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Review Article

Phytochemicals targeting diabetes and malaria: Chemical diversity, mechanistic insights, and prospects for dual-action therapeutics

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ABSTRACT

Diabetes mellitus and malaria are major health challenges in tropical and subtropical regions, creating a need for therapeutic strategies addressing metabolic and infectious disease processes. This review aimed to systematically identify and synthesise plant-derived compounds with reported antidiabetic, antimalarial, or dual antidiabetic–antimalarial activities, with emphasis on their chemical diversity, biological activities, proposed molecular mechanisms, and levels of supporting evidence. A structured literature search was conducted for studies published from January 2015 to December 2025 using Google Scholar, PubMed, ScienceDirect, SciELO, EMBASE, Scopus and Web of Science. Relevant studies reporting antidiabetic, antimalarial or dual activities of plant-derived compounds were evaluated and synthesised according to chemical class, biological activity and proposed molecular mechanisms. Of 2,313 records identified, 272 articles met the eligibility criteria. A total of 258 phytochemicals were identified, including 135 with reported antidiabetic activity, 109 with antimalarial activity and 14 chemically defined compounds with evidence of both activities. Antidiabetic effects involved inhibition of carbohydrate-hydrolysing enzymes, modulation of insulin signalling and glucose uptake, and attenuation of oxidative stress and inflammation. Antimalarial effects included inhibition of parasite enzymes and metabolic processes, interference with haem-associated pathways, and disruption of parasite cellular functions. The dual-action compounds represented diverse classes, including alkaloids, flavonoids, phenolics, terpenoids, triterpenoids and xanthones. The review consolidates the reported chemical and biological diversity of phytochemicals with antidiabetic and antimalarial activities and identifies a focused group of compounds with evidence of dual activity. This provides a basis for prioritising multifunctional natural-product leads while highlighting the need for stronger molecular target validation and translational evidence. Phytochemicals provide a diverse reservoir of compounds with potentially relevant activities against both diseases. The 14 dual-action compounds represent a focused discovery space for multifunctional natural-product leads. However, evidence remains heterogeneous and predominantly preclinical. Future studies should prioritise molecular target validation, structure–activity relationships, pharmacokinetics, bioavailability, safety and efficacy in disease-relevant diabetes–malaria models.

Keywords: Diabetes mellitus; malaria; phytochemicals; antidiabetic activity; antimalarial activity; dual-action therapeutics

Introduction

1.1 Diabetes, malaria and the therapeutic relevance of phytochemicals

Diabetes mellitus and malaria remain major global health challenges, particularly in low- and middle-income countries where the epidemiological transition has resulted in the coexistence of communicable and non-communicable diseases. Diabetes mellitus comprises a group of metabolic disorders characterised by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both, with type 2 diabetes accounting for the majority of cases [1]. The global burden of diabetes continues to increase, with approximately 589 million adults aged 20–79 years estimated to be living with diabetes worldwide, and the majority residing in low- and middle-income countries [2].

Malaria, in contrast, is an infectious disease caused by *Plasmodium* parasites and transmitted predominantly through the bites of infected female *Anopheles* mosquitoes. *Plasmodium falciparum* remains the most important species in terms of severe disease and mortality, particularly in sub-Saharan Africa. According to the World Health Organization (WHO), an estimated 282 million malaria cases and 610,000 malaria-related deaths occurred globally in 2024, with the WHO African Region accounting for approximately 95% of both cases and deaths [3]. The continuing emergence and geographical expansion of antimalarial drug resistance, including reduced susceptibility to artemisinin-based therapies in parts of Africa, further emphasise the need to diversify the chemical space available for antimalarial drug discovery [3,4].

Phytochemicals constitute a chemically diverse group of plant-derived bioactive constituents, encompassing alkaloids, flavonoids, phenolic compounds, terpenoids, glycosides, saponins, xanthones and related secondary metabolites [5,6]. Their structural diversity provides opportunities for interaction with multiple molecular targets involved in metabolic regulation, oxidative stress, inflammation, cellular signalling and pathogen survival. Consequently, plant-derived compounds have attracted sustained interest as potential sources of therapeutic leads for metabolic and infectious diseases [7, 8].
The antidiabetic effects of phytochemicals have been associated with several complementary mechanisms, including inhibition of carbohydrate-hydrolysing enzymes such as α-amylase and α-glucosidase, enhancement of insulin secretion and signalling, improvement of glucose uptake, attenuation of insulin resistance, modulation of oxidative stress and inflammation, and regulation of lipid and glucose metabolism [7,8]. Flavonoids and other polyphenolic compounds, in particular, have been reported to influence pathways involving phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), AMP-activated protein kinase (AMPK), glucose transporter 4 (GLUT4), hepatic gluconeogenesis and pancreatic β-cell function [7,8].

Similarly, plant-derived compounds represent an important source of chemical diversity for antimalarial drug discovery. Natural-product-derived molecules can interfere with essential processes in *Plasmodium*, including haemoglobin digestion and haem detoxification, parasite proteolysis, nucleotide and energy metabolism, redox homeostasis, membrane transport and mitochondrial function [9]. Contemporary antimalarial drug-discovery efforts increasingly emphasise chemically diverse scaffolds capable of overcoming resistance and engaging novel parasite targets [4]. A recent systematic review of plant-derived bioactive compounds against *P. falciparum* further demonstrated the diversity of terpenoids, steroids, flavonoids and other phytochemical classes investigated for antiplasmodial activity, with mechanisms including modulation of β-haematin formation and haemoglobin degradation [10].

The biological breadth of phytochemicals is particularly relevant to the present review because many natural products exhibit polypharmacological properties rather than acting exclusively through a single molecular target. Such multitarget activity creates a conceptual basis for investigating whether individual phytochemicals can simultaneously influence host metabolic dysfunction and parasite survival. This possibility is especially pertinent in populations in which diabetes and malaria may coexist, thereby providing a rationale for investigating phytochemicals not merely as separate antidiabetic or antimalarial agents, but as potential dual-action therapeutic scaffolds.

1.2 Biological interplay between diabetes and malaria

Although diabetes and malaria have distinct primary aetiologies, their coexistence may have clinically relevant biological consequences, particularly in malaria-endemic regions undergoing a rapid increase in the prevalence of metabolic disorders. Evidence for a direct epidemiological association remains limited, but available observational studies suggest that diabetes may be associated with increased susceptibility to malaria and, in some populations, greater risk of severe malaria [11]. This potential relationship is biologically plausible because diabetes is associated with chronic hyperglycaemia, altered immune responses, inflammation, endothelial dysfunction and changes in erythrocyte physiology, all of which may influence host–parasite interactions [12].

Hyperglycaemia is of particular interest because glucose represents an essential metabolic substrate for *P. falciparum*. Experimental evidence indicates that parasite growth is influenced by glucose availability, and recent ex vivo investigations demonstrated positive associations between blood glucose, glycated haemoglobin and parasite growth in samples obtained from individuals with diabetes [13]. The same study found that parasite rosetting was associated with type 2 diabetes and measures of glycaemic status, providing experimental support for a potential link between diabetic physiology and parasite virulence.

Erythrocyte-mediated mechanisms may provide an additional connection between the two diseases. *P. falciparum* rosetting, in which infected erythrocytes adhere to uninfected erythrocytes, is associated with severe malaria and may contribute to microvascular obstruction [14]. Ch'ng et al. [13] reported increased rosetting in erythrocytes obtained from individuals with type 2 diabetes and observed associations

between rosetting, blood glucose and glycated haemoglobin. These findings suggest that alterations in the diabetic host environment may influence parasite–erythrocyte interactions, although the mechanisms and clinical significance of this relationship require further investigation.

Microvascular dysfunction represents another potentially convergent pathological feature. Diabetes is characterised by endothelial dysfunction and impaired microvascular homeostasis, whereas severe malaria involves sequestration and adhesion of parasitised erythrocytes within the microcirculation. Consequently, abnormalities in vascular function, erythrocyte behaviour and inflammatory signalling may contribute to overlapping pathological processes in individuals affected by both conditions [13,14].

Taken together, the available evidence does not yet establish diabetes and malaria as a clinically defined syndemic or demonstrate a uniform causal relationship between the two diseases. Rather, it identifies a biologically plausible interface involving glucose availability, erythrocyte behaviour, inflammation, endothelial dysfunction and parasite growth. This interface provides a rational basis for investigating therapeutic strategies capable of simultaneously modulating host metabolic dysfunction and parasite survival.

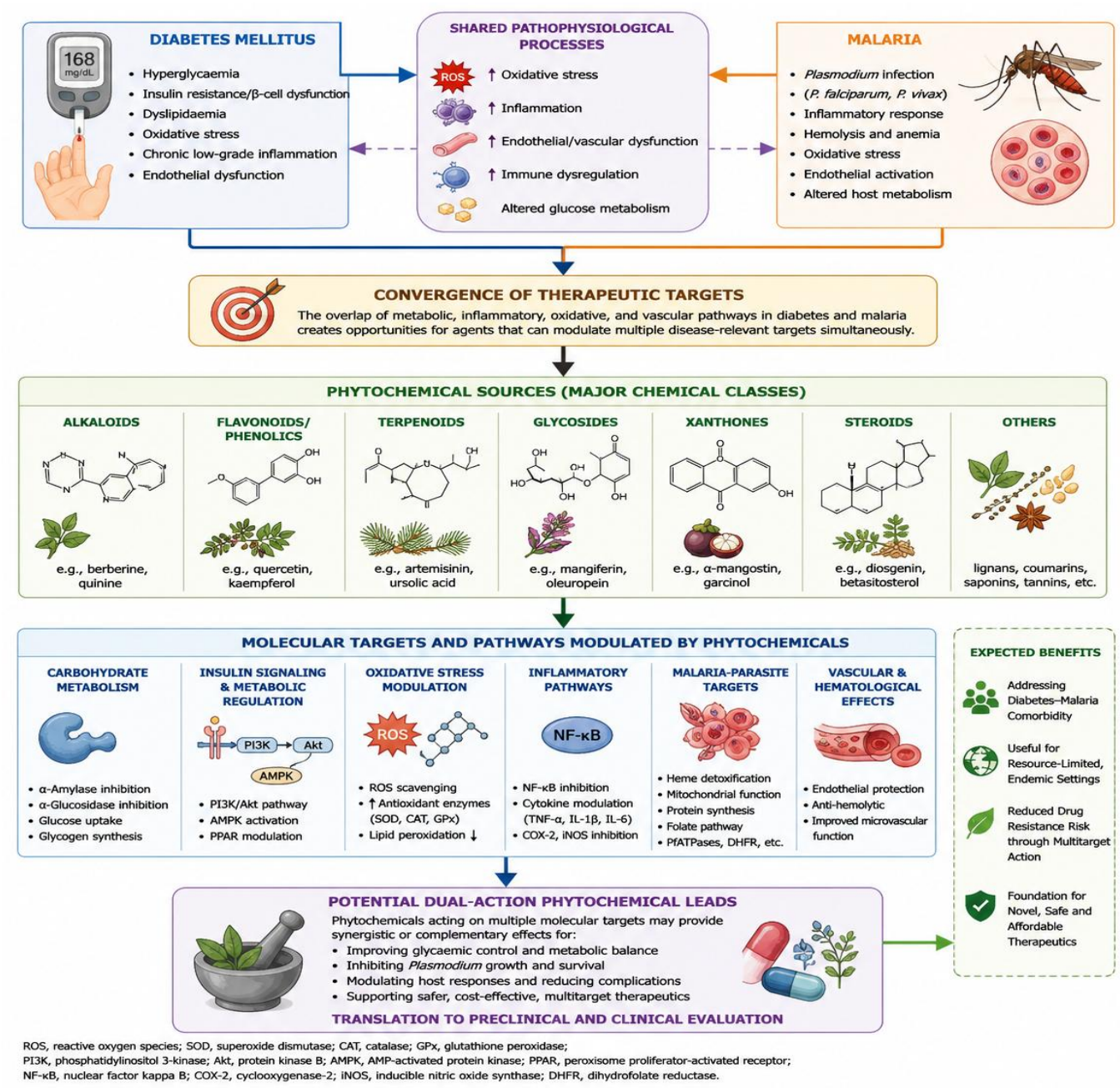


Figure 1. Conceptual framework linking diabetes–malaria comorbidity with multitarget phytochemicals.

1.3 Rationale for dual-action phytochemicals

The potential biological interface between diabetes and malaria provides a rationale for investigating therapeutic agents capable of influencing both disease processes. Conventional pharmacotherapy generally addresses the two conditions through distinct therapeutic targets; however, multifunctional compounds may offer an alternative drug-discovery strategy when multiple pathological pathways contribute simultaneously to disease progression. In this context, the objective is not necessarily for a single compound to act on an identical molecular target in both diseases, but rather to achieve complementary pharmacological effects on host metabolic dysfunction and parasite survival.

Plant-derived compounds are particularly attractive for such an approach because natural-product scaffolds frequently exhibit structural complexity and polypharmacological activity. Flavonoids, phenolics, alkaloids, terpenoids and related compounds have been reported to influence multiple pathways involved in glucose homeostasis, oxidative stress, inflammation and cellular signalling, while many structurally diverse natural products also exhibit activity against essential *Plasmodium* processes [4,7,8,10].

The concept of dual-action phytochemicals therefore extends beyond the conventional identification of separate antidiabetic and antimalarial natural products. Instead, it seeks to identify chemical scaffolds for which evidence exists of both activities in the same molecule (Figure 1). Such compounds may act through parallel host–parasite targets, convergent biological processes such as redox regulation, or multiple independent molecular interactions. The identification and mechanistic validation of these compounds could establish a foundation for multifunctional natural-product drug discovery.

Nevertheless, dual biological activity should not automatically be interpreted as evidence of therapeutic superiority. A candidate compound must demonstrate sufficient potency against both disease processes, appropriate selectivity, adequate pharmacokinetic exposure, acceptable toxicity and reproducible efficacy in relevant biological models. Accordingly, the present review distinguishes compounds with experimentally demonstrated dual activity from phytochemicals for which dual activity remains hypothetical or is supported primarily by computational prediction.

