation, inflammation, hypoxia, oxidative stress, metabolic disturbance, and microcirculatory impairment to brain injury. The overall synthesis indicates that BBB repair and neuroprotection are biologically relevant endpoints for adjunctive

PROFESIONAL HEALTH JOURNAL
Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v7i2.1511

therapy, although the current evidence remains predominantly experimental and requires further clinical validation.

The importance of this study lies in its integration of pathogenic mechanisms, adjunctive therapeutic targets, and BBB-related outcomes into a unified translational framework. This review is relevant because parasite clearance alone may not adequately prevent neurovascular injury or long-term neurological sequelae in cerebral malaria. Further research should evaluate BBB-directed adjunctive therapies in clinically relevant models and human studies, apply standardized BBB-centered and neuroprotective endpoints, incorporate biomarker-guided stratification, and include long-term neurological follow-up to determine whether these strategies can improve survival and reduce neurological disability.

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Volume 7, No. 2 (Page. 893-920)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
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