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Review Article

## Anti-malarial compounds from the Rubiaceae family: phytochemistry, ethnomedicine and therapeutic prospects

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**Abstract:** Malaria continues to be one of the most persistent infectious diseases worldwide and the emergence of drug-resistant *Plasmodium* strains increasingly threatens the effectiveness of current therapies. Throughout history, nature has served as an important source of medicinal agents and among the plant families explored for medicinal value, the Rubiaceae family has drawn considerable attention due to its versatile use in ethnomedicine for treating fever, malaria and various infectious disorders. This family, comprising of a wide diversity of medicinal plants, represents a rich reservoir of biologically active secondary metabolites with significant pharmacological potential. The journey from traditional remedies to modern therapeutics is best exemplified by the discovery of quinine from *Cinchona*, which established the importance of Rubiaceae in antimalarial research and inspired the search for additional bioactive molecules within the family. Phytochemical investigations have revealed that Rubiaceae species contain diverse compounds including alkaloids, anthraquinones, flavonoids, terpenoids, iridoids, triterpenes, phenolic compounds and phytosterols. Several of these constituents, such as quinine, damnacanthal, morindone, nordamnacanthal, quercetin derivatives, phytol,  $\alpha$ -amyirin and  $\beta$ -sitosterol, have notable antiplasmodial activity through multiple mechanisms, including inhibition of heme detoxification, induction of oxidative stress, interference with parasite metabolism and disruption of essential cellular pathways. This review explores the ethnopharmacological significance of Rubiaceae plants and highlights the major bioactive compounds associated with antimalarial activity. By connecting traditional medicinal knowledge with contemporary phytochemical and pharmacological evidence, the Rubiaceae family emerges as a promising source of novel antimalarial candidates that may contribute to future drug discovery and help address the growing challenge of antimalarial resistance.

**Keywords:** Anti-malaria, bioactive compounds, pharmacology, *Plasmodium*, Rubiaceae, traditional medicine

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## Introduction

Malaria is one of the most significant parasitic diseases affecting global public health, particularly in tropical and subtropical regions (Okello and Aucamp, 2026). The disease is caused by protozoan parasites of the genus *Malaria*, primarily transmitted through the bite of infected female Anopheles mosquitoes (Baron, 1996). Despite substantial progress in malaria control programs, the emergence of resistance to conventional antimalarial drugs and insecticides continues to present a major challenge to disease management. Drug resistance in *Plasmodium* species, especially *Plasmodium falciparum*, has stimulated extensive efforts to identify novel therapeutic agents from natural sources (Alruwaili et al., 2026). Ethnopharmacology investigates the traditional medicinal use of plants and other natural products (Brouwer et al., 2005). It has played a pivotal role in the discovery of several clinically important antimalarial drugs. Traditional medicinal systems across Asia, Africa and South America have historically utilized plant-based remedies for treating fever and malaria-related symptoms (Kamaraj et al., 2023). The success of plant-derived antimalarial compounds such as Quinine, isolated from the bark of *Cinchona* species and Artemisinin from *Artemisia annua* demonstrates the importance of ethnomedicinal knowledge as a guide for modern drug discovery. (Ceravolo et al., 2021) Traditional practices often provide preliminary evidence of therapeutic efficacy, helping researchers prioritize plants for phytochemical and pharmacological investigations. Plant-derived bioactive compounds exhibit antimalarial activity through diverse mechanisms of action. Alkaloids, flavonoids, terpenoids, quinones, coumarins, iridoids and phenolic compounds have all been reported to interfere with parasite survival and development (Wink, 2012). Alkaloids such as quinine act by disrupting heme detoxification pathways within the parasite (de Villiers and Egans, 2021). Terpenoids, particularly sesquiterpenes, can induce oxidative damage and inhibit parasite growth (Barrera et al., 2013). Flavonoids may affect fatty acid biosynthesis, mitochondrial function and heme polymerization (Qin et al., 2025), whereas quinones and anthraquinones can alter redox processes and parasite metabolism (Sanchez and Alegría, 2009). These phytochemicals frequently act synergistically, contributing to the therapeutic efficacy observed in traditional plant preparations. Among medicinal plant families, the Rubiaceae family occupies an important position in ethnomedicine and natural product research. Rubiaceae is one of the largest angiosperm families, comprising approximately 13,000 species distributed among more than 600 genera worldwide (Ball et al., 2023). Members of this family are widely used in traditional medicine for the treatment of fever, infections, inflammation, gastrointestinal disorders and malaria-like illnesses (Suresh Rao et al., 2025). The integration of ethnopharmacological knowledge with phytochemical and pharmacological investigations provides a rational approach for identifying novel antiplasmodial compounds. Understanding the antimalarial potential of Rubiaceae-derived bioactives may contribute significantly to the development of safer, effective and affordable therapeutic agents against malaria.