1.4 Aim and scope of the review

This review synthesises published evidence on plant-derived phytochemicals with antidiabetic, antimalarial or dual antidiabetic–antimalarial activity, with particular emphasis on chemical classes, molecular mechanisms and therapeutic relevance. The literature search identified 2,313 records and, following screening and eligibility assessment, 272 articles were included. These studies yielded 258 phytochemicals, comprising 135 with reported antidiabetic activity, 109 with antimalarial activity and 14 with evidence of both activities.

Rather than providing an exhaustive catalogue of individual compounds, the review focuses on representative chemical classes and mechanisms and critically examines the comparatively small group of phytochemicals with reported dual activity. Particular attention is given to the convergence of molecular processes relevant to glucose homeostasis and *Plasmodium* survival, together with the translational challenges associated with bioavailability, pharmacokinetics, toxicity and validation in cellular, animal and clinical models. By integrating these findings, the review aims to identify promising chemical scaffolds and mechanistic opportunities for the development of multifunctional natural-product therapeutics targeting diabetes and malaria.

Methods

2.1 Literature search strategy

We conducted a structured literature search to identify published evidence on plant-derived phytochemicals with antidiabetic, antimalarial, or dual antidiabetic–antimalarial activity. The literature search covered publications from January 2015 to December 2025 and used seven bibliographic databases and scholarly information sources: PubMed, ScienceDirect, SciELO, Google Scholar, EMBASE, Scopus, and Web of Science. The search strategy aimed to maximise retrieval of studies addressing antidiabetic or antimalarial activity, as well as studies reporting both activities in the same phytochemical.

Search terms were organised around three principal concepts: phytochemical or plant-derived compounds, diabetes-related activity, and malaria-related activity. The principal terms included “phytochemicals,” “plant-derived compounds,” “natural products,” “antidiabetic,” “antihyperglycemic,” “hypoglycemic,” “antimalarial,” “antiplasmodial,” and “antiparasitic.” Combinations of these terms were used with Boolean operators to identify relevant publications. Where appropriate, we incorporated related synonyms and terminology variations to improve retrieval sensitivity.

We structured reporting of the literature identification, screening, eligibility assessment, and study-selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and its accompanying explanation and elaboration guidance [15,16]. PRISMA 2020 served as a reporting framework to promote transparent presentation of literature identification, screening, and selection, rather than as a substitute for a prespecified systematic-review protocol.

We applied the search strategy, eligibility criteria, and selection process consistently across the identified literature. The final search and screening process generated the records reported in the PRISMA flow diagram (Figure 2).

2.2 Eligibility criteria and study selection

Studies were eligible for inclusion if they reported experimental or mechanistically supported evidence concerning plant-derived phytochemicals with antidiabetic, antimalarial, or dual antidiabetic–antimalarial activity and were published between

January 2015 and December 2025. The initial literature assessment considered evidence involving crude plant extracts, fractions, oils, isolated compounds, and chemically characterised phytochemicals.

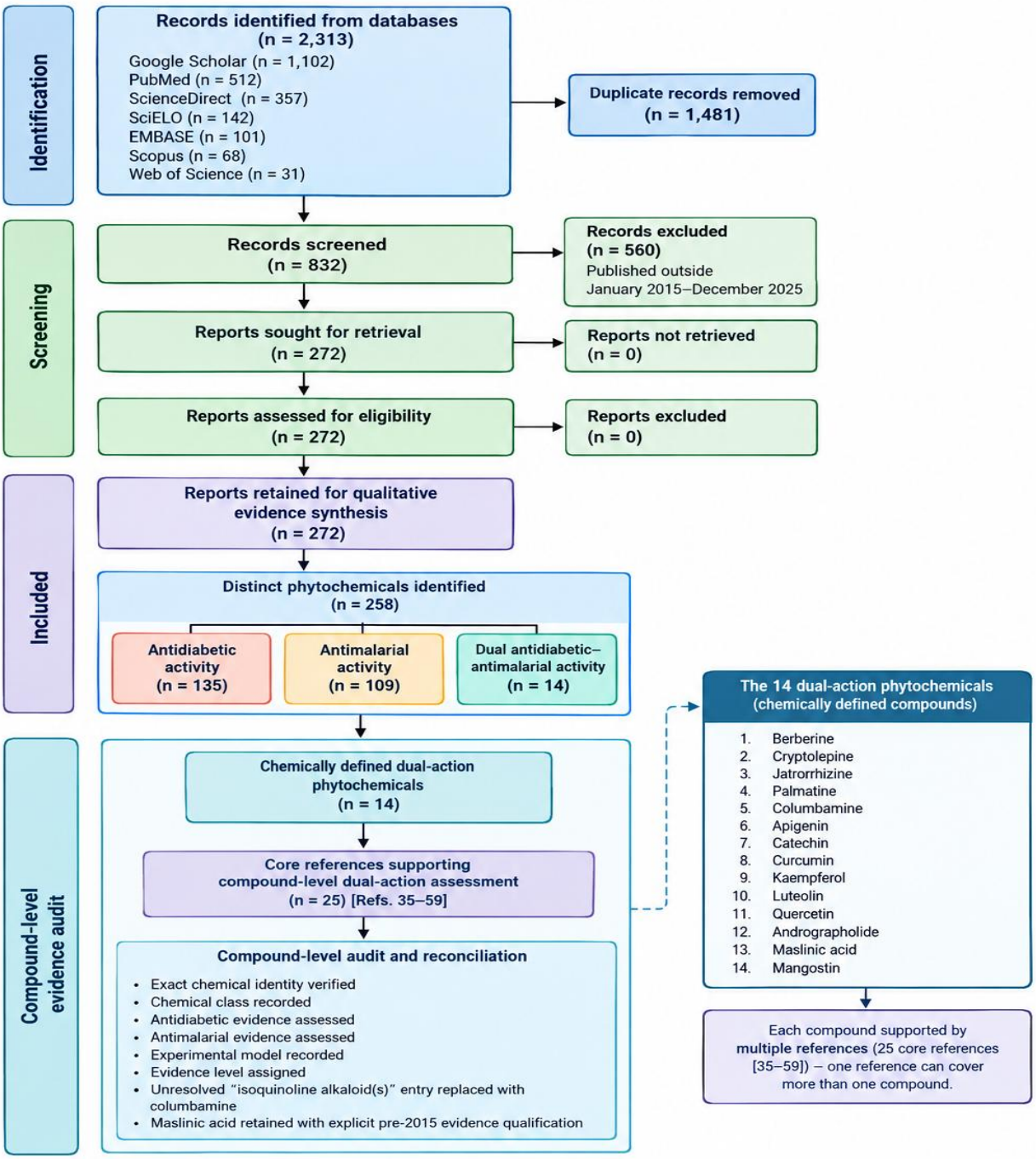


Figure 2. PRISMA 2020 flow diagram showing the identification, screening, eligibility assessment and retention of reports for qualitative synthesis of evidence, and subsequent compound-level evidence audit. Adapted from Page et al. [16].

Note: The 25 core references represent the principal compound-level evidence base for the 14 dual-action phytochemicals and should not be interpreted as a separate PRISMA study-selection stage. The complete manuscript bibliography contains 63 references, including methodological, background, mechanistic and translational sources.

Studies were excluded when they did not provide evidence relevant to the objectives of the review, did not concern plant-derived materials or phytochemicals, were published before 2015 or after 2025, or were not available in English. We also excluded studies that lacked sufficient information to establish the identity of the investigated phytochemical or its reported biological activity when this prevented classification according to the predefined evidence categories.

Three reviewers independently screened the retrieved records for eligibility. The screening process was conducted

sequentially, beginning with removal of duplicate records, followed by assessment of publication-period eligibility and screening for relevance to the review objectives. Reviewers independently assessed potentially eligible records and resolved eligibility disagreements through discussion and consensus.

The initial literature search identified 2,313 records. After removing 1,481 duplicate records, 832 records remained for further assessment. The publication year of these records was subsequently verified against the predefined January 2015–December 2025 eligibility period. We excluded 560 records because they fell outside the specified publication period, leaving 272 records for full-text evaluation and synthesis.

Applying the publication-period criterion at the screening stage served as an additional eligibility check to ensure that records outside the predefined review period were not inadvertently retained. The PRISMA 2020 flow diagram (Figure 2; [16]) summarises the study identification and selection process.

2.3 Data extraction and synthesis

Relevant information was extracted from eligible publications and organised according to phytochemical identity, chemical class, plant source, reported biological activity, experimental evidence, experimental model, molecular target and proposed or established mechanism of action. Information concerning the level of experimental evidence was also considered, with particular attention to biochemical, cellular, animal and human studies.

The extracted evidence was synthesised narratively according to chemical class and biological mechanism rather than subjected to quantitative meta-analysis. This approach was adopted because the included studies differed substantially in phytochemical identity, plant source, experimental model, biological endpoint, assay methodology and reported mechanism, limiting the comparability required for quantitative pooling.

Particular emphasis was placed on recurrent molecular targets and pathways associated with glucose metabolism, insulin signalling, oxidative stress, inflammation, parasite survival, haemozoin formation and other processes relevant to diabetes and malaria. Phytochemicals reported to possess both antidiabetic and antimalarial activities were analysed separately to identify potential dual-action chemical scaffolds.

The synthesis therefore integrated evidence across different experimental systems while distinguishing experimentally demonstrated biological activity from mechanistic interpretation and proposed therapeutic potential.

2.4 Evidence classification

For the purposes of this review, a phytochemical was classified as antidiabetic when the eligible literature reported a biological effect relevant to glucose homeostasis or diabetes-associated metabolic dysfunction. A phytochemical was classified as antimalarial when the available evidence demonstrated inhibition of *Plasmodium* growth, parasite survival, parasite-associated molecular targets, or other experimentally documented antiplasmodial activity.

A phytochemical was classified as having dual antidiabetic–antimalarial activity only when evidence for both antidiabetic and antimalarial activity was reported for the same chemically identified phytochemical. Evidence from crude extracts or mixtures was not considered sufficient to establish dual activity for an individual compound unless the active phytochemical had been identified and directly associated with both biological activities.

The final synthesis identified 258 phytochemicals across the eligible literature, comprising 135 with reported antidiabetic activity, 109 with reported antimalarial activity, and 14 with evidence of both activities. These compounds were further evaluated according to chemical class, reported molecular targets, experimental model, level of experimental evidence and therapeutic relevance.

3. Chemical Diversity and Antidiabetic Activity of Phytochemicals

The literature synthesis identified 135 phytochemicals with reported antidiabetic activity, representing a chemically diverse group comprising flavonoids and phenolics (68), alkaloids (32), glycosides (11), terpenoids and steroids (10), xanthones (6), polysaccharides (2), and other bioactive compounds (6). This distribution indicates that antidiabetic activity is not restricted to a single structural class but occurs across chemically distinct natural-product scaffolds. The predominance of flavonoids and phenolic compounds is consistent with the extensive literature describing their effects on carbohydrate digestion, glucose transport, insulin signalling, oxidative stress and inflammation [7,8, 17].

Mechanistically, the identified phytochemicals influenced several interconnected components of glucose homeostasis, including inhibition of intestinal carbohydrate-hydrolysing enzymes, enhancement of insulin secretion or sensitivity, stimulation of glucose uptake, modulation of hepatic glucose production, regulation of lipid metabolism, and attenuation of oxidative and inflammatory stress. Recent mechanistic reviews similarly indicate that flavonoids and related natural products can simultaneously affect α-amylase and α-glucosidase activity, IRS/PI3K/AKT signalling, AMPK/GLUT4-mediated glucose uptake, gluconeogenesis, glycogenesis and inflammatory pathways [7,17].

This mechanistic diversity is important because type 2 diabetes is characterised by interacting abnormalities in insulin action, β-cell function, hepatic glucose production, lipid metabolism, inflammation and cellular stress. Consequently, phytochemicals capable of modulating more than one metabolic pathway may provide useful chemical starting points for multifunctional antidiabetic drug discovery. Nevertheless, mechanistic breadth should not be equated with therapeutic efficacy, because much of the evidence remains preclinical and the pharmacological relevance of individual compounds

depends on absorption, metabolism, tissue exposure, potency and safety.

3.1 Flavonoids and phenolic compounds

Flavonoids and phenolic compounds constituted the largest chemical group identified in the review, accounting for 68 of the 135 phytochemicals with reported antidiabetic activity. Representative compounds included quercetin, rutin, naringenin, fisetin, apigenin, genistein, hesperidin, epigallocatechin gallate (EGCG), luteolin, pterostilbene, resveratrol and related phenolic compounds. The prominence of this class is consistent with recent evidence describing multiple mechanisms through which flavonoids can regulate glucose metabolism and insulin responsiveness [7,17].

One major mechanism involves inhibition of intestinal α-amylase and α-glucosidase, which can reduce the enzymatic hydrolysis of dietary carbohydrates and consequently attenuate the postprandial increase in blood glucose. Other flavonoids influence intracellular insulin signalling and glucose transport through pathways involving IRS/PI3K/AKT and AMPK/GLUT4 [7,17]. These mechanisms are not mutually exclusive, and individual compounds may influence several metabolic nodes simultaneously.

Acacetin provides an experimentally characterised example of this multifunctional activity. In cultured L6 skeletal-muscle cells, acacetin increased glucose uptake by promoting GLUT4 translocation and activating a CaMKII–AMPK-dependent pathway. The study also reported involvement of aPKCλ/ζ phosphorylation and intracellular reactive oxygen species in the response, while AMPK activation was associated with reduced lipid accumulation in HepG2 cells [18]. These findings support a glucose-uptake mechanism for acacetin but remain primarily cellular evidence rather than proof of clinical antidiabetic efficacy.

EGCG has similarly been investigated through several complementary mechanisms, including carbohydrate-digesting enzyme inhibition, modulation of insulin signalling and enhancement of glucose uptake. More broadly, recent reviews identify PI3K/AKT, AMPK/GLUT4 and carbohydrate-digestive enzymes among the recurrent molecular systems through which flavonoids exert hypoglycaemic effects [7,17].

Pterostilbene provides another example of a phenolic compound with evidence extending beyond enzyme inhibition. Experimental work has shown that pterostilbene can improve impaired insulin signalling associated with advanced glycation end products by enhancing IRS-1/PI3K/AKT signalling. In cell and mouse models, pterostilbene treatment improved glucose-related metabolic parameters and reduced AGE accumulation, supporting its potential as a glucose-sensitising compound [18]. Nevertheless, these findings should be interpreted primarily as preclinical evidence.

The biological effects of other flavonoids, including naringenin, luteolin, quercetin and related compounds, have been associated with modulation of PI3K/AKT, AMPK/GLUT4, hepatic gluconeogenesis, glycogen synthesis, oxidative stress and inflammatory signalling [17]. However, the magnitude and reproducibility of these effects vary according to compound structure, dose, experimental system and bioavailability.

An important consideration is that flavonoid activity should therefore not be interpreted solely in terms of direct enzyme inhibition. Their reported antioxidant and anti-inflammatory properties may provide complementary protection against cellular stress associated with chronic hyperglycaemia, while modulation of insulin signalling and glucose transport may influence systemic glucose handling. The overall antidiabetic potential of this chemical class is consequently better conceptualised as a combination of postprandial glucose regulation, insulin sensitisation, glucose uptake and protection against metabolic stress rather than as a single-target mechanism.

3.2 Alkaloids

Alkaloids represented the second-largest chemical class, comprising 32 of the phytochemicals identified with reported antidiabetic activity [19]. Representative compounds included 1-deoxynojirimycin, capsaicin, evodiamine, harmine, harmane, mahanimbine, nuciferine, piperine, thymoquinone, trigonelline, vindogentianine and vindoline.

The mechanisms reported for antidiabetic alkaloids were heterogeneous and included inhibition of carbohydrate-hydrolysing enzymes, modulation of insulin signalling, enhancement of glucose uptake, regulation of oxidative stress and interference with protein tyrosine phosphatase 1B (PTP1B). Such mechanistic diversity is consistent with the broader pharmacological behaviour of plant-derived alkaloids, many of which interact with multiple enzymes and signalling proteins.

1-Deoxynojirimycin is particularly relevant as a naturally occurring iminosugar capable of inhibiting α-glucosidase activity, thereby reducing intestinal carbohydrate digestion. Other alkaloids have been investigated through insulin-signalling and glucose-transport mechanisms. Mahanimbine, for example, has been reported in experimental models to promote glucose uptake and GLUT4-associated responses, whereas piperine and related alkaloids have been investigated for effects on glucose metabolism, oxidative stress and insulin sensitivity.

PTP1B represents another mechanistic target of interest because its activity negatively regulates insulin-receptor signalling. Natural compounds capable of inhibiting PTP1B may therefore enhance downstream IRS/PI3K/AKT signalling and improve insulin responsiveness. However, inhibition observed in biochemical assays does not necessarily translate into effective inhibition in vivo because compound exposure, selectivity and pharmacokinetics determine whether the target can be reached at therapeutically relevant concentrations.

The alkaloid group therefore illustrates an important characteristic of phytochemical antidiabetic activity: individual compounds may influence distinct points within the same metabolic network, including carbohydrate digestion, insulin signalling, glucose transport and cellular stress. Nevertheless, most evidence remains preclinical, and compounds supported only by biochemical or cellular assays require further

pharmacokinetic, toxicological and in-vivo validation before therapeutic claims can be made.

3.3 Glycosides and polysaccharides

Eleven glycosidic compounds were identified among the antidiabetic phytochemicals, including amarogentin, charantin, ginsenosides, isovitexin, isorhamnetin, malonyl ginsenosides, pelargonidin-3-O-glucoside, stevioside, steviol and vitexin. Their reported activities included modulation of insulin secretion, glucose uptake, insulin sensitivity and glucose and lipid metabolism.

Ginsenosides are particularly well characterised among plant-derived glycosides. Evidence from experimental and review studies indicates that ginsenosides can influence several pathways relevant to diabetes, including IRS1/PI3K/AKT, AMPK, FoxO1, PPAR-associated signalling, inflammatory pathways and oxidative-stress responses [20-22]. These multiple mechanisms provide a plausible basis for their reported effects on glucose metabolism and insulin resistance. Importantly, however, the available evidence remains predominantly preclinical, and differences in ginsenoside structure, metabolism and bioavailability complicate direct comparison among individual compounds.

Glycosylation can substantially influence the physicochemical and pharmacokinetic properties of natural products. Differences in sugar moieties may alter aqueous solubility, membrane permeability, intestinal metabolism and biotransformation, meaning that structurally related glycosides may display markedly different biological profiles. Consequently, the antidiabetic effects of glycosides should be interpreted at the level of individual compounds rather than assumed to be a general property of the chemical class.

Only two polysaccharide entries were identified in the present synthesis: galactomannan gum and ganoderans A and B. Their reported effects included delayed glucose absorption, modulation of protein tyrosine phosphatase 1B and immunomodulatory activity. Because polysaccharides differ substantially from low-molecular-weight phytochemicals with respect to absorption, digestion, metabolism and tissue accessibility, their biological actions should be considered separately from conventional small-molecule phytochemicals.

3.4 Terpenoids and steroids

Ten terpenoid or steroid compounds were identified, including betulinic acid, biochanin A, corosolic acid, forskolin, gymnemic acid IV, nerolidol, oleanolic acid, pentacyclic triterpenes, β-sitosterol and ursolic acid. Their reported antidiabetic effects involved glucose and lipid homeostasis, insulin sensitivity, carbohydrate digestion, intracellular signalling and oxidative-stress regulation.

Corosolic acid provides an example of a triterpenoid acting on insulin-related glucose transport. Experimental studies have shown that corosolic acid enhanced glucose uptake and promoted GLUT4 translocation through insulin-signalling mechanisms, with pharmacological inhibition of PI3K attenuating the response. The compound has also demonstrated inhibitory activity against several protein tyrosine phosphatases relevant to insulin signalling (Jung et al., 2008). Although this study predates the temporal scope of the present review, it illustrates the mechanistic basis for a compound identified in the review; such older primary studies should therefore only be cited if the review methodology permits background references outside the formal search dataset.

More recent evidence continues to support the importance of AMPK, AKT and GLUT4 as convergent pathways through which plant-derived triterpenoids and related compounds may influence glucose metabolism. For example, an in-vivo and in-silico study of phytochemicals associated with *Potentilla fulgens* reported increased GLUT4, AKT2 and AMPK expression and improved glucose and insulin-related parameters in diabetic mice; docking analyses additionally identified interactions between several constituent phytochemicals, including ursolic acid, and these metabolic targets [23].

The broader terpenoid group is therefore relevant to multifunctional antidiabetic drug discovery because these compounds may influence glucose uptake, insulin signalling, lipid metabolism and cellular stress simultaneously. Nevertheless, evidence should be interpreted according to experimental level, since molecular docking and enzyme assays provide mechanistic hypotheses rather than evidence of clinical efficacy.

3.5 Xanthones and other bioactive phytochemicals

Six xanthone-related compounds were identified, including 1,3,7,8-tetrahydroxyxanthone, 1,3,5,8-tetrahydroxyxanthone, madecassoside, mangiferin, gambogic acid and oblongixanthones F–H. Their reported antidiabetic activities included carbohydrate-digesting enzyme inhibition, modulation of insulin sensitivity, attenuation of oxidative stress and protection against diabetes-associated cellular injury.

Mangiferin is particularly noteworthy because it has been investigated across several components of glucose regulation, including α-amylase and α-glucosidase inhibition, insulin signalling, oxidative-stress modulation and glucose metabolism. Its chemical structure and multiple reported biological activities make it a useful example of a natural-product scaffold with potentially complementary metabolic effects [24].

The interpretation of mangiferin and related xanthones should nevertheless distinguish biochemical activity from systemic efficacy. Inhibition of α-amylase or α-glucosidase in an isolated enzyme system demonstrates a potential mechanism for reducing carbohydrate digestion but does not establish that sufficient concentrations of the compound reach the intestinal or systemic target following oral administration. Accordingly, compounds such as mangiferin should be prioritised according to the convergence of biochemical, cellular, animal and pharmacokinetic evidence rather than enzyme inhibition alone.

Six additional compounds—allicin, bakuchiol, ellagic acid, ellagitannins, 8-debenzoylpaeoniflorin and paeoniflorin—were grouped separately because they did not fit conveniently within the major chemical classes used in the present synthesis. Their

reported activities included modulation of insulin signalling, attenuation of oxidative stress, effects on advanced glycation and changes in glucose and lipid metabolism. These compounds further illustrate the breadth of structural scaffolds represented within the antidiabetic phytochemical literature.

3.6 Convergent antidiabetic mechanisms

Despite substantial structural diversity, the 135 antidiabetic phytochemicals identified in this review converged on a comparatively restricted network of metabolically important processes (Figure 3). Six major mechanistic nodes were apparent: (i) inhibition of α-amylase and α-glucosidase; (ii) enhancement of insulin secretion and preservation of pancreatic β-cell function; (iii) restoration of insulin signalling through IRS/PI3K/AKT-associated pathways; (iv) activation of AMPK and enhancement of glucose uptake through GLUT4; (v) modulation of hepatic gluconeogenesis and glycogen synthesis; and (vi) attenuation of oxidative stress and inflammatory signalling [7,17].

The convergence of structurally unrelated phytochemicals on these pathways is potentially important for multifunctional drug discovery. Rather than acting exclusively at a single metabolic target, several phytochemicals appear capable of influencing multiple interconnected nodes within glucose homeostasis. Ginsenosides, for example, have been associated with IRS1/PI3K/AKT, AMPK/FoxO1, PPAR-associated and inflammatory pathways, while flavonoids have been linked to carbohydrate-enzyme inhibition, PI3K/AKT, AMPK/GLUT4, hepatic glucose regulation and redox pathways [17,18,21].

This convergence provides a mechanistic basis for considering selected phytochemicals as potential multitarget antidiabetic scaffolds. However, multitarget activity should not be interpreted as automatically beneficial. Excessive promiscuity may produce off-target effects, pharmacokinetic interactions or toxicity, while activity against multiple targets in vitro may be pharmacologically irrelevant if systemic concentrations remain below the required effective range.

Accordingly, the evidence hierarchy is critical. Compounds supported only by enzyme-inhibition assays provide preliminary mechanistic evidence; cellular studies provide stronger evidence of target engagement in a biological context; animal studies provide evidence of integrated pharmacological activity; and controlled human studies provide the most clinically relevant evidence. The present review therefore places greater translational value on compounds for which activity has been reproduced across complementary experimental systems rather than on compounds supported exclusively by isolated biochemical assays.

This mechanistic convergence is also central to the dual-action hypothesis developed later in this review. If selected phytochemicals can influence metabolic pathways such as AMPK, PI3K/AKT, oxidative-stress and inflammatory signalling while simultaneously affecting essential biological processes in *Plasmodium*, they may represent a distinct class of multifunctional natural-product scaffolds worthy of further investigation.

4. Antimalarial Phytochemicals and their Molecular Mechanisms

The literature synthesis identified 109 phytochemicals with reported antimalarial or antiplasmodial activity. These compounds encompassed alkaloids (33), terpenoids and steroids (24), xanthones and related aromatic scaffolds (17), flavonoids and phenolics (16), glycosides (16), and saponins (3). The chemical diversity represented in this dataset illustrates the broad structural space available from plant-derived natural products for antimalarial drug discovery. Contemporary reviews have similarly documented extensive antiplasmodial chemical diversity spanning alkaloids, terpenoids, flavonoids, phenolics, xanthones, quinones, steroids, glycosides and other specialized metabolites [25-28].

The biological activities of these compounds were associated with several essential processes in Plasmodium, including haemoglobin digestion and haem detoxification, proteolysis, nucleotide and energy metabolism, redox homeostasis, mitochondrial function, membrane transport, ion regulation and parasite-stage progression. Such mechanistic diversity is particularly relevant to contemporary antimalarial drug discovery because resistance to established therapies continues to create a need for chemically and mechanistically differentiated antiplasmodial scaffolds [4,29].

Table 1. Representative antidiabetic phytochemicals, chemical classes, principal molecular mechanisms and levels of evidence

Chemical class	No. identified	Representative phytochemicals	Principal mechanisms	Evidence level
Flavonoids and phenolics	68	Acacetin, EGCG, ferulic acid, hesperidin, luteolin, naringenin, pterostilbene, quercetin, rutin	α-Amylase/α-glucosidase inhibition; IRS/PI3K/AKT; AMPK/GLUT4; insulin sensitivity; antioxidant and anti-inflammatory effects	Biochemical, cellular, animal and limited clinical evidence; class-level evidence supported by Cheng et al. [7] and Wang et al. [17]
Alkaloids	32	1-Deoxynojirimycin, capsaicin, evodiamine, mahanimbine, nuciferine, piperine, thymoquinone, trigonelline	Carbohydrate-enzyme inhibition; PTP1B; insulin signalling; glucose uptake; oxidative-stress modulation	Predominantly preclinical
Glycosides	11	Amarogentin, charantin, ginsenosides, isovitexin, isorhamnetin, stevioside, steviol, vitexin	AMPK; IRS/PI3K/AKT; insulin secretion; glucose uptake; glucose/lipid regulation	Predominantly preclinical, with some human evidence for selected preparations

Chemical class	No. identified	Representative phytochemicals	Principal mechanisms	Evidence level
Terpenoids and steroids	10	Betulinic acid, biochanin A, corosolic acid, oleanolic acid, β-sitosterol, ursolic acid	AMPK; insulin signalling; glucose uptake; carbohydrate digestion; lipid metabolism; oxidative-stress modulation	Mainly preclinical
Xanthones	6	Mangiferin, gambogic acid, tetrahydroxyxanthones	α-Amylase/α-glucosidase inhibition; insulin sensitivity; antioxidant and cytoprotective effects	Mainly biochemical, cellular and animal evidence
Polysaccharides	2	Galactomannan gum; ganoderans A and B	Delayed glucose absorption; PTP1B modulation; immunometabolic effects	Mainly preclinical
Other bioactive phytochemicals	6	Allicin, bakuchiol, ellagic acid, ellagitannins, paeoniflorin derivatives	Insulin signalling; oxidative-stress reduction; antiglycation; gluconeogenesis and metabolic regulation	Mainly preclinical

Table note: The numerical distribution represents the phytochemicals identified in the present review. Mechanistic classifications summarise evidence reported in the eligible literature and should not be interpreted as evidence that every compound within a class acts through every listed pathway. Representative recent mechanistic sources include Cheng et al. [7], Ashagrie et al. [8], and Wang et al. [17].