## Methodology

The present study is based on an extensive survey of published literature related to the family Rubiaceae. We consulted scientific databases, including Google Scholar, Scopus, PubMed, Plants of

the World Online (POWO) and Web of Science, to retrieve correct taxonomic name, peer-reviewed research articles, review papers, ethnobotanical surveys and pharmacological studies. A variety of keywords such as “Rubiaceae”, “anti-plasmodial”, “bioactives”, “anti-malaria”, “ethnomedicine” and “ethnopharmacology” were used to identify relevant publications. Additionally, regional floras, books and reports that document traditional knowledge and distribution patterns were examined. Only studies containing verifiable scientific or ethnomedicinal data were included in the analysis. The information gathered was critically analyzed and systematically organized into thematic sections to ensure clarity and coherence (Kumar, 2025; Sahu et al., 2026).

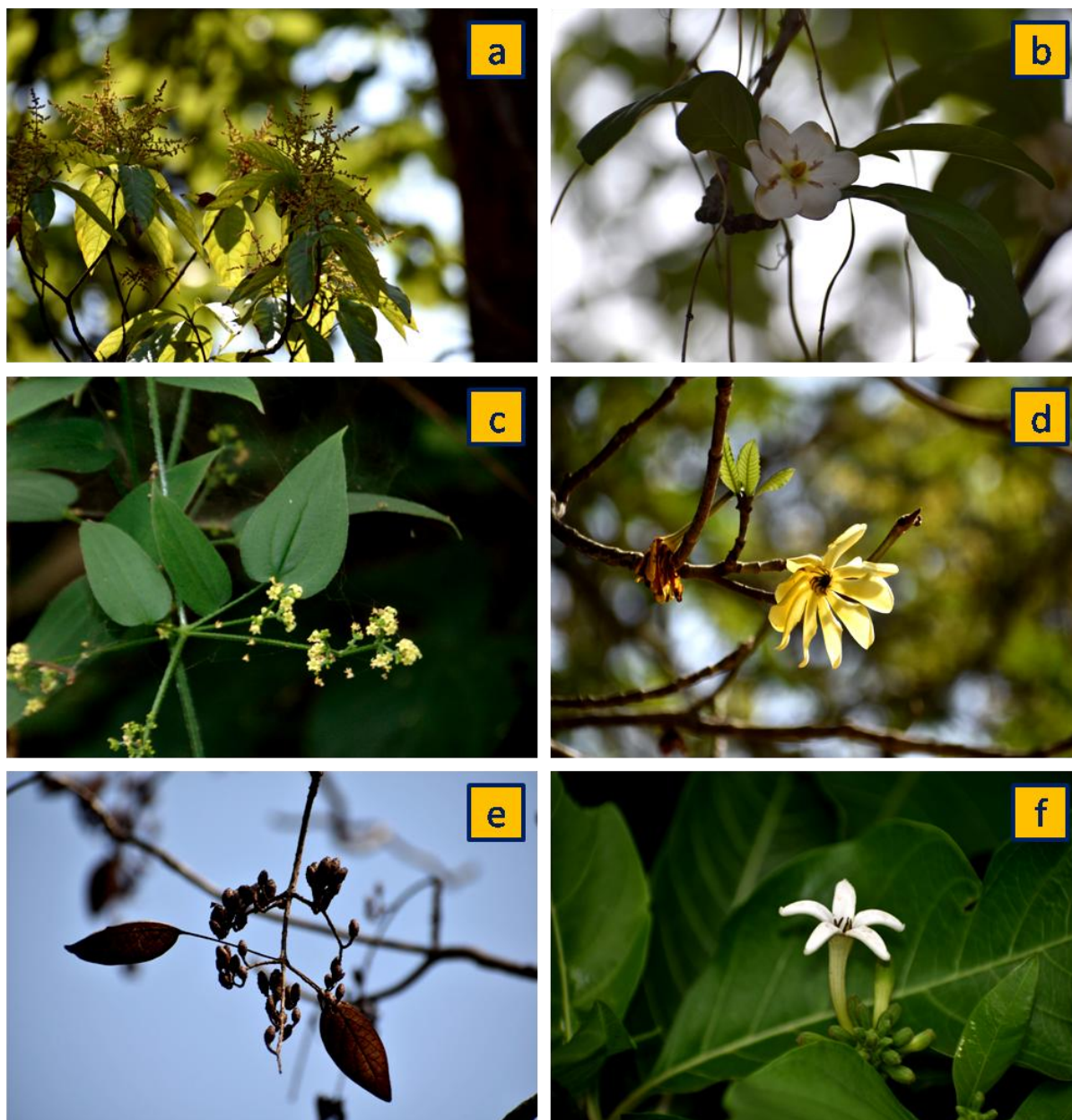


Plate 1: Plant species of family Rubiaceae; (a) *Wendlandia tinctoria*, (b) *Tamilnadia uliginosa*, (c) *Rubia cordifolia*, (d) *Gardenia latifolia*, (e) *Hymenodictyon orixense* and (f) *Morinda pubescens*

### Ethnopharmacological significance of selected members of Rubiaceae

The Rubiaceae family is characterized by a broad range of secondary metabolites, including alkaloids, anthraquinones, flavonoids, terpenoids, iridoids, triterpenes and phenolic compounds (Martins and Nunez, 2015). Several medicinally important genera within Rubiaceae, including *Morinda*, *Mitragyna*, *Wendlandia*, *Adina* and *Gardenia*, have attracted considerable attention due to their rich phytochemical diversity and pharmacological potential (González et al., 2023). Several of these constituents possess documented antiplasmodial activity (Table 1). Anthraquinones such as damnacanthal, nordamnacanthal, morindone and alizarin derivatives from *Morinda* species have demonstrated antiparasitic potential (Rushdan et al., 2023). Sterols including  $\beta$ -sitosterol and stigmasterol may contribute to antimalarial effects either directly or through synergistic interactions with other phytoconstituents (García et al., 2025). Flavonoids including quercetin, kaempferol, apigenin and naringenin derivatives exhibit inhibitory effects against *Plasmodium* species, while terpenoids such as phytol and  $\alpha$ -amyrin have also shown promising activity (Rasheed et al., 2026). Therefore, the Rubiaceae family (Plate 1) represents an important source of bioactive molecules for antimalarial drug discovery.

Table 1: Ethnomedicinal uses and anti-malarial bioactives in selected species of Rubiaceae

Species	Common name	Native region	Potential bioactive compound with anti-plasmodial properties	Ethnomedicinal use(s)	Source(s)
<i>Adina cordifolia</i> (Roxb.) Hook.f. & Benth.	Yellow Teak	Outer Himalayan ranges, Bhutan, Myanmar, Indian subcontinent, China and Peninsula Malaysia.	Naringenin-7-methyl ether-4'-O- $\alpha$ -L-rhamnopyranoside, $\alpha$ -Amyrin, flavonoids, alkaloids and other terpenoids	Bark and leaves are used for treating cold and fever.	Rokade and Pawar, (2013)
<i>Benkara malabarica</i> (Lam.) Tirveng.	Phirika (Regional Odia)	Southern India, Sri Lanka and Myanmar	$\beta$ -Sitosterol, Scopoletin, n-Hexadecanoic acid (palmitic acid), alkaloids and flavonoids	Root and bark are used for cough, wound healing and rheumatic pain.	Sureshrao et al., (2025)