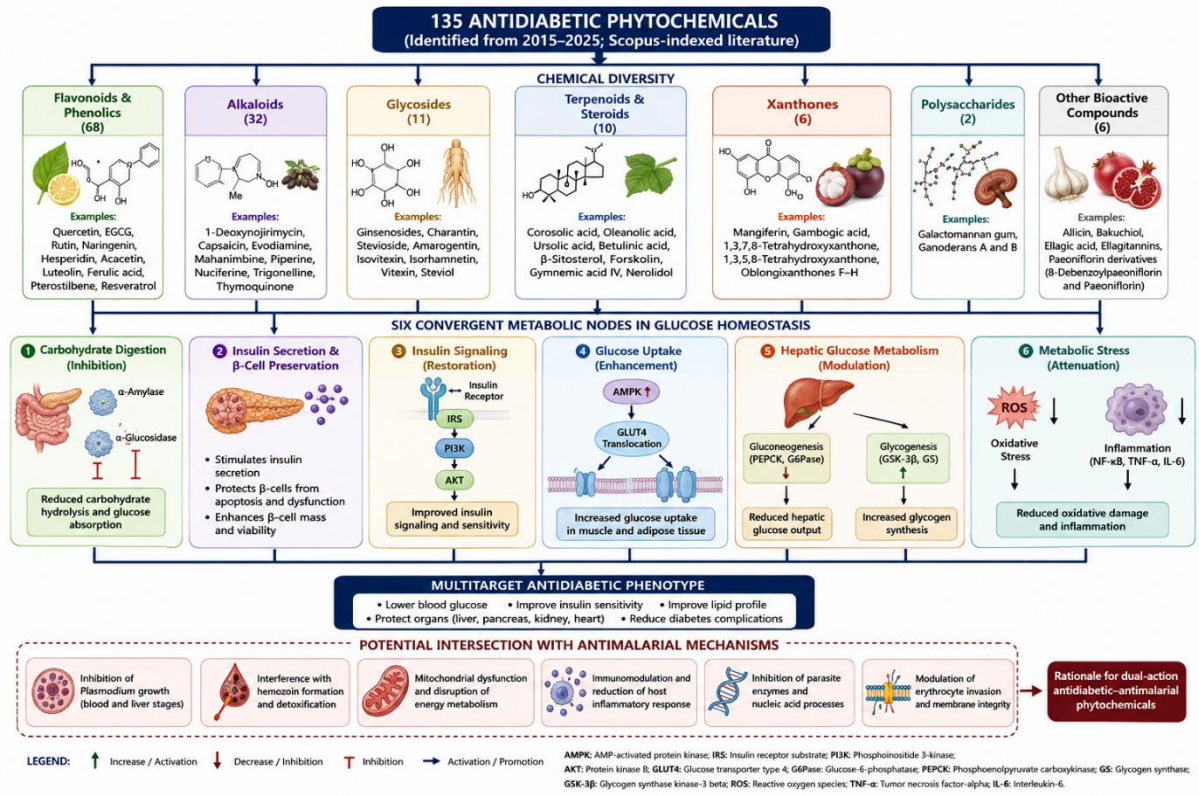


Figure 3. Convergence of structurally diverse antidiabetic phytochemicals on major metabolic pathways relevant to glucose homeostasis.
The figure synthesises mechanisms reported across the eligible literature, including inhibition of carbohydrate-digesting enzymes, modulation of insulin secretion and β-cell function, restoration of insulin signalling through IRS/PI3K/AKT, AMPK/GLUT4-mediated glucose uptake, regulation of hepatic glucose metabolism, and attenuation of oxidative and inflammatory stress. The lower panel illustrates potential biological intersections between these antidiabetic mechanisms and processes relevant to antimalarial activity, providing a conceptual basis for investigating dual-action antidiabetic–antimalarial phytochemicals [7,8,17].

4.1 Alkaloids

Alkaloids constituted the largest chemical class in the present synthesis, comprising 33 compounds. The identified structures included indole, isoquinoline, protoberberine, bisindole, β-carboline, phenanthroindolizidine and related nitrogen-containing scaffolds. Representative compounds included akuammine-related alkaloids, alstonine, berberine, cryptolepine, cycleanine, lycorine, tabernaemontine and other structurally diverse alkaloids. The prominence of alkaloids in antimalarial research is consistent with recent reviews showing that nitrogen-containing natural products provide a particularly broad source of antiplasmodial scaffolds with activity against both drug-sensitive and drug-resistant *P. falciparum* strains [26,30].

Berberine illustrates the mechanistic diversity of this class. In addition to its broad pharmacological activity, berberine and related protoberberine alkaloids have been investigated against parasite enzymes and metabolic pathways, including targets

associated with folate and nucleotide metabolism. More generally, protoberberine and related alkaloids have demonstrated activity against P. falciparum strains with differing drug-susceptibility profiles, supporting their continued investigation as antimalarial lead structures [26,30].

Cryptolepine and structurally related indoloquinoline alkaloids represent another important group. Their antiplasmodial activity has been reported against P. falciparum, including resistant strains, and their mechanisms have been associated with interference with parasite growth, nucleic-acid-associated processes and other intracellular functions. The structural planarity and extended aromatic systems of several indoloquinoline alkaloids may facilitate interactions with biological macromolecules, although the therapeutic relevance of such interactions depends on selectivity and exposure [30].

The diversity of alkaloid scaffolds is further illustrated by the isolation of new phenanthroquinolizidine alkaloids with activity against both chloroquine-sensitive and chloroquine-resistant *P. falciparum*. For example, 15β-hydroxycryptopleurine-N-oxide demonstrated low-nanomolar activity against FCR3 and K1 strains in vitro, although its relatively narrow selectivity window also highlights the importance of cytotoxicity assessment during natural-product lead optimisation [31].

Taken together, the alkaloid group demonstrates that antimalarial activity can arise through multiple pharmacological mechanisms rather than through a single canonical target. Nevertheless, parasite-growth inhibition observed in vitro should not automatically be interpreted as evidence of therapeutic efficacy. Selectivity over host cells, metabolic stability, pharmacokinetic exposure, resistance propensity and in-vivo efficacy remain essential criteria for advancement of alkaloid-derived antimalarial candidates [4,26].

4.2 Terpenoids and steroids

Terpenoids and steroidal compounds constituted the second-largest class, with 24 compounds identified in the literature synthesis. The group included diterpenoid and triterpenoid scaffolds as well as limonoid-related compounds and steroidal structures. Representative examples included andrographolide, azadirachtin, gedunin, nimbolide, nimbinene, perillyl alcohol, salannin and related terpenoid metabolites.

Terpenoids occupy an important position in natural-product antimalarial research because their structural diversity permits interaction with parasite enzymes, membranes and intracellular signalling systems. Reviews of plant-derived antimalarial compounds have documented diterpenes, triterpenes, limonoids and related terpenoids among compounds exhibiting activity against P. falciparum and other Plasmodium species [26,27].

Andrographolide is particularly relevant to the present review because it subsequently appears among the compounds considered for dual antidiabetic–antimalarial activity. Recent evidence confirms antiplasmodial activity of andrographolide and related derivatives, although the available evidence is predominantly preclinical and mechanistic heterogeneity remains substantial. A recent systematic review concluded that andrographolide has demonstrated antiprotozoal activity against P. falciparum but also emphasised the need for further investigation of efficacy, mechanisms, safety and clinical potential (Mohammadi et al., 2025).

Neem-derived limonoids, including azadirachtin, gedunin, nimbolide, nimbinene and salannin, have also attracted attention because of their antiplasmodial activity. However, the mechanistic evidence is not uniform across individual compounds. Consequently, these compounds should be described as terpenoid or limonoid antimalarial candidates rather than assigning a single molecular target to the entire group [26,27].

The potential importance of terpenoids is therefore not simply their abundance but their ability to provide structurally distinct chemical matter. Such structural diversity may be advantageous for addressing parasite targets that are poorly served by current antimalarial chemotypes and for generating molecules with differentiated mechanisms of action [4].

4.3 Flavonoids and phenolic compounds

Sixteen flavonoid and phenolic compounds were identified in the present synthesis. Representative compounds included apigenin, artocarpin, asebogenin, caffeic acid, gallic acid, luteolin, phaseolin, resveratrol and related polyphenolic structures. These compounds have been associated with several antiplasmodial mechanisms, including interference with haem detoxification, parasite proteases, nucleotide metabolism, energy metabolism and oxidative homeostasis [25,27].

The haem detoxification pathway represents an important vulnerability of blood-stage Plasmodium. During haemoglobin digestion, free haem is released and must be converted into the relatively inert crystalline pigment haemozoin. Interference with haem detoxification can therefore increase parasite exposure to toxic haem species. This pathway is a validated pharmacological vulnerability and remains an important framework for investigating natural-product antimalarial activity [32].

Several flavonoids have been investigated for effects on haem or β-haematin formation. Experimental and computational studies have also examined flavonoids against multiple parasite targets. In a multiple-target screening study, 44 Citrus-derived flavonoids were evaluated against PfDHODH, PfDHFR-TS and PfATP4; luteolin emerged as a moderately active compound against both chloroquine-sensitive and chloroquine-resistant *P. falciparum*, with the findings supported by in-silico target analyses and whole-cell testing [33]. Importantly, the study illustrates the value of combining computational prediction with whole-cell assays rather than treating docking scores alone as evidence of antimalarial efficacy.

Luteolin is consequently of particular interest because it illustrates the potential for a single flavonoid scaffold to interact with multiple parasite-associated pathways. Its reported interactions with PfDHODH and PfATP4 suggest possible effects on nucleotide biosynthesis and parasite ion homeostasis, respectively [33]. Such observations provide a mechanistic

rationale for further experimental investigation but should be distinguished from experimentally validated target engagement.

Resveratrol and related polyphenols have also demonstrated antiplasmodial effects in experimental systems. Their activity has been associated with disruption of parasite redox balance and inhibition of parasite proliferation. However, because polyphenols may undergo extensive metabolism and exhibit limited systemic bioavailability, the biological activity of the parent compound in vitro may not directly predict activity following oral administration [27].

Overall, the flavonoid and phenolic group illustrates an important characteristic of plant-derived antimalarial chemistry: structurally related compounds may influence multiple parasite vulnerabilities, while structurally unrelated compounds may converge on the same biological pathway. This convergence provides a useful basis for structure–activity relationship studies and multitarget lead discovery.

4.4 Glycosides and saponins

Sixteen glycosidic compounds were identified in the antimalarial dataset. Representative compounds included datiscosides, galtonosides, 11-epi-toonacilin, azadironolide, verbascoside and other glycosylated natural products. Several compounds were reported to inhibit P. falciparum growth, including activity against parasite strains with different drug-susceptibility profiles [27, 28].

The antimalarial mechanisms of glycosides were less consistently defined than those of several alkaloids and terpenoids. Nevertheless, their inclusion in the present dataset is pharmacologically relevant because glycosylation can substantially alter aqueous solubility, membrane interaction, cellular uptake, metabolism and pharmacokinetic behaviour. Consequently, the biological activity of a glycosylated natural product cannot necessarily be predicted from the activity of its aglycone.

This distinction is especially important for natural-product drug discovery because glycosides may undergo hydrolysis or metabolic transformation before reaching systemic circulation. Therefore, future evaluation should consider both the parent glycoside and potentially active metabolites, together with measurements of exposure and parasite susceptibility [27].

Only three saponin entries were identified in the present synthesis: monodesmosidic saponins and paniculatosoids A–C. Their reported activity against P. falciparum suggests that saponin-rich chemical space deserves further investigation. However, saponins can interact strongly with biological membranes and may display haemolytic or cytotoxic effects depending on their structural characteristics. Their antimalarial development should therefore incorporate selectivity and membrane-toxicity assessments at an early stage.

The relatively small number of glycosides and saponins in the present dataset should not be interpreted as evidence of intrinsically weak antimalarial potential. Rather, it may reflect the comparatively smaller number of studies in which these structurally complex metabolites have been isolated, chemically characterised and tested as individual compounds [27,28].

4.5 Xanthones and related aromatic scaffolds

Seventeen xanthone-related or oxygenated aromatic compounds were identified in the literature synthesis. Representative members included β-mangostin, cowanin, garciniaxanthone, cochinchinone D, cochinchinoxanthone and balsaminol-related structures. Xanthones and related polyoxygenated aromatic scaffolds have attracted considerable interest because of their ability to interact with parasite enzymes and to interfere with intraerythrocytic parasite development [25,27].

Garcinia-derived xanthones provide particularly useful examples of this chemical class. α-Mangostin, for instance, has demonstrated strong in-vitro activity against a chloroquine-resistant *P. falciparum* strain and showed antimalarial activity in a *P. berghei* mouse model, providing evidence that the Garcinia xanthone scaffold can produce activity beyond an isolated biochemical assay [34]. The magnitude of activity observed in vitro nevertheless needs to be interpreted alongside selectivity, pharmacokinetics and toxicity.

Other xanthone-related compounds have been investigated against parasite enzymes involved in haemoglobin digestion and metabolism. Such findings are consistent with the broader observation that natural-product antimalarial compounds can interfere with food-vacuole-associated proteolysis and other essential parasite processes [4,27].

The xanthone group is therefore potentially valuable for medicinal chemistry because oxygenated aromatic scaffolds offer opportunities for systematic substitution, derivatisation and structure–activity optimisation. However, the high lipophilicity of some xanthones may compromise aqueous solubility and systemic exposure, making physicochemical optimisation an important component of lead development.

4.6 Convergent molecular mechanisms of antimalarial phytochemicals

Despite the substantial structural diversity represented by the 109 phytochemicals, their reported activities converged on a limited number of essential biological processes in Plasmodium (Figure 4). Six interconnected mechanistic categories were identified: (i) disruption of haemoglobin digestion and haem detoxification; (ii) inhibition of parasite proteases and other essential enzymes; (iii) interference with nucleotide and energy metabolism; (iv) perturbation of mitochondrial function and redox homeostasis; (v) disruption of membrane transport and ion regulation; and (vi) inhibition of parasite development and progression through intraerythrocytic stages [4,29,32].

4.6.1 Haemoglobin digestion and haem detoxification

Haemoglobin digestion is central to the biology of blood-stage P. falciparum. Proteolytic degradation of host haemoglobin releases haem, which is toxic to the parasite unless detoxified through crystallisation into haemozoin. Consequently,

interference with haem metabolism or haemozoin formation can produce lethal intracellular stress [32].

Natural products that interfere with this pathway are therefore of considerable interest. Flavonoids and xanthone-related compounds identified in the present synthesis have been associated with inhibition of haem or β-haematin formation, providing a plausible mechanism for antiplasmodial activity. Nevertheless, biochemical inhibition of β-haematin formation should be distinguished from demonstration of haemozoin inhibition within intact parasites.

4.6.2 Parasite proteases and essential enzymes

The parasite food vacuole contains proteases, including falcipains and plasmepsins, that participate in haemoglobin degradation. Other essential enzymes participate in glycolysis, nucleotide biosynthesis, redox regulation and membrane physiology. Consequently, inhibition of parasite enzymes represents a major strategy for natural-product antimalarial discovery [4,29].

Several phytochemicals in the present dataset have been associated with protease or metabolic-enzyme inhibition. These include flavonoid and xanthone-related compounds investigated against falcipains, plasmepsins and other parasite enzymes. However, target attribution should be considered strongest when supported by biochemical inhibition, genetic validation or resistance-selection evidence rather than molecular docking alone.

4.6.3 Pyrimidine and energy metabolism

Plasmodium depends heavily on specialised metabolic pathways for nucleotide production and energy generation. PfDHODH, for example, is an established parasite target involved in pyrimidine biosynthesis, while glycolytic enzymes provide essential metabolic functions during blood-stage growth [4,29].

The present review identified phytochemicals associated with DHODH, lactate dehydrogenase and other metabolic targets. Luteolin provides a useful example because its activity has been investigated against PfDHODH and other parasite targets using a combined computational and whole-cell strategy [33]. Such multitarget activity is potentially attractive because disruption of more than one metabolic node may reduce the probability that a parasite population can readily compensate through a single resistance mechanism.

4.6.4 Mitochondrial function and redox homeostasis

The parasite mitochondrion is essential for several aspects of parasite metabolism and is therefore an important antimalarial target. Modern antimalarial drug discovery has identified mitochondrial electron transport, nucleotide biosynthesis and associated metabolic processes as important vulnerabilities [4,29].

Several phytochemicals in the present synthesis have been associated with mitochondrial disruption or altered oxidative balance. Resveratrol and related polyphenols have been investigated for their capacity to perturb parasite redox homeostasis, whereas selected alkaloids and xanthone-related compounds have been associated with mitochondrial effects. These mechanisms may be particularly important because oxidative and metabolic stress can converge to disrupt parasite survival.

4.6.5 Membrane transport and ion regulation

Maintenance of intracellular ion concentrations is essential for Plasmodium survival. PfATP4, a parasite plasma-membrane P-type ATPase involved in sodium regulation, has emerged as a validated antimalarial target and has become a focus of modern target-based drug discovery [4,29].

The identification of luteolin as a compound with predicted interactions with PfATP4, accompanied by whole-cell antiplasmodial activity, illustrates the potential value of natural products for discovering chemically distinct modulators of parasite ion homeostasis [33]. Importantly, computational target prediction should be regarded as hypothesis-generating unless supported by direct target-validation experiments.

4.6.6 Parasite-stage progression and survival

Several phytochemicals in the present dataset inhibit parasite proliferation without a fully resolved molecular target. Phenotypic inhibition remains valuable in antimalarial drug discovery because parasite survival depends on the coordinated operation of numerous biological pathways, and compounds identified through phenotypic screening may subsequently reveal previously unrecognised targets [4].

This is particularly relevant to natural products because chemical scaffolds generated by plants frequently occupy regions of chemical space that are underrepresented in conventional synthetic libraries. Phenotypic activity against resistant parasites may therefore identify compounds capable of circumventing existing resistance mechanisms, provided that adequate selectivity and pharmacokinetic properties can subsequently be demonstrated [26, 27].

4.7 Mechanistic convergence and implications for antimalarial drug discovery

The 109 antimalarial phytochemicals identified in this review therefore demonstrate two complementary forms of diversity: chemical diversity**,** arising from multiple natural-product scaffolds, and mechanistic diversity**,** arising from interference with distinct but interconnected parasite processes. This combination is important in the context of contemporary antimalarial drug discovery because resistance can emerge when parasite populations are exposed repeatedly to compounds acting through the same biological vulnerability [4].

The natural-product chemical space represented by alkaloids, terpenoids, flavonoids, xanthones, glycosides and saponins may consequently provide opportunities for identifying compounds with mechanisms that differ from established antimalarial drugs. Such compounds could serve as direct drug leads, pharmacophores for semisynthetic

optimisation, or starting points for hybrid and combination strategies [4,30].

Most importantly for the present review, the mechanistic map generated in Figure 4 provides the antimalarial counterpart to the metabolic map developed in Section 3. The intersection of these two mechanistic spaces provides a rational framework for identifying phytochemicals that may simultaneously influence glucose metabolism and Plasmodium survival. Such compounds are considered separately in Section 5 as potential dual-action antidiabetic–antimalarial phytochemicals.

The 109 phytochemicals identified in the literature synthesis are distributed across six major chemical classes and converge on interconnected parasite vulnerabilities involving haem detoxification, proteolysis, nucleotide and energy metabolism, mitochondrial/redox homeostasis, membrane transport and ion regulation, and parasite-stage progression. The mechanistic framework synthesises experimental and mechanistic evidence and distinguishes potential target interactions from therapeutically validated efficacy [4,27,29,32].

Table 2. Representative antimalarial phytochemicals, chemical classes, principal molecular mechanisms and predominant evidence levels

Chemical class	No. identified	Representative phytochemicals	Principal molecular targets/mechanisms	Predominant evidence
Alkaloids	33	Alstonine, berberine, cryptolepine, cycleanine, lycorine, tabernaemontine and akuammine-related alkaloids	Parasite enzyme inhibition; nucleic-acid/metabolic interference; mitochondrial and cellular effects; inhibition of parasite proliferation	Predominantly in vitro; selected in-vivo and mechanistic evidence
Terpenoids/steroids	24	Andrographolide, azadirachtin, gedunin, nimbolide, nimbinene, perillyl alcohol, salannin	Parasite growth inhibition; metabolic-enzyme interference; membrane/cellular effects; possible multitarget activity	Predominantly in vitro and in vivo; limited clinical/preclinical evidence for selected compounds
Flavonoids/phenolics	16	Apigenin, artocarpin, asebogenin, luteolin, quercetin, resveratrol, catechin	Haem/β-haematin interference; parasite proteases; PfDHODH; PfATP4; redox modulation	In vitro, in silico and mechanistic studies
Glycosides	16	Datiscosides, galtonosides, 11-epi-toonacilin, azadironolide, verbascoside	Parasite-growth inhibition; possible membrane, metabolic and intracellular effects	Predominantly in vitro
Xanthones and related aromatic compounds	17	α-/β-Mangostin, cowanin, garciniaxanthone, cochinchinone D, cochinchinoxanthone, balsaminol-related compounds	Parasite enzyme inhibition; haemoglobin-digestion-associated pathways; mitochondrial/cellular effects; intraerythrocytic growth inhibition	Predominantly in vitro and mechanistic; selected in-vivo evidence
Saponins	3	Monodesmosidic saponins; paniculatosoids A–C	Parasite-growth inhibition; possible membrane-associated effects	In vitro and selected animal evidence
Total	**109**	—	Multiple complementary parasite targets and pathways	—

The Counts correspond to phytochemicals identified in the present literature synthesis. Representative compounds are provided to illustrate chemical and mechanistic diversity and do not imply that all compounds within a chemical class act through all mechanisms listed. Mechanistic assignments should be interpreted according to the experimental evidence available for each individual compound.

5. Dual-Action Phytochemicals Targeting Diabetes and Malaria

The preceding sections demonstrate substantial chemical and mechanistic diversity among phytochemicals investigated for antidiabetic and antimalarial activity. The most distinctive finding of the present synthesis is the comparatively small subset of compounds for which the literature reports activity relevant to both disease processes. Of the 258 phytochemicals identified across the eligible literature, 14 were classified in the present synthesis as having reported dual antidiabetic–antimalarial activity. These comprised five alkaloid-related compounds, six flavonoid/phenolic compounds, two terpenoid/triterpenoid compounds and one xanthone.

The 14-compound subset represents approximately 5.4% of the total phytochemical pool identified in the review. This relatively small proportion should not be interpreted as evidence that dual biological activity is inherently uncommon. Rather, it may reflect the fact that antidiabetic and antimalarial activities are usually investigated independently, using different experimental systems, biological endpoints and target frameworks. Consequently, compounds capable of producing activity in both domains may remain unidentified unless screening strategies deliberately integrate metabolic and antiparasitic endpoints.

The dual-action concept is biologically plausible because diabetes and malaria can involve partially overlapping processes, including altered glucose availability, oxidative stress, inflammation, endothelial dysfunction and changes in erythrocyte biology. Nevertheless, the pharmacological mechanisms responsible for the two activities do not necessarily have to be identical. A compound may act on host glucose metabolism while independently targeting an essential parasite process. Alternatively, a common physicochemical or biochemical property, such as redox activity, may generate apparently complementary effects in the host and parasite. The present review therefore treats “dual action” as a pharmacological phenotype rather than as evidence that a single molecular target mediates both activities.

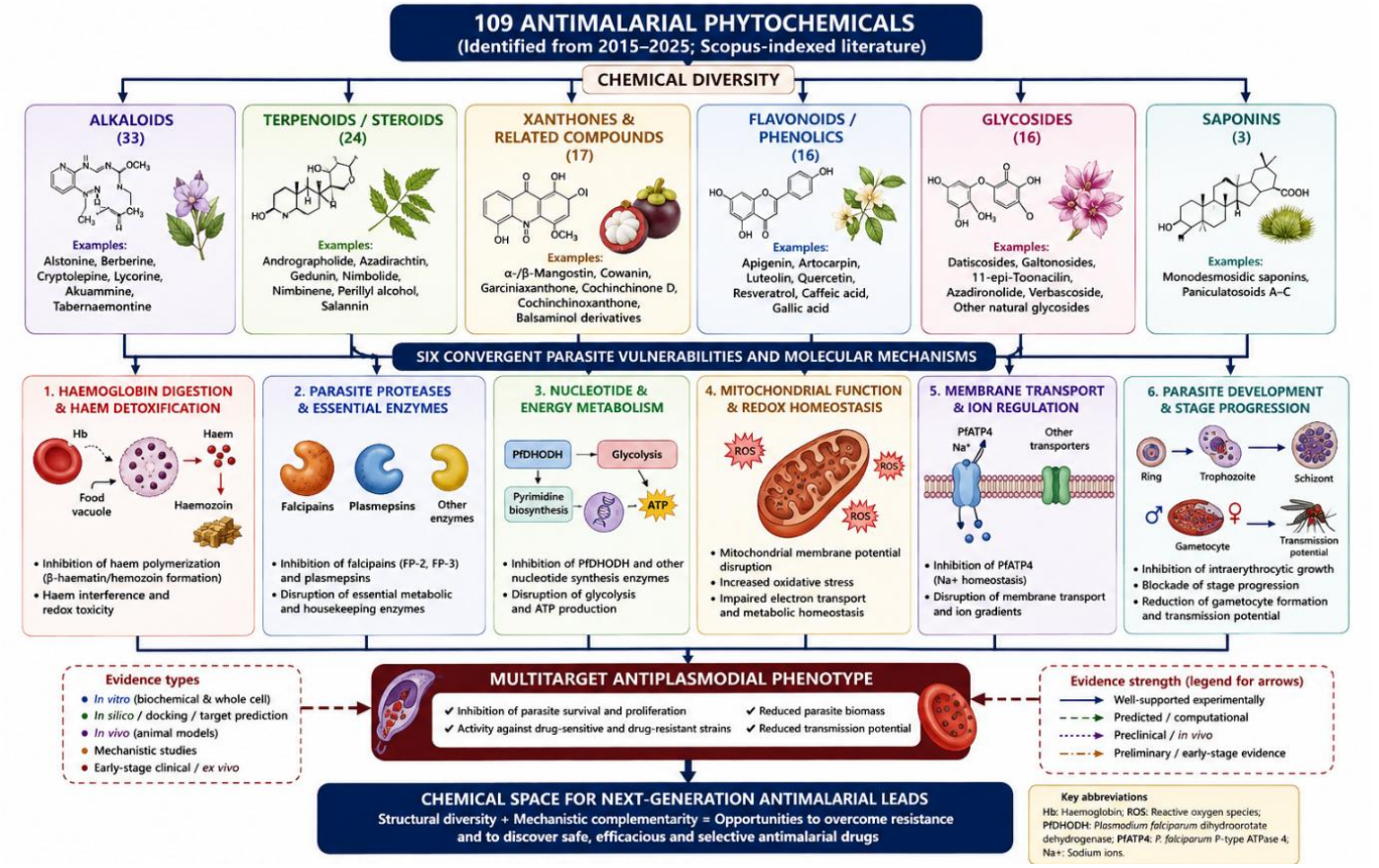


Figure 4. Chemical diversity and convergent molecular mechanisms of antimalarial phytochemicals identified in the review.