<i>Blumea balsamifera</i> (L.) DC.	Sambong/ Ngai Camphor	Tropical and Subtropical Asia	Caryophyllene oxide, $\beta$ - Caryophyllene, Phytol, Quercetin, Stigmasterol and $\alpha$ -Amyrin	Whole plant or leaves are used for skin ailments.	Chaniad et al., (2022)
<i>Ceriscoides turgida</i> (Roxb.) Tirveng.	Mountain Gardenia	Indian subcontinent and Indo- China	Flavonoids, terpenoids, phenolic compounds and alkaloids	Roots are used for leucorrhoea and to treat indigestion in children.	Kumar et al., (2025)
<i>Gardenia latifolia</i> Aiton (Plate 1d)	Indian Boxwood	India and Bangladesh	4'- Hydroxywogonin, Isoquercitrin, Rutin, Methoxylated flavones, Scortechinones, Chlorogenic acid, Dicafeoylquinic acid, Sinapoyl- cafeoyl derivatives, Sinapinic acid, Betulinic acid, 5- Deoxystrigol and 2-Ketoepimanool	Fruits are used for skin ailments.	Reddy et al., (2021); Alshabi and Shaikh, (2022)
<i>Hymenodictyon orixense</i> (Roxb.) Mabb. (Plate 1e)	Bridal Couch Tree	Indian subcontinent, Indo-China, Philippines	Scopoletin, loganin, Stigmasterol and trace alkaloids	Leaf paste is used for wound healing.	Reddy and Chaturvedi, (2010); Kumari and Jain, (2025)
<i>Morinda pubescens</i> Sm. (Plate 1f)	Indian Mulberry	Indian subcontinent, Indo-China and Jawa	Morindone, Damnacanthal, Nordamnacanthal and Soranjidiol	Leaf juice is administered to children for promoting digestion.	Ravikumar et al., (2012); Jaiswal et al., (2025)
<i>Rubia cordifolia</i> L.	Indian Madder	Greece, Sudan to	Purpurin, Mollugin,	Roots are used for blood	Kumari et al., (2021);

(Plate 1c)		South Africa and Asia	Furomollugin, Munjistin and Alizarin	detoxification and	Wen et al., (2022)
<i>Tamilnadia uliginosa</i> (Retz.) Tirveng. & Sastre (Plate 1b)	Divine Jasmine	Indo-China and Indian subcontinent	Phytol and 3,7,11,15-Tetramethyl hexadecen-1-ol (phytol related alcohol)	Fruits and leaves are used in treatment of skin ailments, dysentery and as hair tonic.	Deepthy and Radhamany, (2015); Sureshrao et al., (2025)
<i>Wendlandia tinctoria</i> (Roxb.) DC. (Plate 1a)	Banabasan ga (Odia regional)	Indian subcontinent, Southern and Indo-China	Naringenin, Apigenin, Kaempferol, Liquiritigenin, Glabridin, B-Sitosterol and Stigmasterol	Used as antidote to snake bite.	Hossain et al., (2023)

### Future aspects

Future research on antimalarial bioactives of the Rubiaceae family should focus on the phytochemical exploration of under investigated species to identify novel antiplasmodial compounds. Advanced analytical techniques such as GC–MS, LC–MS/MS, NMR spectroscopy and metabolomic approaches can facilitate the isolation and characterization of active constituents. Further studies should evaluate their efficacy against drug-resistant *Plasmodium* strains, investigate mechanisms of action, assess synergistic interactions with existing antimalarial drugs and determine safety through toxicological and pharmacokinetic studies. Additionally, integrating computational tools, including molecular docking and artificial intelligence-based screening, with ethnopharmacological and pharmacological approaches may accelerate the development of effective and standardized antimalarial agents from Rubiaceae plants.

### Conclusion

The Rubiaceae family possesses significant ethnopharmacological importance and represents a rich source of structurally diverse bioactive compounds with potential antimalarial properties. Traditional medicinal applications of Rubiaceae plants for fever and malaria treatment are supported by phytochemical and pharmacological studies. Secondary metabolites such as alkaloids, anthraquinones, flavonoids, terpenoids, triterpenoids and phytosterols have been reviewed to have shown promising antiplasmodial activities through various mechanisms affecting parasite growth and survival. Compounds including quinine, morindone, damnacanthal, nordamnacanthal, quercetin derivatives, phytol,  $\alpha$ -amyrin and  $\beta$ -sitosterol may contribute significantly to the antimalarial potential

of Rubiaceae species. However, despite encouraging findings, many bioactive compounds remain insufficiently explored, particularly regarding their mechanisms of action, toxicity profiles and clinical applicability. Therefore, continued investigation of Rubiaceae-derived phytochemicals through integrated ethnopharmacological, phytochemical and pharmacological studies may facilitate the development of novel antimalarial therapies and provide valuable alternatives for combating emerging drug resistance in malaria parasites.

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