5.1 Chemical diversity of the dual-action phytochemicals

The 14 compounds span several structurally distinct chemical classes, supporting the proposition that dual antidiabetic–antimalarial activity is not restricted to a single natural-product scaffold. The alkaloid group comprises berberine, cryptolepine, jatrorrhizine and palmatine, together with an isoquinoline-related entry that requires clarification at the compound level. The flavonoid/phenolic group comprises apigenin, catechin, curcumin, kaempferol, luteolin and quercetin. Andrographolide and maslinic acid constitute the terpenoid/triterpenoid group, while mangostin represents the xanthone group.

This structural breadth is important from a medicinal-chemistry perspective. The compounds differ in heteroatom content, aromaticity, hydroxylation, methoxylation, ring fusion, stereochemistry and overall lipophilicity. Nevertheless, their reported activities converge on biological processes relevant to glucose homeostasis and Plasmodium survival. The dual-action space should therefore be viewed as a mechanism-oriented chemical space, rather than simply as a collection of structurally related compounds.

The evidence matrix in Table 3 distinguishes between demonstrated biological activity and proposed molecular mechanisms. This distinction is necessary because enzyme inhibition, molecular docking, cellular activity, parasite-growth inhibition and animal efficacy represent different levels of pharmacological evidence. In particular, a predicted interaction with a parasite protein should not be presented as equivalent to experimentally validated target engagement.

5.2 Alkaloids: parallel modulation of metabolic and parasite targets

5.2.1 Berberine

Berberine is one of the strongest candidates in the dual-action dataset because both its antidiabetic and antimalarial pharmacology have been investigated extensively. On the metabolic side, berberine has been associated with glucose-lowering effects through multiple mechanisms, including modulation of carbohydrate digestion and glucose transport, AMPK-associated metabolic regulation, insulin sensitivity and intestinal glucose handling. A systematic review and meta-analysis of clinical studies concluded that berberine can produce clinically relevant glucose-lowering effects in people with type 2 diabetes, although heterogeneity among studies and limitations in the evidence base remain important considerations [35]. A recent mechanistic review likewise describes AMPK, glucose metabolism, lipid metabolism and insulin-related pathways among the major biological effects of berberine [36].

Its antimalarial activity is supported by a separate body of literature. Berberine has demonstrated antiplasmodial activity and has been investigated against parasite-associated targets, including DHFR–TS. Importantly, molecular-docking evidence

for DHFR–TS should be classified as predicted target interaction, rather than definitive target validation [37]. Thus, berberine provides a particularly useful example of parallel host–parasite pharmacology: its glucose-regulatory effects are directed principally toward host metabolic pathways, whereas its antimalarial effects involve parasite growth and metabolism. The principal limitation is translational. Berberine's pleiotropic pharmacology is accompanied by complex pharmacokinetics and relatively limited systemic bioavailability. Accordingly, its classification as a dual-action compound identifies a promising pharmacological scaffold but does not establish it as a dual-purpose clinical therapy.

5.2.2 Cryptolepine

Cryptolepine is an indoloquinoline alkaloid derived principally from *Cryptolepis sanguinolenta*. The post-2015 literature documents a broad pharmacological profile encompassing antiplasmodial, antidiabetic, anti-inflammatory and other biological activities [38]. The review literature specifically describes cryptolepine as possessing antimalarial and antihyperglycaemic/antidiabetic properties, making it one of the more plausible members of the dual-action group.

The antimalarial pharmacology of cryptolepine is substantially better established than any specific antidiabetic molecular mechanism. Its planar indoloquinoline structure has been associated with interactions with parasite-associated targets and intracellular processes, while cryptolepine derivatives have been investigated as antimalarial lead structures. The evidence therefore supports antiplasmodial activity with mechanistic investigation, but the molecular basis of its antidiabetic activity should not be presented as definitively established.

Cryptolepine also illustrates an important development issue for dual-action natural products: biological potency must be interpreted alongside host-cell toxicity and selectivity. A compound capable of interacting strongly with parasite macromolecules may also interact with host DNA or other cellular targets. Consequently, therapeutic selectivity must remain a central criterion during optimisation.

5.2.3 Jatrorrhizine

Jatrorrhizine is a protoberberine-type isoquinoline alkaloid occurring in several medicinal plants. Contemporary reviews document its pharmacological activities and report antiprotozoal activity against *P. falciparum*. A review published in *Frontiers in Pharmacology* reports antiplasmodial activity against the chloroquine-resistant K1 strain and summarises its broader pharmacological profile [39].

The Nigerian-flora literature provides particularly useful evidence because jatrorrhizine was isolated alongside palmatine and columbamine from *Enantia chlorantha*. Jatrorrhizine demonstrated activity against chloroquine-sensitive *P. falciparum* D6, with an IC50 of approximately 2.2 µM in the reported assay.

However, the evidence supporting its antidiabetic classification is less robust than that for berberine. Consequently, jatrorrhizine should be described as a reported dual-action candidate with stronger antiplasmodial evidence than compound-specific antidiabetic target validation. This evidence asymmetry is important and should be visible in Table 3.

5.2.4 Palmatine

Palmatine is another protoberberine alkaloid represented in the dual-action dataset. Its antidiabetic activity has been investigated experimentally against α-amylase, α-glucosidase and dipeptidyl peptidase-IV (DPP-IV). In an in-vitro study, palmatine inhibited all three enzymes, with the strongest inhibition observed against α-amylase; molecular docking was subsequently used to investigate the interactions with the enzyme targets [40].

Palmatine also demonstrated antiplasmodial activity against *P. falciparum* D6 in the *E. chlorantha* alkaloid study, with a reported IC50 of approximately 1.90 µM.

The evidence therefore supports a particularly clear parallel-target model: carbohydrate-metabolising enzymes on the host/metabolic side and parasite-growth inhibition on the antimalarial side. Nevertheless, the antidiabetic evidence is primarily biochemical/in-vitro, whereas the antimalarial evidence is primarily parasite-cell based. This difference should prevent the compound from being described as a clinically validated dual-action therapeutic.

5.2.5 The unspecified "isoquinoline alkaloid" entry

The original manuscript lists "isoquinoline alkaloid(s)" as one of the five alkaloid dual-action compounds. This terminology should not be retained in the final compound-level table.
Isoquinoline alkaloid is a chemical class, not an individual phytochemical. The Nigerian *Enantia chlorantha* study, for example, specifically identified jatrorrhizine, palmatine and columbamine rather than an unspecified isoquinoline alkaloid.

5.3 Flavonoids and phenolics: the largest dual-action chemical subgroup

Six flavonoid/phenolic compounds—apigenin, catechin, curcumin, kaempferol, luteolin and quercetin—were identified in the manuscript as dual-action compounds. Their prominence is consistent with the broader representation of flavonoids and phenolics among the 135 antidiabetic phytochemicals identified in the review.

5.3.1 Apigenin

Apigenin is a flavone with documented effects on glucose metabolism, oxidative stress and inflammatory signalling. Its antidiabetic pharmacology includes modulation of glucose metabolism and pathways associated with insulin sensitivity and carbohydrate utilisation.

Its antiplasmodial activity has been investigated alongside other flavonoids, particularly in relation to haem-targeted mechanisms. Studies of flavonoid structure–activity relationships demonstrate that selected flavonoids can bind haem and interfere with parasite haem detoxification, although the magnitude of activity depends strongly on structural substitution patterns (e.g., methoxylation) [41].

Apigenin should therefore be classified as a dual-action candidate supported by cellular/biochemical antimalarial evidence and preclinical metabolic evidence, rather than as a compound with a single validated molecular target shared by diabetes and malaria.

5.3.2 Catechin

Catechin illustrates a potentially distinctive redox-based model of dual activity. Its antidiabetic relevance is associated principally with antioxidant activity and modulation of glucose and metabolic homeostasis. Its antimalarial activity, however, has been experimentally associated with increased oxidative stress within *P. falciparum*.

A particularly informative study isolated (+)-catechin from *Garcinia celebica* and demonstrated inhibition of chloroquine-resistant *P. falciparum* growth. Catechin inhibited parasite development at the trophozoite and schizont stages, with the study providing evidence that oxidative stress contributed to the antiplasmodial effect [42].

This apparent host–parasite redox asymmetry is conceptually important. A compound with antioxidant effects in mammalian metabolic systems may, under parasite-specific conditions, contribute to oxidative injury within the parasite. However, this should be regarded as a mechanistic hypothesis requiring concentration-dependent and compartment-specific validation rather than an established therapeutic principle.

5.3.3 Curcumin

Curcumin is a polyphenolic compound with extensive preclinical evidence for effects on glucose metabolism, insulin signalling, inflammation and oxidative stress. A systematic review of studies of curcumin in diabetes concluded that the compound has demonstrated beneficial effects across several metabolic endpoints, although the heterogeneity of formulations, doses and clinical studies limits definitive conclusions regarding therapeutic efficacy [43].

Its antimalarial activity has also been investigated experimentally. Curcumin and curcumin-derived compounds have demonstrated activity against *P.* falciparum, while PfATP6 has been proposed as a target for curcumin-related antimalarial activity. Importantly, studies of curcumin analogues have combined molecular docking with whole-cell parasite assays, illustrating the distinction between predicted target binding and experimentally observed parasite inhibition [44].

In addition, experimental work in *P. berghei*-infected mice reported dose-dependent suppression of parasitaemia and investigated GSK3β-associated mechanisms [45]. Curcumin therefore represents one of the more experimentally developed flavonoid/phenolic candidates in the dual-action group, although its poor aqueous solubility and limited bioavailability remain important translational barriers.

5.3.4 Kaempferol

Kaempferol has substantial preclinical evidence for antidiabetic activity. A comprehensive review identified effects on glucose metabolism, insulin resistance, pancreatic β-cell preservation, lipid metabolism and diabetes-associated complications [46].

Its antimalarial activity has been associated with parasite enzyme inhibition and oxidative processes. For example, experimental work examining plant secondary metabolites against *P. falciparum* plasmepsin V reported noncompetitive inhibition by kaempferol and proposed interference with parasite protein export as a possible mechanism.

The evidence therefore supports kaempferol as a preclinical dual-action scaffold**,** with relatively stronger mechanistic development on the antidiabetic side than on the antimalarial side.

5.3.5 Luteolin

Luteolin is particularly important because it illustrates the possibility of multitarget activity within both pharmacological domains. Its antidiabetic effects include carbohydrate-enzyme inhibition, antioxidant activity and effects on glucose transport and insulin-associated signalling.

On the antimalarial side, luteolin has been investigated against multiple *P. falciparum* targets. Computational studies have evaluated its interactions with PfDHFR-TS, PfDHODH and falcipain-2 using molecular docking, molecular dynamics and MM-GBSA calculations [47].

Independent experimental work on Citrus flavonoids has also examined luteolin against PfDHODH and PfATP4 in combination with whole-cell antiplasmodial assays, providing a stronger basis for considering these target interactions as mechanistically relevant hypotheses rather than docking-only observations.

Luteolin therefore represents a multitarget candidate, but the evidence hierarchy should remain explicit: molecular-dynamics or docking predictions are mechanistic hypotheses unless supported by direct biochemical or genetic target validation.

5.3.6 Quercetin

Quercetin is one of the most extensively investigated flavonoids in relation to both metabolic and antiparasitic pharmacology. Its antidiabetic evidence includes modulation of glucose and lipid metabolism, oxidative stress, inflammation and diabetes-associated complications. A systematic review and meta-analysis of rodent models of diabetic nephropathy reported beneficial effects on metabolic, inflammatory and oxidative parameters [22].

Quercetin has also demonstrated antiprotozoal activity, including activity against drug-resistant *P. falciparum* strains. A recent review summarising the evidence reported susceptibility

of multiple *P. falciparum* strains and noted interactions with other flavonoids such as luteolin and apigenin.

Mechanistically, flavonoid–haem interactions are particularly relevant. Studies of polymethoxylated flavonoids have demonstrated that heme binding can influence parasite haem detoxification and that structural substitution affects the strength of this interaction (Dounia et al., 2020).

Quercetin should consequently be classified as a broad preclinical dual-action scaffold, rather than as a clinically validated dual-purpose drug.

5.4 Terpenoids and triterpenoids

5.4.1 Andrographolide

Andrographolide is the principal diterpenoid lactone associated with *Andrographis paniculata* and is among the most compelling dual-action candidates in the present dataset.

On the antidiabetic side, experimental work using 3T3-L1 adipocytes demonstrated that andrographolide increased glucose uptake and increased PPARγ and GLUT4 expression, with 5.6 μM identified as the most effective concentration in that experimental system [48].

Its antimalarial activity is supported by experimental investigations of *A. paniculata* diterpenoids against *P. falciparum*. Dwivedi et al. [49] evaluated antimalarial activity in vitro and characterised antimalarial-active diterpenoid fractions, supporting the relevance of andrographolide-containing chemical space to parasite inhibition.

Earlier experimental work has also reported in-vitro antiplasmodial and chloroquine-resistance-reversal activity for andrographolide-containing preparations. The overall evidence therefore supports a parallel host–parasite model, in which PPARγ/GLUT4-associated glucose handling is distinct from parasite-directed activity.

This compound is particularly attractive because its two pharmacological activities do not need to depend on a shared target. Instead, the therapeutic proposition is that a single scaffold may simultaneously influence host metabolic dysfunction and parasite survival. Nevertheless, andrographolide's physicochemical and pharmacokinetic limitations require optimisation before its dual-action potential can be translated.

5.4.2 Maslinic acid

Maslinic acid is a pentacyclic triterpenoid with documented metabolic and antiparasitic properties. The present manuscript classifies it as a dual-action compound but acknowledges that its mechanistic evidence is comparatively underdeveloped.

A major methodological issue must nevertheless be acknowledged: the direct experimental demonstration of maslinic-acid activity against *P. falciparum* cited in the literature was published before the review's 2015 cutoff. The study demonstrated dose-dependent inhibition of Dd2 and 3D7 intraerythrocytic parasite growth and stage arrest [50].

Therefore, maslinic acid should not be presented as a dual-action compound established solely from primary studies within the 2015–2025 search window. If it is retained, the manuscript should explicitly state that its inclusion derives from post-2015 secondary literature or from the authors' broader evidence synthesis, while acknowledging that the pivotal direct antiplasmodial experiment predates the formal search window.

Its antidiabetic activity is sufficiently plausible to retain it as a candidate scaffold, but its evidence level should be classified as preclinical/undercharacterised, not as a validated dual-action lead.

5.5 Xanthones: mangostin as a dual-action scaffold

Mangostin is the sole xanthone represented in the manuscript's 14-compound dual-action group. The antidiabetic evidence is supported by recent investigations of Garcinia xanthones. α-Mangostin has demonstrated α-amylase and α-glucosidase inhibitory activity, while γ-mangostin has shown antihyperglycaemic activity in diet-induced diabetic mice and effects involving AMPK, PPARγ and glucose uptake [51]. A 2024 *Journal of Ethnopharmacology* review likewise identified α-mangostin among plant-derived compounds with α-glucosidase inhibitory activity.

Its antimalarial evidence is also experimentally relevant. Mangostin has been investigated against *P. falciparum*, including effects on infected erythrocyte membranes and antiplasmodial activity. A 2020 study reported in-vitro antiplasmodial and chloroquine-resistance-reversal effects of mangostin, while a subsequent 2024 study examined its effects on the functional integrity of infected and uninfected erythrocyte membranes [52, 53].

The present evidence therefore supports mangostin as a preclinical dual-action xanthone scaffold, although the specific molecular mechanism linking its antidiabetic and antimalarial activities remains incompletely resolved [54]. The original manuscript's statement that its antimalarial action specifically reflects inhibition of haemoglobin degradation should consequently be softened unless a direct mechanistic study is cited.

5.6 Evidence hierarchy for the 14 dual-action compounds

The most important conceptual contribution of this section is that "dual action" should not be treated as a binary property. The 14 compounds differ substantially in the strength, reproducibility and biological level of their evidence. The present synthesis therefore proposes a five-level evidence hierarchy:

- **Level I — Biochemical evidence:** activity demonstrated against an isolated enzyme or biochemical process.
- **Level II — Cellular/parasite evidence:** inhibition demonstrated in cultured mammalian cells or *Plasmodium*-infected erythrocytes.
- **Level III — Mechanistically supported preclinical evidence:** cellular activity accompanied by biochemical,

pharmacological or mechanistic evidence linking the phenotype to a defined pathway or target.

- **Level IV — In-vivo evidence:** reproducible activity demonstrated in an appropriate animal model.
- **Level V — Human/clinical evidence:** evidence generated in human clinical studies with relevant endpoints.

Under this framework, most of the 14 compounds remain in **Levels I–III**, while only selected compounds have stronger animal evidence. The existence of evidence on both sides of the diabetes–malaria interface should therefore not be confused with demonstration of clinical dual efficacy.

5.7 Three mechanistic models of dual action

The evidence supports three conceptual models for dual-action phytochemicals (Figure 5).

Model 1: Parallel host–parasite targeting. A single compound acts through a host metabolic mechanism while independently affecting a parasite-specific target or process. Andrographolide provides an illustrative example through PPARγ/GLUT4-associated glucose regulation on the host side and antiplasmodial activity on the parasite side [48,49].

Model 2: Convergent redox modulation.
The same broad physicochemical property may generate different consequences in host and parasite systems. Catechin illustrates this possibility: antioxidant activity is relevant to metabolic protection, whereas increased oxidative stress contributes to parasite growth inhibition [42]

Model 3: Distributed multitarget engagement.
A single phytochemical interacts with several molecular targets distributed across metabolic and parasite pathways. Luteolin and quercetin provide useful examples, although many proposed parasite targets remain computationally predicted rather than experimentally validated [47]. These three models provide a mechanistic framework for distinguishing genuine multifunctionality from the simple observation that a compound happens to possess two unrelated biological activities.

5.8 Therapeutic significance and limitations

The identification of dual-active phytochemicals provides a rational starting point for multifunctional drug discovery, but it should not be interpreted as evidence that these compounds can replace established antidiabetic or antimalarial therapies. The principal scientific value of the 14-compound group is that it identifies chemical scaffolds for which both pharmacological domains can be investigated within a unified experimental framework.

The major translational challenges include potency, selectivity, pharmacokinetics, bioavailability, toxicity and target validation. These limitations are especially important for natural products because concentrations that produce enzyme inhibition or parasite killing in vitro may not be achievable in relevant tissues following administration.

Future investigations should therefore progress from reproducible dual phenotypic screening to biochemical target validation, genetic target deconvolution, structure–activity relationship analysis, ADMET profiling, pharmacokinetic/pharmacodynamic studies and appropriately designed in-vivo models. Importantly, experiments should eventually evaluate the compounds in comorbidity-relevant models, because antidiabetic and antimalarial efficacy demonstrated independently does not necessarily predict efficacy in a diabetic host infected with *Plasmodium*.

Table 3. Evidence matrix for 14 chemically defined dual-action phytochemicals targeting diabetes and malaria

No.	Compound	Chemical class	Antidiabetic evidence	Antimalarial evidence	Principal/proposed mechanisms	Experimental model(s)	Evidence level*
1	**Berberine**	Isoquinoline/protoberberine alkaloid	Glucose-lowering effects; α-glucosidase inhibition; AMPK and insulin-sensitivity pathways	Antiplasmodial activity; DHFR–TS interaction proposed	AMPK; glucose transport; DHFR–TS	Clinical synthesis; biochemical; parasite culture; in silico	III–V
2	**Cryptolepine**	Indoloquinoline alkaloid	Reported antihyperglycaemic and insulin-related effects	Potent antiplasmodial activity; parasite cellular/DNA-associated mechanisms proposed	Insulin/glucose regulation; parasite DNA/cellular processes	Preclinical; parasite culture	II–III
3	**Jatrorrhizine**	Protoberberine alkaloid	Reported insulin-secretion and metabolic effects	*P. falciparum* D6 activity; activity also reported against resistant strains	Insulin-related pathways; parasite target unresolved	In vitro; preclinical; parasite culture	II–III
4	**Palmatine**	Protoberberine alkaloid	α-Amylase, α-glucosidase and DPP-IV inhibition	*P. falciparum* D6 inhibition	Carbohydrate-digestive enzymes; DPP-IV; parasite growth	Enzyme assay; docking; parasite culture	I–II
5	**Columbamine**	Protoberberine/isoquinoline alkaloid	α-Glucosidase-related activity; reported antihyperglycaemic	*P. falciparum* D6 inhibition; IC50 ≈2.16 μM reported	Carbohydrate metabolism; parasite target unresolved	Enzyme/bioautography; parasite culture;	I–II

No.	Compound	Chemical class	Antidiabetic evidence	Antimalarial evidence	Principal/proposed mechanisms	Experimental model(s)	Evidence level*
			activity in alkaloid-containing preparations			preclinical alkaloid preparations	
6	**Apigenin**	Flavone	Glucose-metabolic regulation; suppression of gluconeogenic processes; antioxidant effects	Antiplasmodial activity; β-haematin/haem-related mechanisms proposed	Glucose metabolism; haem detoxification	Biochemical; cellular; parasite assays	I–III
7	**Catechin**	Flavan-3-ol	Antioxidant and glucose-regulatory activity	*P. falciparum* growth inhibition associated with oxidative stress	Redox modulation	Cellular/metabolic models; parasite culture	II–III
8	**Curcumin**	Polyphenol	Glucose control; insulin signalling; PPARγ/GLUT4-associated mechanisms	Antiplasmodial activity; GSK3β/PfATP6-associated mechanisms proposed	PPARγ; GLUT4; GSK3β; PfATP6	Cellular; animal; clinical synthesis; in silico	II–IV
9	**Kaempferol**	Flavonol	Glucose uptake; insulin sensitivity; β-cell protection; AMPK/Akt	Parasite enzyme and oxidative mechanisms; PfPMV activity reported	AMPK/Akt; PfPMV; redox processes	Cellular; biochemical; animal	II–III
10	**Luteolin**	Flavone	α-Glucosidase inhibition; GLUT4-related activity; antioxidant effects	PfLDH, PfDHODH, PfDHFR-TS and PfATP4 interactions/activity proposed	Carbohydrate metabolism; parasite metabolic enzymes	Enzyme assays; parasite culture; docking/MD	I–III
11	**Quercetin**	Flavonol	Glucose/lipid metabolism; insulin and glucokinase-related effects; antioxidant activity	Activity against *P. falciparum*; β-haematin/haem-related mechanisms proposed	Glucose metabolism; haem detoxification	Animal; cellular; biochemical	II–III
12	**Andrographolide**	Diterpenoid lactone	Increased glucose uptake; PPARγ and GLUT4 expression	Antiplasmodial activity; interference with parasite metabolism/growth	PPARγ; GLUT4; parasite metabolism	3T3-L1 cells; parasite culture; preclinical	II–III
13	**Maslinic acid**	Pentacyclic triterpenoid	Reported antidiabetic/metabolic activity	Inhibits intraerythrocytic *P. falciparum*; stage arrest; PfSUB1/M16 protease mechanisms proposed	Metabolic enzymes; PfSUB1; parasite metalloproteases	Parasite culture; preclinical metabolic studies	II–III†
14	**Mangostin**	Xanthone	α-Amylase/α-glucosidase inhibition; antihyperglycaemic effects reported for mangostin congeners	Antiplasmodial activity; erythrocyte/parasite membrane and cellular effects	Carbohydrate digestion; parasite membrane/cellular processes	Enzyme assays; animal; parasite culture	II–IV

Evidence levels: I = biochemical/enzyme evidence; II = cellular or parasite evidence; III = mechanistically supported preclinical evidence; IV = in-vivo evidence; V = human/clinical evidence.

† Maslinic acid qualification: the direct primary evidence for antimalarial activity predates the formal 2015–2025 search window. Moneriz et al. [55] demonstrated inhibition of P. falciparum Dd2 and 3D7 and subsequently investigated PfSUB1 and M16-family proteases as possible targets.

5.9. Audit and reconciliation of the dual-action phytochemical dataset

A compound-level audit was undertaken to verify the 14 phytochemicals initially classified in this review as possessing both antidiabetic and antimalarial activity. This audit was necessary because the original dataset contained an imprecise entry described as "isoquinoline alkaloid(s)" rather than identifying the corresponding molecule. The underlying literature indicates that this category should be represented by columbamine, which was isolated together with the structurally related isoquinoline alkaloids jatrorrhizine and palmatine from *Enantia chlorantha* and demonstrated antiplasmodial activity against *Plasmodium falciparum* [56]. The three compounds were reported individually, with jatrorrhizine, palmatine and columbamine exhibiting IC50 values of approximately 2.20, 1.90 and 2.16 µM, respectively, against the chloroquine-sensitive D6 strain.

The classification of columbamine as a dual-action phytochemical is further supported by post-2015 evidence for antidiabetic activity. Gaurav et al. [57] identified columbamine in an antidiabetic polyherbal formulation using TLC–MS bioautography and reported its association with α-glucosidase inhibitory activity. In addition, experimental work on *Coptis chinensis* identified columbamine among its principal alkaloids and reported antihyperglycaemic effects of the alkaloid-containing preparation in cellular and streptozotocin-induced diabetic models [58]. Thus, columbamine provides a chemically defined replacement for the previously vague "isoquinoline

alkaloid(s)" entry and restores the compound-level integrity of the 14-member dataset.

A second methodological issue concerns maslinic acid. The direct experimental evidence demonstrating inhibition of *P. falciparum* by maslinic acid was published before the 2015–2025 literature window specified in the Methods. Moneriz et al. [59] demonstrated dose-dependent inhibition of intraerythrocytic *P. falciparum* Dd2 and 3D7 parasites and subsequently reported evidence implicating parasite proteolytic processes, including PfSUB1 and M16-family metalloproteases, as potential targets. Consequently, maslinic acid is retained in the present synthesis because subsequent literature continues to recognise its antimalarial and metabolic pharmacology, but its evidence status is explicitly qualified. Its inclusion should not be interpreted as evidence that the pivotal primary antimalarial experiment was generated within the formal 2015–2025 search window. Instead, maslinic acid is retained as a historically established dual-action candidate corroborated by subsequent literature, with the pre-2015 primary evidence transparently identified.

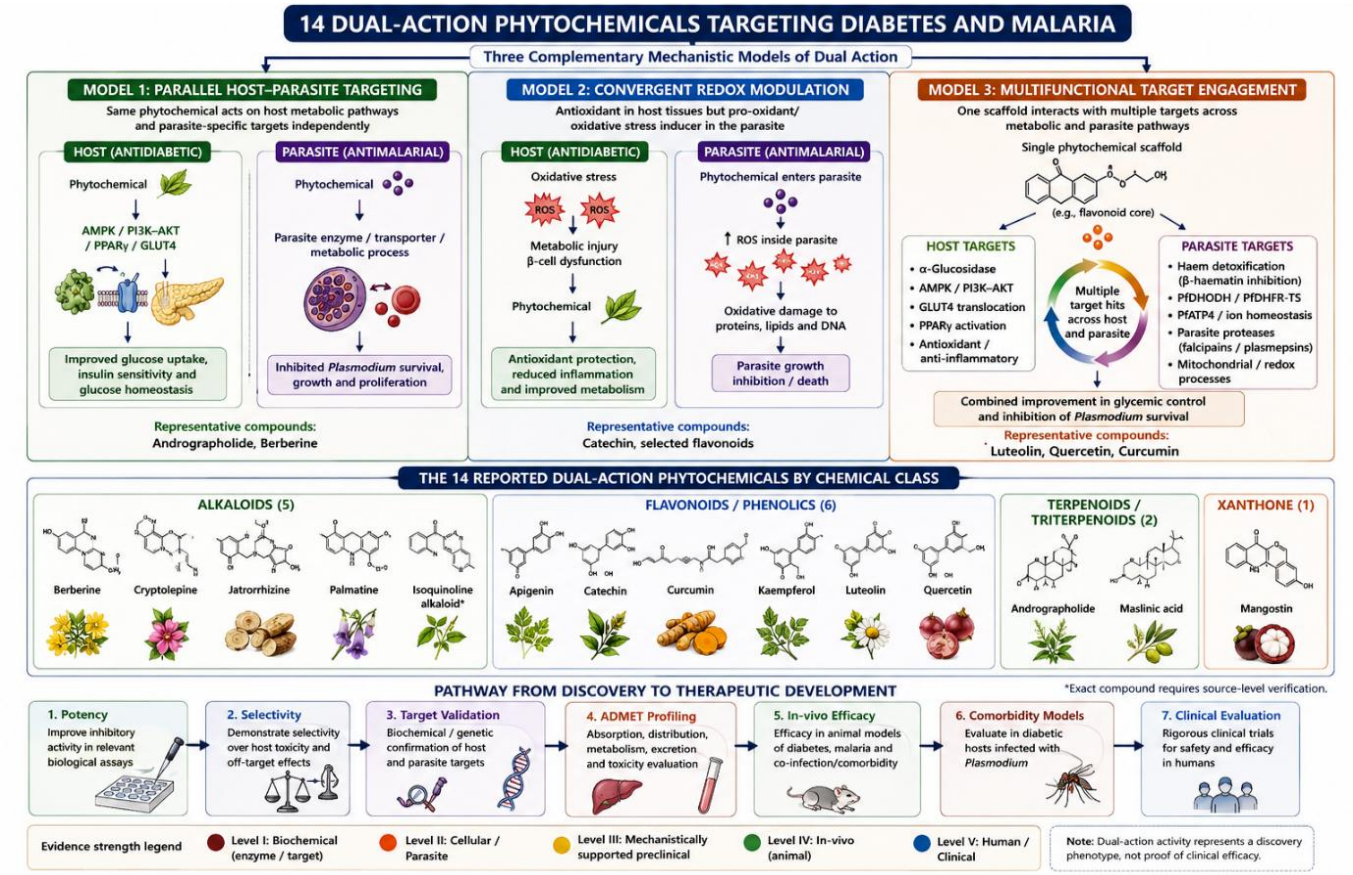


Figure 5. Integrated conceptual framework for dual-action phytochemicals targeting host metabolic dysfunction and Plasmodium survival

The 14 compounds identified in the present synthesis can be conceptualised through three complementary pharmacological models: (1) parallel host–parasite targeting, in which a compound independently modulates host metabolic pathways and parasite survival mechanisms; (2) convergent redox modulation, in which redox activity may protect host metabolic tissues while promoting parasite oxidative stress; and (3) multifunctional target engagement, in which a single chemical scaffold interacts with multiple metabolic and parasite-associated targets. The framework emphasises that dual biological activity represents a discovery phenotype rather than evidence of clinical efficacy. Progression toward therapeutic development requires target validation, structure–activity optimisation, ADMET assessment, selectivity studies and in-vivo validation.

6. Translational Challenges and Future Directions

The identification of 14 chemically defined dual-action phytochemicals provides a useful discovery framework, but their reported biological activities remain insufficient for therapeutic development. Most evidence is derived from biochemical, cellular, parasite-culture or computational studies, while target engagement, pharmacokinetics, safety and efficacy in disease-relevant models remain incompletely established. Natural-product drug discovery increasingly combines phenotypic screening with target identification, structural optimisation and systems-level approaches to overcome these translational barriers [60].

6.1 Target Validation and Mechanistic Confirmation

A major priority is to distinguish observed biological activity from experimentally validated molecular mechanisms. Molecular docking and related computational approaches can generate useful hypotheses, but predicted ligand–target interactions should not be presented as definitive mechanisms without biochemical, genetic or cellular validation. This is particularly important for antimalarial phytochemicals because *Plasmodium* possesses numerous potentially druggable pathways, including folate metabolism, mitochondrial function, parasite proteases, haem metabolism and essential transport systems [4, 61].

For the 14 dual-action compounds, future studies should therefore combine target-based assays, genetic target deconvolution, metabolomics and transcriptomic/proteomic profiling to determine whether the proposed host and parasite targets are causally responsible for the observed effects. This distinction is especially important because evidence for the two activities often originates from different experimental systems.

6.2 Pharmacokinetics, Bioavailability and Formulation

Biological potency does not necessarily translate into therapeutic efficacy. Many phytochemicals exhibit poor aqueous solubility, chemical instability, rapid metabolism or inadequate systemic exposure, collectively limiting their druggability [62]. Consequently, promising dual-action candidates should undergo early ADME/ADMET profiling, followed where necessary by formulation optimisation using approaches such as lipid-based systems, nanoparticles or other delivery platforms. Formulation should, however, follow demonstration of reproducible pharmacological activity and an acceptable therapeutic window.

6.3 Selectivity, Toxicity and Structure–Activity Relationships

Multitarget activity may enhance pharmacological efficacy but can also increase off-target effects and toxicity. Candidate compounds should therefore be evaluated against relevant human cells alongside parasite selectivity, with attention to hepatic, renal, pancreatic and cardiovascular safety where appropriate. Early integration of physicochemical and toxicological profiling can help identify liabilities before costly late-stage development [63].

The 14-compound dataset also provides a rational starting point for structure–activity relationship (SAR) studies. Systematic modification of hydroxylation, methoxylation, glycosylation, heterocyclic substitution and stereochemistry could determine whether antidiabetic and antimalarial activities can be simultaneously retained or selectively enhanced. Such optimisation is essential for converting naturally occurring bioactive molecules into drug-like multifunctional leads [60].

6.4 Diabetes–Malaria Comorbidity and Combination Strategies

An important research gap is the scarcity of experimental models directly reproducing diabetes–malaria comorbidity. Demonstrating activity against diabetes and malaria independently does not establish efficacy in a comorbid host. Future studies should therefore examine whether metabolic correction influences parasite burden, disease progression or treatment response. The manuscript already identifies this distinction as important for validating the dual-action concept.

An alternative strategy is rational combination therapy involving a phytochemical with an established antidiabetic or antimalarial drug. Combination-index and response-surface analyses could distinguish synergistic, additive and antagonistic interactions and potentially identify combinations in which moderate individual activities produce greater overall efficacy.

6.5 Computational Discovery and Translational Research Framework

The 258-compound dataset provides an opportunity for cheminformatics, molecular docking, molecular dynamics, network pharmacology, machine learning and QSAR modelling to prioritise dual-action scaffolds. However, computational predictions should remain hypothesis-generating until experimentally confirmed.

A rational development pathway should therefore progress from:

compound authentication → dual-activity confirmation → target validation → SAR optimisation → ADMET profiling → comorbidity-relevant in-vivo testing → pharmacokinetic/pharmacodynamic evaluation → safety assessment → clinical investigation.

For clinical studies, dual-action candidates should ultimately demonstrate both glycaemic benefit and antimalarial efficacy, rather than merely one pharmacological endpoint.

Table 4. Translational priorities for development of dual-action phytochemicals

Development stage	Key question	Recommended approach
Activity confirmation	Does the compound reproducibly act against both conditions?	Independent biochemical, cellular and parasite assays
Target validation	Are proposed targets causally involved?	Enzyme assays, genetics, target deconvolution
Lead optimisation	Can both activities be retained/enhanced?	SAR, medicinal chemistry, QSAR
Drug-likeness	Can adequate exposure be achieved safely?	ADME/ADMET, PK/PD, formulation
Comorbidity efficacy	Does activity persist in diabetes–malaria coexistence?	Diabetic–*Plasmodium* animal models
Translation	Does dual activity produce clinical benefit?	Controlled studies with glycaemic and parasitological endpoints

6.6. Limitations of the Study

Despite the PRISMA-structured approach adopted in this review, several limitations should be acknowledged. First, the literature search depended on the databases selected and the search terms used; therefore, relevant studies not indexed in the searched databases or using different terminology may have been missed. Restricting the review to English-language publications may also have omitted relevant evidence published in other languages. In addition, as with most literature-based reviews, publication bias cannot be completely excluded, particularly because studies reporting positive or statistically significant findings are more likely to be published and indexed than studies reporting negative or inconclusive results.

A further limitation was the substantial heterogeneity among the included studies. The reported antidiabetic and antimalarial activities were assessed using diverse experimental systems, including different biochemical assays, cell-based models, parasite strains, animal models, experimental conditions, and outcome measures. Potency was also inconsistently reported, with differences in parameters such as IC_{50}, EC_{50}, percentage inhibition, and effective dose, as well as variations in assay conditions and exposure periods. These differences limit direct quantitative comparison of the reported activities and preclude meaningful statistical pooling or meta-analysis.

The review was also constrained by inconsistencies in identifying and classifying some phytochemicals in the primary literature. In particular, differences in nomenclature, chemical identification, and the level of experimental evidence occasionally required careful compound-level verification before inclusion as a dual-action phytochemical. Although efforts were made to resolve such discrepancies using the available primary evidence, the possibility of residual misclassification cannot be entirely excluded. Furthermore, unpublished studies, grey literature, and other non-indexed sources were not comprehensively represented, which may have contributed to an incomplete capture of the available evidence. Accordingly, the findings of this review should be interpreted primarily as a structured synthesis of the available published evidence rather than as a quantitative estimate of the overall efficacy of dual-action phytochemicals. These limitations also reinforce the need for standardized reporting of compound identity, assay conditions, potency measures, experimental models, and study outcomes in future investigations. Nevertheless, the PRISMA-structured search, screening, and evidence-assessment procedures used in this review provide a transparent framework for synthesizing the currently accessible literature while recognizing the uncertainties and methodological constraints inherent in the underlying evidence base.

Conclusions

This review synthesised the chemical diversity and biological activities of phytochemicals relevant to diabetes and malaria, identifying 258 phytochemicals, including 135 with reported antidiabetic activity, 109 with antimalarial activity, and 14 chemically defined compounds with evidence of both activities. The dual-action compounds represent diverse chemical classes and provide a focused basis for investigating multifunctional natural-product scaffolds targeting metabolic and parasitic processes.

A major strength of the review is its compound-level integration of antidiabetic and antimalarial evidence, including chemical class, experimental models and proposed molecular mechanisms, thereby moving beyond conventional disease-specific cataloguing. The review also provides an evidence-oriented framework for prioritising dual-action candidates.

However, the evidence remains heterogeneous and is predominantly preclinical, with important limitations in molecular target validation, pharmacokinetics, bioavailability, toxicity and direct evaluation in diabetes–malaria comorbidity models. These limitations constrain conclusions regarding therapeutic efficacy and clinical applicability. Consistent with PRISMA 2020 guidance, such limitations should be considered when interpreting the synthesized evidence. Future research should prioritise experimental target validation, structure–activity optimisation, ADMET and pharmacokinetic studies, and efficacy testing in relevant diabetes–malaria models, followed by appropriately designed clinical investigations. Improved standardisation and rigorous characterisation of natural-product preparations will also be essential for reproducible translation from discovery to therapeutic development

Author Contributions

SIRO contributed to the conceptualization, methodology, project administration, supervision, and writing–review and editing of the manuscript. DHM contributed to the investigation, literature search and data curation, formal synthesis of the reviewed evidence, and writing–original draft preparation. AA contributed to literature investigation, data curation, formal analysis/synthesis, and writing–review and editing. COA contributed to methodology, literature investigation, evidence synthesis, visualization, and writing–review and editing. IA contributed to literature investigation, data curation, validation of the reviewed evidence, and writing–review and editing. MUK contributed to formal analysis, validation, interpretation of the literature, and writing–review and editing. UJO contributed to investigation, validation, visualization, and writing–review and editing. All authors critically reviewed and approved the final version of the manuscript and consented to its submission and publication.

Declaration of Generative AI and AI-Assisted Technologies in Scientific Writing

Grammarly was used solely for proofreading, grammar correction, and improvement of language fluency, while QuillBot was used solely for reference formatting. Neither tool was used to conceptualise, draft, generate, interpret, analyse, or develop the manuscript's scientific content. The conceptualisation, scientific interpretation, analysis, and substantive writing of the manuscript were entirely undertaken by the authors. The authors reviewed the complete manuscript, independently verified its

content, and take full responsibility for the accuracy, integrity, and final published version of the work.

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The conceptualisation, scientific content, structure, and design objectives of all figures in this manuscript were developed solely by the authors. The authors used AI-assisted tools for the graphical implementation and visual rendering of selected author-conceptualised figures. The authors reviewed and verified all AI-assisted graphical outputs to ensure that the final figures accurately represented the intended scientific concepts and information presented in the manuscript. AI tools were not used to generate the scientific concepts, interpretations, analyses, or conclusions presented in this work.

Data Availability Statement

All relevant data are available within the manuscript

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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